

GUIDELINE

Mild cognitive impairment: the Manchester consensus

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Abstract

Given considerable variation in diagnostic and therapeutic practice, there is a need for national guidance on the use of neuroimaging, fluid biomarkers, cognitive testing, follow-up and diagnostic terminology in mild cognitive impairment (MCI). MCI is a heterogeneous clinical syndrome reflecting a change in cognitive function and deficits on neuropsychological testing but relatively intact activities of daily living. MCI is a risk state for further cognitive and functional decline with 5–15% of people developing dementia per year. However, ~50% remain stable at 5 years and in a minority, symptoms resolve over time. There is considerable debate about whether MCI is a useful clinical diagnosis, or whether the use of the term prevents proper inquiry (by history, examination and investigations) into underlying causes of cognitive symptoms, which can include prodromal neurodegenerative disease, other physical or psychiatric illness, or combinations thereof. Cognitive testing, neuroimaging and fluid biomarkers can improve the sensitivity and specificity of aetiological diagnosis, with growing evidence that these may also help guide prognosis. Diagnostic criteria allow for a diagnosis of Alzheimer's disease to be made where MCI is accompanied by appropriate biomarker changes, but in practice, such biomarkers are not available in routine clinical practice in the UK. This would change if disease-modifying therapies became available and required a definitive diagnosis but would present major challenges to the National Health Service and similar health systems. Significantly increased investment would be required in training, infrastructure and provision of fluid biomarkers and neuroimaging. Statistical techniques combining markers may provide greater sensitivity and specificity than any single disease marker but their practical usefulness will depend on large-scale studies to ensure ecological validity and that multiple measures, e.g. both cognitive tests and biomarkers, are widely available for clinical use. To perform such large studies, we must increase research participation amongst those with MCI.

Keywords: mild cognitive impairment, dementia, biomarkers, amyloid, tau, CSF, clinical trials, risk reduction, cerebrovascular, neurodegeneration, Alzheimer's, Lewy body, neuropsychology, neuroimaging, older people

Background

In November 2019, four of the authors (JS, DA, JOB and AB) convened a consensus meeting of researchers, clinicians and other stakeholders in Manchester, UK. The objective was to consider the evidence base for the clinical and heuristic utility of the mild cognitive impairment (MCI) concept and provide a roadmap for future clinical practice and translational research across the UK. During the one-day seminar, we attempted to describe the scope of use of MCI as a diagnostic category, determine its utility and explore the implications of its continued use in research and clinical practice. There have been previous attempts to generate consensus on the utility of the term 'Mild Cognitive Impairment' [1], and there is some agreement that defining an at-risk cognitive state may usefully describe patient cohorts at a population level. However, only 5–15% of people with MCI progress to dementia every year. Therefore, in the absence of treatments to slow or halt neurodegeneration, the heterogeneity of the syndrome and the variability of the ensuing trajectory create uncertainty about whether a diagnosis of MCI *per se* is helpful or harmful for the individual. A 'diagnosis' of MCI may present an opportunity for vascular risk reduction and behavioural change in some people, but without clear communication of prognosis might also lead to illness behaviour or increased healthcare utilisation and carer stress. In this paper, we aim to create a tractable problem statement as a framework for future national guidance on minimum standards in diagnosis and management of MCI.

Diagnostic criteria

MCI is defined as objective cognitive impairment on neurocognitive testing in the absence of significant impairment of instrumental activities of daily living (ADL) [2]. This cognitive state is not always accompanied by a subjective awareness of cognitive impairment, so collateral history is important. Conversely, a subjective awareness of cognitive impairment is not always accompanied by objective evidence of either a personal trajectory of cognitive or functional decline or lower than normal cognitive functioning for age, a state somewhat controversially labelled 'subjective cognitive decline' [3].

