European Academy of Neurology/European Alzheimer's Disease Consortium position statement on diagnostic disclosure, biomarker counseling, and management of patients with mild cognitive impairment

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GUIDELINES

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Abstract

Background and purpose: Careful counseling through the diagnostic process and adequate postdiagnostic support in patients with mild cognitive impairment (MCI) is important. Previous studies have indicated heterogeneity in practice and the need for guidance for clinicians.

Methods: A joint European Academy of Neurology/European Alzheimer's Disease Consortium panel of dementia specialists was appointed. Through online meetings and emails, positions were developed regarding disclosing a syndrome diagnosis of MCI, pre- and postbiomarker sampling counseling, and postdiagnostic support.

Results: Prior to diagnostic evaluation, motives and wishes of the patient should be sought. Diagnostic disclosure should be carried out by a dementia specialist taking the ethical principles of "the right to know" versus "the wish not to know" into account. Disclosure should be accompanied by written information and a follow-up plan. It should be made clear that MCI is not dementia. Prebiomarker counseling should always be carried out if biomarker sampling is considered and postbiomarker counseling if sampling is carried out. A dementia specialist knowledgeable about biomarkers should inform about pros and cons, including alternatives, to enable an autonomous and informed decision. Postbiomarker counseling will depend in part on the results of biomarkers. Follow-up should be considered for all patients with MCI and include brain-healthy advice and possibly treatment for specific underlying causes. Advice on advance directives may be relevant.

Conclusions: Guidance to clinicians on various aspects of the diagnostic process in patients with MCI is presented here as position statements. Further studies are needed to enable more evidence-based and standardized recommendations in the future.

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KEYWORDS
biomarker counseling, dementia, diagnostic disclosure, mild cognitive impairment, postdiagnostic support

INTRODUCTION

The concept of mild cognitive impairment (MCI) was coined in the 1980s [1] and brought to the attention of a wider audience as a diagnostic entity from the mid-1990s and onward using operational diagnostic criteria [2–5]. With advancing understanding of the pathophysiology of Alzheimer's disease (AD), the MCI label is used in two ways, as an etiologically heterogeneous syndrome based on clinical and neuropsychological criteria (i.e., MCI in its original sense) and as a clinical diagnosis of a certain stage of AD (i.e., MCI due to AD). This development became possible by the incorporation of biomarkers for AD [6–8] into the diagnostic framework, although the clinical presentation of MCI may be caused by many other disorders.

A patient with MCI will display a syndrome consisting of cognitive impairment but preserved activities of daily living, and a proportion of patients will have evidence of an underlying neurodegenerative brain disorder and progress to dementia. However, the outcome and course of MCI varies considerably dependent on the underlying cause. Population-based studies have demonstrated that a large proportion of patients with MCI will remain stable or revert back to normal cognition, although estimates vary from study to study [9–11].This underlines the difficulty in prognostication. Given the fact that MCI may be caused by very different underlying diseases, spanning from nonprogressive potentially reversible disorders, such as depression, to progressive and ultimately deadly neurodegenerative diseases, careful diagnostic evaluation is paramount to identify the underlying etiology. These considerations were also part of the reasons for a recent American Academy of Neurology Guideline recommending serial cognitive assessments in patients with MCI [12].

Application of biomarkers at the MCI stage and thus potentially diagnosing a neurodegenerative brain disorder at a very early stage raises a number of ethical questions and issues relating to the right information being given to the patient [13–15]. This is related to the concept of risk stratification and the complexity of the biomarker panel available. Therefore, involvement and counseling of the patient before and after a diagnosis has been established are essential.

A number of studies using different methodological approaches ranging from questionnaires [16–18] to interviews [19,20] have raised several issues related to communicating the diagnostic procedure and outcome (e.g., diagnostic disclosure and biomarker counseling in patients with MCI). For example, there is considerable variability across centers regarding diagnostic disclosure [16–18]. Similarly, prebiomarker counseling may not be carried out or may be approached very differently across centers [18]. Some physicians may be overly positive about the diagnostic and prognostic validity of biomarker results and tend to push toward further biomarker studies in patients with MCI [19]. The MCI label may be used very differently, and the understanding as an at-risk state or a valid diagnosis may also vary [18,19] Also, physicians may be overcautious in discussing possible progression [19] which makes it less likely that advanced directives or other planning for the future are discussed [18]. Furthermore, guidelines with regard to diagnostic disclosure routines and biomarker disclosure are not available in all European countries [18].