The definition of MCI in an individual or a cohort depends on which cognitive tests are used and the determination of 'impairment' in instrumental ADLs. The presence or absence of MCI is therefore dependent on the sensitivity and specificity of the tests used, population norms and estimates of premorbid cognitive functioning. Without clear collateral history, decline in an individual's cognitive functioning may be inferred from previous peak occupational or educational attainment [4, 5]. Where doubt remains, two tests separated in time may be required. Using normative neuropsychological criteria, e.g. performance 1.5 standard deviations (SD) lower than the population mean, relies on the availability of comprehensive cognitive testing and well-developed age- and education-adjusted population norms [6]. Using a 1.5 SD cut-off is more sensitive to decline than a 2-SD cut-off [7], but necessarily less specific. In addition, any such

cut-off is arbitrary, and there will be individuals (7% at the 1.5 SD cut-off) who score and have always scored lower than their age-matched peers. Many of these people have stable, normal cognitive function, but may come to medical attention due to age-associated comorbidity, depression or other disorders. Similarly, those with premorbid high cognitive scores have further to decline before reaching the cut-point for impairment and may sometimes be labelled with 'subjective cognitive impairment' before MCI.

Diagnostic criteria for 'MCI' have developed over many decades and international consensus criteria have been developed [2, 8–11]. We now know that neurodegenerative diseases develop many years before symptoms are observed. When applied to cognitively normal populations, imaging and fluid biomarkers of pathological changes underpinning Alzheimer's disease and other common causes of dementia has led to the definition of prodromal (MCI) and pre-clinical stages [12]. Age remains the biggest risk factor for the development of cognitive impairment but many other factors including socioeconomic status, genetics, education, environmental exposure and other comorbidities, e.g. mid-life cardiovascular risk, are associated with worse later-life cognitive function [13–15].

Prevalence and incidence of MCI

The incidence and prevalence rates of MCI are heterogeneous across studies due to variation in definitions and diagnostic criteria. The COSMIC collaboration [8] found an MCI prevalence of 6% in those over 60 years of age across 11 studies, and the updated American Academy of Neurology guideline estimated 6.7% prevalence in 65–69 year olds and 25% for ages 80–84 [16]. A recent meta-analysis estimated 22.5 new cases per 1000 person-years in the 75–79 age group and 60/1000 person-years in the over 85s [17], noting significant heterogeneity in cohort definitions and cognitive measures. There is widespread variation in the rates of MCI diagnosis across UK memory services. Some rarely if ever diagnose the condition, whereas other services' rates may be 20% or more [18].

Aetiology

MCI is defined as a syndrome, agnostic of aetiology, so its underlying causes are heterogeneous. Importantly, not everyone with MCI has a neurodegenerative disease. Neither does every individual have a single underlying cause for their cognitive impairment. Clinical identification of prodromes of Alzheimer, Lewy body, vascular and frontotemporal dementias (FTD) is important, but not always possible, partly because as age increases, overlapping neuropathological processes are the rule [19]. In older people, significant physical comorbidity can create complex interactions between cognitive impairment and frailty. In those with major mental health problems like depressive illness, cognitive impairment can be a prominent component, potentially masking or acting synergistically with underlying neurodegeneration. Sometimes, such states form the part of

a spectrum of disorders with variably overlapping: health anxiety, cognitive sequelae of psychiatric illness (particularly depressive symptoms) and functional neurological disorders. This spectrum, commonly defined as 'Functional Cognitive Disorder' is associated with significant subjective distress, which may not be relieved by negative investigation results [20]. This heterogeneity of aetiologies between and within individuals with cognitive impairment creates wide variation in diagnosis, prognosis and therapeutic approach. Without tissue-based diagnosis, clinico-pathological correlation is exceptionally poor, both in leading centres and routine practice [21], also in UK routine practice [9].

Research diagnostic criteria

Reducing phenotypic heterogeneity in interventional studies increases statistical power and consistent definition of MCI may prevent inappropriate exposure to experimental medicines [22,23]. In observational studies, strict criteria reduce confounding, improving the validity of findings. It is common for diagnostic criteria to start in a research setting and then to move into the clinic over time beginning with tertiary/specialist clinics; criteria commonly also develop over time. One example is the evolution of the MCI concept from a purely amnesic syndrome to include non-amnesic impairments and from single domain complaints to multi-domain impairment, which may have implications both for the underlying pathology and risk of progression. Similarly, the use of biomarkers has begun to transition from research to clinical practice, initially led by structural imaging to exclude alternative pathologies and latterly to provide positive evidence for neurodegeneration or cerebrovascular disease. More recently, molecular markers for specific pathologies have become available [2, 24, 25]. The US Food and Drug Administration has recently issued draft guidance on the use of biomarkers for clinical trial recruitment. The move from research to clinical use must be evaluated in terms of its utility to the patient, especially in the absence of disease-modifying treatments. The earnest pursuit of population 'homogeneity', vital to some research efforts, needs to be moderated in the clinic with an appreciation of individual patients' complexity, comorbidity and individual wishes and the relative cost–benefit for the individual and the wider healthcare system of procedures and testing.

The course of MCI

In keeping with aetiological heterogeneity, rates of progression in MCI are variable. In studies lasting over 5 years, annual rates of progression to dementia have been estimated at between 8 and 15% [26], but there is considerable variation (16% in the Alzheimer's Disease Neuroimaging Initiative cohort). Factors predicting faster progression are shown in Box 1. In UK clinical practice, the duration of follow-up is a source of considerable practice variation (Box 2). Many memory clinics will discharge patients with MCI diagnoses to primary care until and unless they deteriorate, despite the

National Institute for Health and Care Excellence (NICE)'s 2006 Dementia Guideline recommending annual follow-up (the advice in section 1.3.3.3 arguably still relevant as the 2018 guidance did not include MCI [27,28]). Other practice guidelines also recommend follow-up on an annual basis [16]. Rarely, memory services follow the course of cognitive impairment until the threshold for dementia is reached, or no further deterioration is expected. Full implementation of a policy of annual follow-up would have enormous implications for services in acute and mental health trusts across the UK, necessitating significant investment.

Box 1 Factors predicting more rapid progression to dementia

1. Amnesic subtype [80, 81]
2. Multidomain impairment [82]
3. Worse cognitive impairment [80]
4. Significant cerebral WMH [83]
5. APOE4 carrier status
6. Abnormal brain AB₁₋₄₂ on PET or CSF analysis
7. Abnormal tau on PET or CSF analysis
8. Significant atrophy
 - a. Focal hippocampal (MTA score)
 - b. Global cerebral atrophy/ventricular enlargement out of keeping with age
9. Evidence of a personal trajectory of decline
10. Depression
11. Frailty
12. Delirium
13. Poor glycaemic control

Box 2 Potential sources of variability in MCI diagnostic practice

- Referral pathways
- Specialist training
- Care setting
- Lack of NICE guidance on minimum diagnostic standards
- Investigation availability
 - Imaging
 - CSF biomarkers
- Expertise availability
 - Neuropsychology
 - Dementia neuroradiology
- Implementation of diagnostic criteria [84]

Primary prevention

Prevention of the underlying causes of MCI is a major public health challenge. The high numbers of people with dementia and cognitive disorders and their economic impact mean effective public health response is a priority [13]. Reducing cardiovascular risk factors, treating depression, minimising anticholinergic burden and treatment of comorbid conditions including sensory impairments, all have a role in

improving cognitive health. Control of midlife hypertension, smoking cessation and the promotion of social, physical and intellectual activity should be priorities at national and international levels [29]. World Health Organization guidelines currently recommend a Mediterranean diet, reductions in alcohol and targeting obesity amongst other individual interventions with variable levels of evidence [30].

Secondary prevention and management

Patients and the public should be informed about the opportunities for risk reduction. Multidomain interventions including diet and lifestyle alongside cognitive training have demonstrated some effectiveness [31, 32]. Their translation into routine clinical practice would require a significant investment in cognitive health that is currently not evident in, e.g. the National Health Service (NHS) long-term plan. Those with more severe or multidomain impairment who are at the greatest risk of progression may benefit from more frequent follow-up, with the opportunity to combine cognitive and physical health checks in primary care as routine. This setting may also offer the opportunity to address sensory deficits and other remediable risk factors for progression.