Motivated by this and the fact that there is little evidence to guide the clinician in these matters, the European Academy of Neurology (EAN) and the European Alzheimer´s Disease Consortium (EADC) formed an expert panel to develop position statements based on expert opinions, and the available evidence. The scope of this paper includes diagnostic disclosure, biomarker counseling, and postdiagnostic support in patients referred from primary care to a specialized setting for evaluation of cognitive impairment, and who receive a syndrome diagnosis of MCI regardless of the underlying cause. The target audience is physicians and other specialists who are involved in diagnosing patients with MCI and postdiagnostic support.

Differences across Europe will be taken into consideration with regard to organization and capacity. The position paper will also deal with guidance to referring physicians. The position paper applies to patients presenting with cognitive complaints and in whom the MCI syndrome diagnosis is appropriate. These patients will usually fall into a broad definition of MCI such as the Winblad criteria for MCI [5]. However, this position paper is not dealing with any specific set of diagnostic criteria for MCI. It follows that this position paper also is not limited to patients with MCI due to AD. Furthermore, it will not address individual pharmacological treatments of MCI or use of individual biomarkers in diagnostic workup. Rather, the paper aimed to provide guidance to the specialist physician when disclosing a

diagnosis and prognosis of MCI and when the decision on biomarker sampling has been taken.

METHODS

A joint EAN/EADC expert panel consisting of dementia specialists with backgrounds in research and secondary care clinical practice was appointed during meetings of the EADC and EAN in 2018 and 2019. At the beginning of the project, in-person meetings were planned, but due to restrictions on travel and assembly during the COVID-19 pandemic, meetings were replaced by two online video conferences. Positions were developed in the following way: prior to the first meeting, an online survey was carried out among the members of the panel to broadly establish which issues related to the subject of the paper the positions were to be developed on. The data from the survey were presented at the first video conference meeting and formed the basis of the discussions at that meeting. Following, two of the authors (K.S.F., G.W.) drafted an initial proposal for issues to be addressed. This was then circulated to the panel before the second meeting, at which time more in-depth discussion of the specific positions the panel would adopt on the included issues was undertaken. Further discussion via email exchange was carried out following the two meetings. Consensus among all members was necessary before a position could be adopted.

Positions

The paper is structured around four overarching areas: (i) disclosing a syndrome diagnosis of MCI, (ii) Prebiomarker sampling counseling, (iii) Postbiomarker sampling counseling, and (iv) postdiagnostic support. Positions for each area are presented in Tables 1 to 4 and are accompanied by further considerations and motivations for the positions. Areas one and four cover issues that are relevant for any patient undergoing investigations for cognitive impairment and diagnosed with MCI, whether or not biomarker investigations are undertaken. We present a flowchart for a patient undergoing diagnostic evaluation (Figure 1) and how different positions may be relevant at different steps in this process.

Disclosing a syndrome diagnosis of MCI

Mild cognitive impairment may be caused by a variety of different medical conditions and diseases, and it is important to underline that MCI in itself is not a disease. Rather, it is the manifestation of an underlying condition for which there will almost always be other pointers to guide the physician in identifying the likely cause. Therefore, diagnostic evaluation of MCI is important. Hence, it is important at the beginning of the initial diagnostic interview to inform the patient that the outcome of the diagnostic workup may be a diagnosis of a serious brain disease that is progressive and not treatable. A majority of patients who seek medical attention because they experience cognitive decline are likely to do so out of concern, and it may be reasonable to assume that they want to know as much as possible about the cause of the decline [21–23] However, as well as having the right to know, the patient also has the right not to know [14], and although the action of seeking medical attention often implies a wish to be informed, this may not apply to all patients [24]. Therefore, prior to diagnostic disclosure, the physician should map the patient's wishes regarding how and to what extent the patient wishes to be informed.