Acetylcholinesterase inhibitors (AChEIs) have been shown to be ineffective in the management of 'all cause' MCI as clinically defined, and although they are cheap and generally well tolerated, may cause gastrointestinal and cardiac side effects [33]. It is possible that some biomarker-defined subgroups might benefit more from AChEIs or Memantine, but this requires further study. The advent of disease-modifying medications would offer a chance to address underlying primary neurodegenerative pathologies, turning Alzheimer, Lewy body and frontotemporal lobar degeneration into chronic cognitive conditions to be managed in the context of comorbidities. However, these conditions will probably only be treatable if diagnosed using molecular methods at an early stage.

The role of cognitive testing

The level of specialist knowledge and experience required to administer and interpret many neuropsychological tests is high, which can limit patient access. Simpler, bedside screening tests like the mini-mental state examination (MMSE) [34] and montreal cognitive examination (MoCA) [35] have utility but may exhibit ceiling effects in those with the mildest levels of impairment or high pre-morbid cognitive function. More detailed and sensitive tests may help in early detection but are not always available, and a personal trajectory of decline based on repeated testing may be most sensitive in patients who at baseline differ from the population mean. The boundary between MCI and subjective cognitive impairment is complex and necessarily arbitrary in some cases, depending on a complex interaction between the properties of the test used including ceiling effects and the patient's educational attainment, language and cultural factors. Population-normed tests may produce false-negative

results in those with premorbid functioning well above the mean, and false-positives in those with premorbid scores below the population mean, requiring tools to accurately assess premorbid function [36].

Some modern cognitive tests take the advantage of computerised interfaces and continuous testing at higher temporal resolution [37–39]. These may combine testing modalities and examine multiple neurocognitive domains [40], or focus on single, purportedly highly sensitive domains [37]. The increasing use of computer and smartphone technology in older populations means that there is potential for population norms to be developed with less research effort and expense than traditional methods while accounting for test–retest variability [41]. The aim of computerised testing goes beyond the measurement of trajectories and sensitive subtyping of neurodegenerative diseases [41]. Continuous monitoring may also offer simple measurements of functional status, beyond lists of ADLs, and more sensitively detect functional decline [42]. Computerised testing also invites telemedical applications, providing opportunities for early detection and diagnosis, for triaging those with subjective impairments, and in the era of the severe acute respiratory syndrome coronavirus 2 pandemic may allow at least some assessment of cognitive function while maintaining physical distancing measures. However, moving too rapidly to web-based healthcare risks exacerbating health inequalities. In the UK, internet use is markedly lower in the over-65 age group and lower still in those from ethnic minority backgrounds over 65 [43]. However, since 2011, this age group has seen the largest increase in recent internet use [44].

Structural neuroimaging

The use of structural neuroimaging in the assessment of MCI in the UK is highly variable. Many clinicians requesting neuroimaging do not have access to the images themselves, relying only on written reports. Computed tomography is often used instead of magnetic resonance imaging (MRI) to ‘rule out’ structural causes of cognitive decline, although these are relatively rare. However, this may be because MRI is more costly, not commissioned or not available. The UK has the 2nd lowest number of MRI scanners per capita in the European Union (7.2/million) [45], of which 29% are at least 10 years old. Similarly, the UK has only 232 radiologists describing neuroimaging as a ‘primary specialist interest’ [46] of whom a minority are specialists in neurodegeneration. This suggests a need and opportunity for training and development of neuroradiologists, and decision-support tools trained on the large quantities of structural neuroimaging data acquired every year, which would require national harmonisation efforts. Although age-standardised norms are now available for volumetric analysis of hippocampal structures for the UK population, such analyses are little used clinically [47].

All diagnostic criteria for the major causes of dementia contain guidance on the use of MRI neuroimaging [48–51].

NICE currently recommends structural neuroimaging for subtyping in ‘suspected early dementia’. However, although MCI represents a state of ‘suspected early dementia’, no further guidance is given on selection of appropriate structural imaging. Imaging should not replace a detailed clinical assessment, but can give insights into the presence, absence or degree of neuronal injury. MRI is also a sensitive indicator of cerebrovascular disease. The severity of white matter hyperintensities (WMH) may represent underlying ischemia and impact upon the course of cognitive symptoms [52]. Cerebrovascular disease is associated with a typical pattern of cognitive slowing and executive dysfunction with neuropsychiatric symptoms also affecting broader functioning like depression and apathy [53, 54]. However, relying on MRI images to provide a single attributable cause for complex cognitive and emotional changes is likely to over-emphasise the importance of age-related and often stable WMH, so integration with the clinical and neuropsychological picture is vital.

Nuclear imaging

Nuclear imaging is recommended by NICE for early dementia when the ‘diagnosis is uncertain and Alzheimer’s Disease (AD) is suspected’. For suspected AD and FTD, fluorodeoxyglucose positron emission tomography (FDG-PET) or single positron emission computed tomography (SPECT) scanning is recommended depending on availability; for suspected Dementia with Lewy Bodies (DLB), dopamine SPECT (or myocardial metaiodobenzylguanidine scintigraphy if not available) is suggested. Availability across the UK is, however, patchy; there are currently only 62 UK PET scanners, located usually in University teaching hospitals or research centres [55].

The 2018 NICE diagnostic guidance was limited to ‘suspected dementia’ and does not recommend amyloid-sensitive PET-imaging. However, appropriate use criteria for amyloid PET imaging include ‘Unexplained MCI’ [56] (Box 3). Since the evidence-based review for the 2018 NICE guidelines, several large-scale clinical studies have been published, which have consistently demonstrated the utility of PET in diagnosis and management. The Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study demonstrated changes in patient management in 60% of those with MCI after amyloid-PET although this was mostly driven by increased prescription of AChEIs to patients with a positive scan (an unlicensed indication in the UK); 24% of MCI patients received a change in ‘counselling about safety and future planning’ [57]. Emerging evidence suggests that accurate and timely diagnosis is beneficial even in the absence of disease-modifying therapies [58], but molecular diagnosis may also be a rate limiting factor in accessing novel disease-modifying medication. However, the evidence of clinical benefit, infrastructure and funding lag behind. Both clinical scanning time and relevant radiotracer manufacture in the UK is extremely limited. The potential impact of

PET-amyloid is the subject of ongoing health-economic research.

Box 3 Appropriate use criteria for amyloid-PET, used [with permission] from Johnson et al. [56]

Amyloid imaging is appropriate in the situations listed here for individuals with all of the following characteristics: (i) a cognitive complaint with objectively confirmed impairment; (ii) AD as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert and (iii) when knowledge of the presence or absence of A β pathology is expected to increase diagnostic certainty and alter management.

1. Patients with persistent or progressive unexplained MCI

2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation

3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)

Amyloid imaging is inappropriate in the following situations

4. Patients with core clinical criteria for probable AD with typical age of onset

5. To determine dementia severity

6. Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE) ϵ 4

7. Patients with a cognitive complaint that is unconfirmed on clinical examination

8. In lieu of genotyping for suspected autosomal mutation carriers

9. In asymptomatic individuals

10. Nonmedical use (e.g. legal, insurance coverage or employment screening)

The role of fluid biomarkers:

The development of blood and cerebrospinal fluid (CSF)-based biomarkers could offset the significant capital investment the UK would need to expand PET diagnostic infrastructure and training to ensure access. Molecular biomarkers: phosphorylated tau, total tau, A β ₁₋₄₂ and perhaps neurofilament light (NFL) may offer a better combination of sensitivity and specificity than single-tracer nuclear studies, especially in older populations. However, this would depend on greater acceptance and availability of lumbar puncture in memory-clinic settings.

CSF biomarker testing has been increasingly used in research for over 15 years, with meta-analyses supporting its use to identify AD pathology in the context of MCI [59]. Similarly to imaging, this has moved from being used to exclude infectious or inflammatory processes towards

providing positive evidence for underlying AD pathology. CSF analysis for phosphorylated tau and A β ₁₋₄₂ (or A β ₁₋₄₂/A β ₁₋₄₀ ratio)—whose measurement is increasingly being standardised and automated [56, 60–63] are currently recommended (alongside FDG-PET) in the UK by NICE for the diagnosis of Alzheimer disease in those with suspected neurodegeneration if uncertainty remains after clinical assessment and structural imaging [64]. However, notwithstanding the advice to use in ‘suspected early dementia’, there is no concomitant guidance for use in MCI specifically, although current diagnostic criteria allow for a diagnosis of AD to be made at the MCI stage in the presence of AD biomarkers. CSF examination is rarely performed as part of the diagnostic work-up in the UK in contrast to many European centres [65], although it is safe, well tolerated [66] and cheaper than PET imaging.