TABLE 1 Positions on disclosing a syndrome diagnosis of MCI

1.1	At the initial interview with the patient, the patient should be informed about the potential implications of starting diagnostic workup for cognitive impairment.
1.2	The motives and reasons for seeking medical attention and the ability of the patient to comprehend the information should be taken into account when informing the patient about diagnosis, prognosis, and postdiagnostic support.
1.3	The diagnosis of MCI should be disclosed by a specialist with knowledge and experience in diagnosis and management of MCI and dementia.
1.4	The option to involve family members should be discussed.
1.5	A syndrome diagnosis of MCI should always be disclosed to the patient except when the patient explicitly wishes not to be informed.
1.6	Diagnostic disclosure should always be accompanied by a plan for follow-up and postdiagnostic support.
1.7	Advice on diagnosis, prognosis, and postdiagnostic support should be supported by written information (handouts).
1.8	Avoid all terms referring to dementia when initially disclosing the diagnosis. Using the term *mild cognitive impairment* or *memory/thinking problems of uncertain origin* may be appropriate, but further explanations will usually be necessary, particularly in patients in whom a specific underlying condition is more relevant to disclose.
1.9	Any information conveyed about the prognosis should be done according to available evidence about the underlying cause and when relevant with recommendations for further investigations.

Abbreviation: MCI, mild cognitive impairment.

TABLE 2 Positions on prebiomarker sampling counseling

2.1	Prebiomarker counseling should always be undertaken prior to biomarker studies and should enable the patient to make an informed and autonomous decision.
2.2	Prebiomarker counseling should be delivered by a physician who is a dementia specialist, has knowledge about biomarkers, and preferably with prior knowledge of the individual patient.
2.3	The physician should inform in a balanced and individualized way about the potential benefits and risks, limitations, and alternatives in relation to biomarker studies.

TABLE 3 Positions on postbiomarker sampling counseling

3.1	Biomarker studies should always be followed by postbiomarker counseling and should help the patient understand the results in terms of diagnosis, prognosis, and postdiagnostic support.
3.2	Postbiomarker counseling should be delivered by a physician who is a dementia specialist and has knowledge about biomarkers and the patient.
3.3	The physician should be forthcoming with regard to discussing uncertainty in diagnosis if such exists and when relevant to request a second opinion.
3.4	Counseling with positive AD biomarkers: The patient should be informed that he/she has MCI and is at an increased risk of progression to Alzheimer´s dementia.
3.5	Individual rate of progression is difficult to predict, and some patients will remain stable for a long period of time.
3.6	Counseling with biomarkers positive for another specific neurodegenerative dementia disorder: The patient should be informed that he or she has MCI and is at an increased risk of progression to the specific dementia disorder.
3.7	Individual rate of progression is difficult to predict, and some patients will remain stable for a long period of time.
3.8	Counseling with conflicting biomarkers: The patient should be informed that the underlying cause and prognosis of the MCI syndrome is uncertain.
3.9	Further diagnostic tests may be considered, and re-evaluation should be arranged.
3.10	Counseling with negative biomarkers: The patient should be informed that the underlying cause of the MCI syndrome is not likely to be a progressive neurodegenerative disease.

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

Withholding a diagnosis for reasons such as wishing to spare the person from what may be perceived as a potentially stressful message is not acceptable, as data from patients with dementia [25,26] and MCI [27] indicate that diagnostic disclosure is safe and may even decrease anxiety. It is important to acknowledge that there may be many other factors involved when a person seeks medical evaluation. The person might only want reassurance that everything is normal and may be surprised or feel it is unwanted knowledge to be told that it is not so. It may also be that the patient is not interested in diagnostic evaluation at all, but that a caregiver took the initiative to have the person undergo evaluation [28].

Language impairment, reduced ability to reason, and lack of insight may be obstacles for delivery of information and should be taken into account when disclosing the diagnosis. Before initiating the process of counseling, it is essential to determine clinical competency of the patient. Usually, most patients with MCI will have the appropriate capacity; however, in some neurodegenerative disorders (e.g., frontotemporal dementia), clinical competency may be impaired early on. Four core components of clinical competency need to be considered [29]: (i) understanding (i.e., the ability to comprehend information relevant to a decision), (ii) appreciation (i.e., the ability to apply that information to one's own situation); (iii) reasoning (i.e., the ability to evaluate the potential consequences of one's own decisions); and (iv) expression of choice (i.e., the ability to communicate one's own choices). Clinical competency may be evaluated by specific interviews, vignette methods, neuropsychological tests [30–35], but also by general clinical judgement, taking into consideration the aforementioned core components. Factors such as cultural, social, and educational background and psychiatric comorbidities should also be considered. Involvement of a family member or other caregiver may help to bridge this gap, and it is important to always highlight and even encourage the possibility of having a