In recent years there have been major advances in the development of blood-based biomarkers for AD (plasma A β and p-tau) and for all-cause neurodegeneration (serum NFL) [67, 68]. Clinical development and roll out of these measures would have major impacts on the molecular diagnosis of early neurodegeneration.

However, it will be necessary to develop age-specific norms and validate the sensitivity and specificity of both plasma and CSF biomarkers in representative samples including older people (including those with multiple pathologies, or age-related amyloidosis) and those with depression and severe enduring mental illness.

Measuring diagnostic test performance entails value judgements about the cost of false-positives and false-negatives (the loss-function) [69]. In the absence of a disease-modifying medication, false-positive diagnoses may have greater impact on the patient than false-negatives. In the presence of an expensive disease modifier, there would be commensurate health and economic concerns of false-positive diagnosis. However, false-negative diagnoses might then represent missed opportunities for intervention before irreversible neuronal injury occurs. The impetus to use available molecular tests in MCI is strong, but concerns remain around their cost-utility. Health economic analyses are underway to examine patient and health-system cost-benefit [67]. Early evidence suggests identifying and reassuring people at lowest risk of progression (i.e. biomarker negative patients) may provide the greatest health economic benefit [70–72], and 74% of the general public indicate they would wish to know if they had Alzheimer’s before any symptoms develop [73, 74]. Although qualitative interviews demonstrate that some with established cognitive impairment do not wish to know their prognosis, these people tend to be older, or managing other comorbidities [75]. Despite the ‘mild’ moniker, an MCI diagnosis can profoundly impact the individual and their perceived daily functioning, as well as family members and relationships. So, research on MCI should include not only measures of economic and healthcare utilisation, but also examine the psychosocial impact of investigation and diagnosis on patients and carers.

Clinical benefits of accurate diagnosis may include the resolution of uncertainty for patient and clinician, discharge from regular clinic visits, referral to more appropriate specialties, advance care planning, access to clinical trials, advice on current and future treatments, and counselling, support and education.

Research participation

Patients should be offered research participation as a routine part of clinical care. In some settings, this may mean merely data collection. In others, clinical trials may be an option. National infrastructure like the 'Join Dementia Research' register should be routinely offered, in addition to information about participation in immediately locally available studies (<https://www.joindementiaresearch.nihr.ac.uk/>). Engagement in research will always be the subject of shared decision-making between practitioner and patient; however, research activity may be associated with better outcomes at individual and organisational levels [76, 77].

Many studies of putative disease-modifying therapies and all studies of AChEs in MCI presumed due to AD were performed before the advent of molecular biomarkers or did not mandate them as inclusion criteria. This means that some interventional studies, including major Phase 3 trials [23] will have included individuals not likely to develop AD dementia, reducing their statistical power. It follows that if a pivotal trial included biomarker-positivity as an inclusion criterion, similar evidence of biomarker positivity would be required for the drug to be used in clinical practice. The research community increasingly recognises the need for early detection and diagnosis in order to prepare for the advent of disease modification [78, 79]. The importance of homogeneity in clinical trial populations means that trial-ready populations for disease modification are increasingly likely to be drawn only from sites with the ability to perform molecular diagnostics (please see Supplementary Data for additional material and full reference list).

Recommendations

- There is currently no NICE guidance on MCI. This means there is no guidance as to how a large proportion of cases seen in UK cognitive and memory clinics should be investigated and managed. This leads to wide variation in clinical practice and hinders optimal management of these patients. NICE guidelines for the investigation and follow-up of the MCI syndrome are urgently required.
- MCI should be considered a clinical syndrome with heterogeneous underlying pathologies and not a diagnosis in its own right. Clinicians should attempt to provide patients with an explanation for their decline in cognition, which in some cases will include using biomarkers for the early detection of neurodegeneration.
- Over-investigation of people with subjective cognitive problems but little objective evidence of cognitive decline may exacerbate health anxieties where present.

- For patients falling within the rubric of MCI, it is important to identify and treat potentially modifiable contributions to their cognitive dysfunction including but not limited to the treatment of physical illness, depression and other psychiatric disorders, isolation, optimisation of hearing and visual disturbance, recommendations and interventions to promote alcohol cessation, and rationalisation of medications (e.g. anticholinergics, hypnotics and opiates).
- Given the heterogeneity of MCI, decisions about whom to investigate and the depth of that investigation, including the utility of molecular biomarkers, should be made on an individual basis. However, as for patients with dementia, blood screening is recommended, and patients with objective cognitive decline are likely to be offered structural imaging.
- Patients with MCI should have equitable access to neuropsychological testing and expertise.
- Procedures for implementing monitoring technologies of cognition and functional deterioration in clinical practice are required.
- NICE guidance for dementia supports the use of CSF biomarkers in the diagnosis of Alzheimer's disease. Given the complexity of diagnosing patients with MCI and emerging evidence that CSF can aid in prognostication, CSF sampling may be useful on an individual by individual basis in patients with MCI in whom a diagnosis of Alzheimer's disease is suspected. The NHS requires evidence-based guidance on the use of biomarkers in mild cognitive impairment, and this should form part of any NICE guidance. The advent of disease-modifying therapies for prodromal Alzheimer's disease would mean that significant investment in biomarker and neuroimaging infrastructure would be necessary to ensure timely access for NHS patients. This will require significant planning and engagement with commissioners and providers.
- Patients with MCI should be offered review at least annually in either primary or secondary care.
- All patients with MCI should be offered access to research.
- Research on MCI should include not only measures of economic and healthcare utilisation, but also examine the psychosocial impact of being diagnosed with MCI on patients and carers.

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Axovant, personal fees from Lundbeck, personal fees from Nutricia, outside the submitted work; he has been employed by the Department of Health for England. Alistair Burns is Consultant Editor for the International Journal of Geriatric Psychiatry, NHS England, National Clinical Director for Dementia, non-pecuniary lectures for various organisations, pecuniary medico-legal reports and private practice, pecuniary, DVLA report writing. Dr Isaacs has attended an advisory board for Biogen, had registration fees and expenses paid for by Roche to attend the 2019 AD/PD conference and has been a Principal Investigator on clinical trials in prodromal AD sponsored by Roche. Dr Ben Underwood is the clinical director of the Windsor Research Unit/Gn-odde Goldman Sachs Unit for Translational Neuroscience in Cambridge, which does academic and commercial clinical trials in dementia. He is the CRN lead for the east of England for dementia and national lead for stratified medicine in dementia. He is married to Dr Rosalind Tandy, the clinical commissioner for mental health in West Suffolk. Jill Rasmussen is the Royal Coll General Practitioners Clinical Representative for Dementia and has received payments for consultancy/advisory boards/speaker bureaus from a number of Pharmaceutical Companies from psi-napse, an Independent consultancy. Dr Dunne is clinical director of the Greater Manchester (GM) Dementia Research Centre, NIHR-CRN Dementia lead for GM and has been a Principal Investigator on NIHR and Industry-funded clinical trials. Dennis Chan is funded by the Wellcome Trust, Alzheimer's Research UK and the UCL Sainsbury Wellcome Centre.

References

The full list of references can be found in [Appendix 2](#).