TABLE 4 Positions on postdiagnostic support

4.1	Medical follow-up should be considered in all patients with an MCI diagnosis. An individualized care plan should be agreed and delivered in writing.
4.2	Patients should be encouraged to seek medical attention if they are worried about progression of symptoms.
4.3	Patients with MCI should be offered postdiagnostic support that could include psychosocial support, caregiver support, management of medical issues and comorbidities, and specific treatment for an underlying condition.
4.4	Advice on brain-healthy living (e.g., physical and mental activity, social interaction, smoking cessation, healthy eating, low intake of alcohol, sleep hygiene) should always be given.
4.5	Treatment of comorbidities may slow the rate of progression and improve quality of life.
4.6	If the underlying disease is likely to progress, it may be pertinent to discuss the likely future development and how to plan for this.

Abbreviation: MCI, mild cognitive impairment.

family member present at the disclosure consultation. A second person may provide emotional support, and together with written information can help the patient remember what was said [36].

In some instances, the MCI syndrome is due to a disease where disclosing a diagnosis of MCI may not be as relevant. For example, patients with depression may experience cognitive impairment as well as depressive symptoms. It may not facilitate the patients' management or understanding of the underlying depression causing the cognitive impairment if the patient is diagnosed with MCI. Instead, cognitive impairment may be better explained to the patient as a part of depression. However, this will vary from patient to patient, and in some patients with depression, it may be relevant to disclose a diagnosis of MCI due to depression. When disclosing a diagnosis of MCI, terms such as *a form of mild dementia*, *predementia*, or *no dementia* should be avoided, as this may cause confusion with regard to the diagnosis and may be associated with negative connotations, because not all patients with MCI will progress to dementia [11].

The physician may be uncertain with regard to the interpretation of biomarkers due to a conflicting biomarker pattern, unusual clinical presentation, or a complex medical history. Uncertainty may also stem from a lack of knowledge on the part of the physician [20]. Knowledge of and experience with MCI and dementia is essential to mitigate such situations, and together with the complexity of the diagnostic disclosure procedure underline the importance of an experienced physician carrying this out.