- Petersen RC. Mild cognitive impairment. *Lancet* 2006; 367:1979. doi: [10.1016/S0140-6736\(06\)68881-8](#).
- Winblad B, Palmer K, Kivipelto M *et al.* Mild cognitive impairment—beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. *J Intern Med* 2004; 256: 240–6.
- Petersen RC. Mild cognitive Impairment: Aging to Alzheimer's Disease. New York: Oxford University Press, 2003.
- Sachdev PS, Lipnicki DM, Kochan NA *et al.* The prevalence of mild cognitive impairment in diverse geographical and Ethn-ocultural regions: the COSMIC collaboration. *PLoS One* 2015; 10: e0142388.
- Jack CR, Lowe VJ, Weigand SD *et al.* Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain* 2009; 132: 1355–65.
- Vos SJB, Xiong C, Visser PJ *et al.* Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *The Lancet Neurology* 2013; 12: 957–65.
- Dubois B, Hampel H, Feldman HH *et al.* Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement* 2016; 12: 292–323.
- Livingston G, Sommerlad A, Orgeta V *et al.* Dementia prevention, intervention, and care. *The Lancet* 2017; 390: 2673–734.
- Petersen RC, Lopez O, Armstrong MJ *et al.* Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology. *Neurology* 2018; 90: 126–35.
- Gillis C, Mirzaei F, Potashman M *et al.* The incidence of mild cognitive impairment: a systematic review and data synthesis. *Alzheimers Dement (Amst)* 2019; 11: 248–56.
- Cook LD, Nichol KE, Isaacs JD. The London memory service audit and quality improvement programme. *BJPsych Bulletin* 2019; 43: 215–20.
- Rabinovici GD, Carrillo MC, Forman M *et al.* Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development. *Alzheimers Dement (N Y)* 2017; 3: 83–91.
- McWhirter L, Ritchie C, Stone J *et al.* Functional cognitive disorders: a systematic review. *Lancet Psychiatry* 2020; 7: 191–207.
- Beach TG, Monsell SE, Phillips LE *et al.* Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer disease Centers, 2005-2010. *J Neuropathol Exp Neurol* 2012; 71: 266–73.
- Petersen RC, Caracciolo B, Brayne C *et al.* Mild cognitive impairment: a concept in evolution. *J Intern Med* 2014; 275: 214–28.
- Dubois B, Feldman HH, Jacova C *et al.* Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol* 2014; 13: 614–29.
- Pink J, O'Brien J, Robinson L *et al.* Dementia: assessment, management and support: summary of updated NICE guidance. *BMJ* 2018; 361: k2438. doi: [10.1136/bmj.k2438](#).
- World Health O. Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization, 2019. xiii; 78.
- Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. *Cochrane Database Syst Rev* 2012; CD009132.
- Chan D, Gallaher LM, Moodley K *et al.* The 4 mountains test: a short test of spatial memory with high sensitivity for the diagnosis of pre-dementia Alzheimer's disease. *J Vis Exp* 2016. doi: [10.3791/54454](#).
- Sternin A, Burns A, Owen AM. Thirty-five years of computerized cognitive assessment of aging—where are we now? *Diagnostics (Basel)* 2019; 9: 114.
- OECD. Magnetic resonance imaging (MRI) units (indicator). 2019. Available at <https://data.oecd.org/healthqt/magnetic-resonance-imaging-mri-units.htm> (accessed 24 November 2019).
- Royal College of Radiologists. Clinical Radiology Workforce Census 2018 Report: The Royal College of Radiologists; 2019 [updated April 2019. Available from: https://www.rcr.ac.uk/system/files/publication/field_publication_files/clinical-radiology-uk-workforce-census-report-2018.pdf.
- Nobis L, Manohar SG, Smith SM *et al.* Hippocampal volume across age: Nomograms derived from over 19,700 people in UK biobank. *NeuroImage: Clinical* 2019; 23. doi: [10.1016/j.nicl.2019.101904](#).
- McKeith IG, Boeve BF, Dickson DW *et al.* Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology* 2017; 89: 88–100.

52. McKhann GM, Knopman DS, Chertkow H *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7: 263–9.
62. Olsson B, Lautner R, Andreasson U *et al.* CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol* 2016; 15: 673–84.
67. National Institute for Health and Care Excellence. Dementia—assessment, management and support for people living with dementia and their carers. NICE; 2018. Available at <https://www.nice.org.uk/guidance/ng97> (24 November 2019, date last accessed).
75. Wittenberg R, Knapp M, Karagiannidou M *et al.* Economic impacts of introducing diagnostics for mild cognitive impairment Alzheimer's disease patients. *Alzheimers Dement* (N Y) 2019;5:382–7.
77. Detecting and diagnosing Alzheimer's disease: Enhancing our understanding of public attitudes to improving early detection and diagnosis. vol. 31. London: Alzheimer's Research UK, 2019.

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