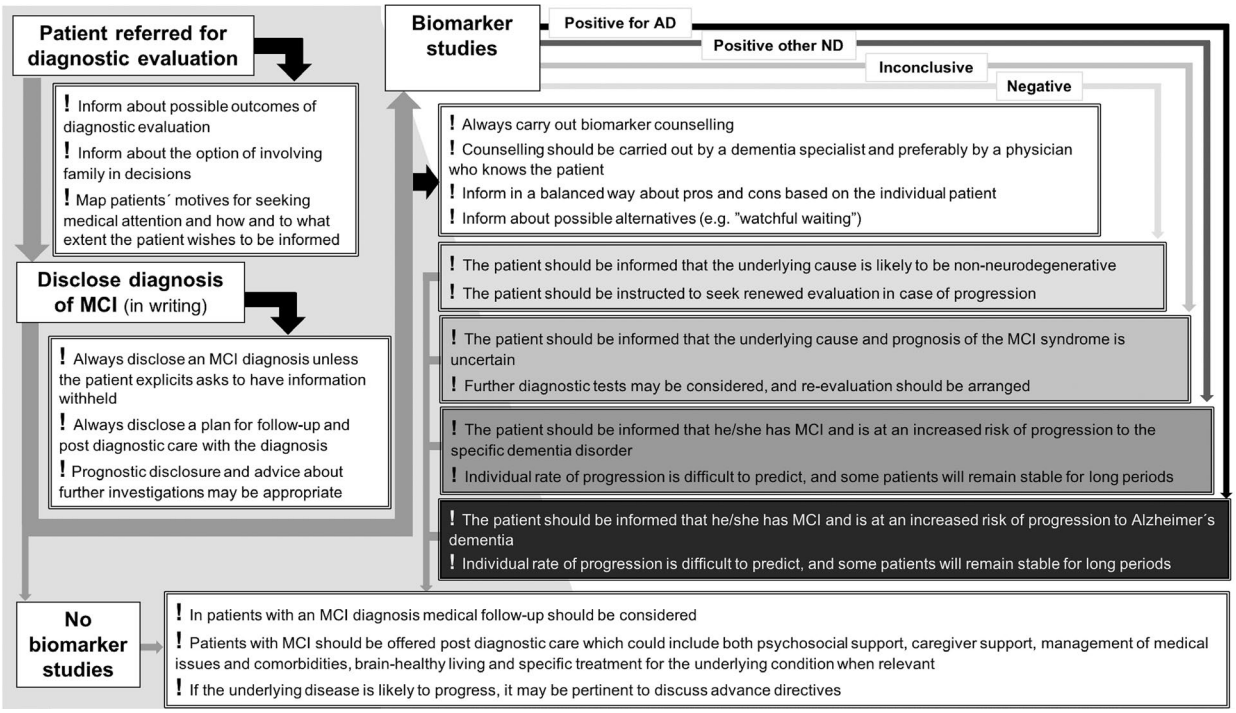

FIGURE 1 Flowchart describing the diagnostic process for mild cognitive impairment (MCI) patients. AD, Alzheimer's disease. ND (Neurodegenerative dementia disorder).

A plan for follow-up should be presented along with the diagnosis. Depending on the underlying causes and diagnostic uncertainty, follow-up may include additional diagnostic tests and may be carried out in less-specialized settings and with variable frequency.

Prebiomarker sampling counseling

Biomarkers relevant to the underlying cause and prognostication of MCI may include a number of biological measures. In the present context we refer to investigations beyond structural imaging (computed tomography or magnetic resonance imaging), neuropsychological assessment, and blood samples, which includes cerebrospinal fluid sampling and positron emission tomography imaging. It is important to highlight that, like dementia, the cause of MCI may potentially be reversible, such as tumors or vitamin deficiency, and further progression may be preventable (e.g., with vascular risk factors), and thus all biomarkers may hold important clues to the diagnosis. Another common and treatable cause is depression [37], an important differential diagnosis for the physician to consider. For these reasons and because the delineation of MCI from dementia may be difficult, withholding diagnostic procedures in individual patients because they have MCI as opposed to dementia may not be appropriate. For biomarkers of AD pathology, appropriate use criteria have been published [38,39].

Biomarkers may not be available in all centers, but diagnostic efforts should nevertheless be directed at establishing the underlying cause of MCI using the tools available, such as careful history from patient and caregiver, physical and neurological examination, blood sampling and structural scan, mood assessment, investigation of alcohol and substance abuse, careful review of drugs in use (e.g., drugs with central anticholinergic effects), and attention to red flags/diagnostic clues that may provide the diagnosis. It is possible to diagnose neurodegenerative diseases that may underlie MCI with an acceptable certainty even if more advanced biomarkers are not available [40]. Biomarkers for AD are still in an early stage of validation compared to biomarkers for cancer diagnosis [41]. Biomarker sampling should only be considered if the physician expects the biomarkers to add to the diagnostic or prognostic accuracy or to have consequences for postdiagnostic support. A number of different factors may play a role in the expected benefit regarding added diagnostic certainty. For example, due to the increasing rate of amyloid positivity in cognitively unimpaired persons with advancing age, the added value of measures of β-amyloid will diminish with advancing age. It is also important to discuss the goal of performing biomarker sampling [42] and to inform the patient about the possible expected benefits in terms of improved diagnostic accuracy to balance expectations. This may include details such as whether biomarkers may be better at ruling in or ruling out neurodegenerative disorders, because the certainty of negative biomarkers is usually higher. Furthermore, biomarkers may also be relevant for research purposes. The physician should keep in mind that what constitutes benefits or risks with regard to biomarker studies may vary according to wishes and beliefs of the patient, age, cultural background, and other factors. For example, a more definitive diagnosis may be viewed by some patients as an inescapable destiny that the patient does not have any impact on [24]. However, as already discussed, many patients will have an explicit wish to know as much as possible [24], and certainty may empower the patient. An often-discussed disadvantage of diagnosing a neurodegenerative brain disorder at an early stage is that at present there is no cure or disease-modifying therapy [14]. However, although such therapy is not available, symptoms and comorbidities are manageable. The risk of a false positive AD diagnosis has also been raised [43].

The physician's perception of the advantages and disadvantages for individual patients will also vary. The improved diagnostic accuracy may translate into a more precise prognosis, may lead to change in treatment options, better possibility for more relevant advance planning, and the possibility for the patient to participate in research including drug trials [44–46]. Assessment of biomarkers are in general safe and are associated with relatively little discomfort [47–49]. The physician should diligently discuss the aforementioned pros and cons of biomarker sampling and present relevant alternatives (e.g., re-evaluation after a certain time period–watchful waiting) and the degree of uncertainty regarding the diagnosis so that the patients will be able to decide for themselves. The physician should not advocate for biomarker studies in all cases [19]. It is important that the process of counseling does not take on a routine form and is individualized to truly enable the patient to make an autonomous decision. Prebiomarker counseling should further facilitate postbiomarker counseling by conveying the rationale of sampling and the possible outcomes in terms of the possible impact on diagnosis. The same physician who carries out prebiomarker counseling should ideally carry out postbiomarker counseling to ensure a continuous chain of care and information.

Postbiomarker sampling counseling

Interpretation of biomarker results in clinical practice remains a challenge. At present, predictive models of progression at the individual patient level, including validation in clinical settings, are still lacking further development [50–52]. This means that the physician has to extrapolate from group level to individual patient level, adding uncertainty to the prognostic prediction for the individual patient. Furthermore, patient-related factors such as age, symptoms, comorbidity, and concomitant pathology, which may at times be of uncertain impact, should be taken into consideration when interpreting biomarker results.

At present, biomarkers for deposition of β-amyloid and phosphorylated tau remain the most mature molecular biomarkers, and abnormal results are usually taken to be associated with AD [7,8,53,54]. However, as already indicated, a number of factors may complicate their interpretation. Such factors include, for example, the common occurrence of two or more pathological lesions contributing to symptoms (e.g., AD pathology and Lewy

body pathology) [55], asymptomatic abnormal β-amyloid deposition with increasing age [56], and the fact that abnormal levels of β-amyloid may occur in patients with diseases not usually associated with amyloid pathology [57,58]. This underlines the importance of interpreting biomarkers as a panel rather than individually. Although a large proportion of patients with MCI and biomarkers indicative of a specific neurodegenerative disease will progress to dementia, a significant number of patients may remain stable or show very slow progression for an appreciable amount of time [10,11] and may therefore not progress to dementia within their lifetime (e.g., if the patient is diagnosed at an advanced age). For these reasons, caution is advisable when disclosing results of biomarker studies, especially with regard to prognosis, and avoiding a deterministic interpretation of biomarker results in terms of progression from MCI to dementia is advised. On the other hand, false reassurance may also mean that patients miss out on opportunities to plan ahead at a stage where the cognitive impairment still permits it. Patients should therefore be informed about the spectrum of possible disease trajectories, as a more accurate prognosis at the individual level is not possible at present. If biomarkers are conflicting (e.g., elevated amyloid but normal phosphorylated tau), the uncertainty in the cause and prognosis should be conveyed to the patient. Negative biomarkers may indicate that the impairment may not be due to a neurodegenerative disease but does not definitely rule it out either. A number of different strategies may be employed to reduce diagnostic uncertainty, such as follow-up, which may enable a more accurate diagnosis. As the disease course may reveal clues to a definite diagnosis, additional diagnostic tests or a second opinion may be requested. A large body of evidence exists on how to convey risk to patients across a spectrum of diseases, and it may be beneficial for the physician to apply these when communicating results of biomarkers to the patient [59].

Postdiagnostic support

Postdiagnostic support and follow-up, including a care plan, should be individualized based on the patient's underlying disease and needs. Follow-up may have different objectives, such as to ensure adequate care and treatment, diagnostic clarification (watchful waiting with assessment after 6 or 12 months), and counseling. Neuropsychological testing will usually be important in connection with this and should always be considered. In patients where the underlying condition is likely to be nonprogressive (e.g., depression, alcohol abuse, cerebrovascular disease), the need for follow-up will vary accordingly. In patients with MCI, competency may be preserved. Therefore, follow-up may not have to be preplanned, but could be in the form of instructions to the patient to seek medical attention if he or she has concerns regarding progression or if a caregiver observes progression. One caveat in this regard is that physicians may have difficulty in evaluating clinical competency [60], warranting caution, although most patients with MCI would usually have appropriate capacity.

The setting for follow-up will depend on the objectives, the underlying condition, and local organizations for dementia care. For patients with an underlying neurodegenerative condition, follow-up should be multidisciplinary and include specialist physicians with expertise of MCI and dementia. Where there are diagnostic uncertainties, patients may require follow-up in more specialized centers at least for some time, after which a watchful waiting approach with renewed referrals to a specialized center in case of progression may be arranged.

Management of patients with MCI should be based on a holistic, multidisciplinary approach depending on the underlying cause. It is important to highlight that despite the lack of a disease-modifying therapy for neurodegenerative diseases, management of symptoms and comorbidities, medically and otherwise, is possible. This includes medical treatment of depression, management of behavioral symptoms, awareness and management of possible seizures, review of medication, advice on brain-healthy living (e.g., physical and mental activity, social interaction, smoking cessation, healthy eating, low intake of alcohol, sleep hygiene, and correction of visual and hearing problems), and treatment of modifiable risk factors as has been recommended [12]. Psychosocial support should also be offered to the patient and caregiver. It is important to include the patient in this planning to be a resource for their own well-being. Importance of the chain of care (e.g., communication of diagnostic conclusions to dementia nurses or other physicians who will follow-up with the patient) should be stressed.

Advance directives may be relevant to discuss with patients with MCI if, for example, it is likely that the patient may progress. As noted, most patients with MCI are likely to have retained competency and can actively participate in and plan for the future, as opposed to many patients in the moderate-to-severe dementia stage at which time competency may be lost. Advance directives may cover a range of topics such as decisions relating to the type and extent of medical care the patient may wish to receive in the future, designation of power of attorney related to health, other personal matters, and financial decisions. A will may also be relevant. Discussions related to driving and gun ownership may also be relevant.

CONCLUSION

Since its inception, the concept of MCI has diffused from research into clinical practice. With an aging population and increasing awareness of the importance of seeking medical attention for cognitive impairment [61], the number of patients diagnosed with MCI is likely to be on an upward trajectory. It may be speculated that this has led to an increase in the clinical use of biomarkers in patients with MCI, despite the fact that, at present, diagnostic criteria incorporating biomarkers have only been developed for use in research [6–8,62], and biomarkers may not be recommended at the MCI stage [12,63], although guidance to clinicians regarding the appropriateness of use when

considering measuring AD biomarkers has been published [38,39]. For these reasons and others outlined previously in this paper, positions on a number of key issues related to diagnostic disclosure, pre- and postbiomarker counseling, follow-up, and postdiagnostic support have been formulated. Where possible, positions have been based on existing evidence, but due to the dearth of data, no formal grading of the quality of the evidence has been carried out. There is a need for further research to better understand the needs of patients with MCI regarding counseling and how such counseling may be carried out. At present such efforts are underway [64].

CONFLICT OF INTEREST

The authors report no actual or potential conflict of interest with regard to the submitted work. Outside the submitted work, Timo Grimmer reported having received consulting fees from Biogen, Bracket, Eli Lilly, Functional Neuromodulation, Iqvia, Novartis, Novo Nordisk, and Roche Pharma; lecture fees from Actelion, Biogen, B. Braun, Eli Lilly, Life Molecular Imaging, Novartis, Parexel, and Roche Pharma; and grants to his institution from Actelion and Novartis. Outside the submitted work, Sebastiaan Engelborghs reported having received consulting fees from Biogen, Eisai, Nutricia/Danone, Novartis and unrestricted research grants from ADx Neurosciences and Janssen Pharmaceutica. Outside the submitted work, Lutz Frölich reports personal fees from Axon Neuroscience, Biogen, Boehringer Ingelheim, Eisai, Eli Lilly & Co, GE Healthcare, Janssen-Cilag, Lundbeck A/S, Merck Sharp & Dohme, Nutricia, Pfizer, PharnextharmatrophiX, Avanir; and grants and personal fees from Novartis and Piramal.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable. No new data were generated.

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