

Rationale for Early Diagnosis of Mild Cognitive Impairment (MCI) Supported by Emerging Digital Technologies

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Abstract

Disease-modifying pharmacotherapies for Alzheimer's Disease (AD) are currently in late-stage clinical development; once approved, new healthcare infrastructures and services, including primary healthcare, will be necessary to accommodate a huge demand for early and large-scale detection of AD. The increasing global accessibility of digital consumer electronics has opened up new prospects for early diagnosis and management of mild cognitive impairment (MCI) with particular regard to AD. This new wave of innovation has spurred research in both academia and industry, aimed at developing and validating a new "digital generation" of tools for the assessment of the cognitive performance. In light of this paradigm shift, an international working group (the Global Advisory Group on Future MCI Care Pathways) convened to elaborate on how digital tools may be optimally integrated in screening-diagnostic pathways of AD. The working group developed consensus perspectives on new algorithms for large-scale screening, detection, and diagnosis of individuals with MCI within primary medical care delivery. In addition, the expert panel addressed operational aspects concerning the implementation of unsupervised at-home testing of cognitive performance. The ultimate intent of the working group's consensus perspectives is to provide guidance to developers of cognitive tests and tools to facilitate the transition toward globally accessible cognitive screening aimed at the early detection, diagnosis, and management of MCI due to AD.

Key words: Alzheimer's disease, mild cognitive impairment, cognitive screening, disease modifying, digital, healthcare.

Introduction

The late-stage clinical development and potential near-approval of drugs with modifying effect on Alzheimer's disease (AD) calls for a substantial paradigm shift in the diagnosis and

management of the disease, including the Mild Cognitive Impairment (MCI) stage (also called MCI due to AD or prodromal AD). The availability of disease-modifying therapies will result in unprecedented demand for cognitive performance assessments (i.e., large-scale cognitive screening). Moreover, the progressive rise of lifespan in populous developed countries such as the U.S., EU5, China, and Japan (1, 2) will bring about an exponential increase in the incidence of age-related diseases, including AD. It is expected that widespread demand for cognitive evaluation will likely overwhelm existing healthcare infrastructures and services at both primary care and specialist levels.

Early detection, of MCI or preclinical AD stages, coupled with timely initiation of disease-modifying treatments, has become the clear path to successfully facing the social and medical threat of AD. Gaps on both sides, particularly a paucity of detection tools suitable for practical use in patient populations and the absence of approved disease-modifying therapies, impede progress toward finding effective therapeutics. We focus here on MCI, a syndrome defined by clinical, cognitive, and functional criteria and characterized by objective cognitive decline in one or more cognitive domains with no significant impairment in daily-life activities (3). MCI may result from a variety of underlying causes, including Alzheimer's pathophysiology (4, 5). As a result, watchful monitoring of adults with MCI is a crucial step within the work-up for early identification of AD and will be a critical stage of treatment monitoring as novel disease-modifying AD therapies enter the marketplace. In this publication series, we use the term "MCI" to refer to non-dementia cognitive impairment due to any cause and the terms "MCI due to AD" or "MCI-AD" to refer specifically to MCI associated with positive biomarkers

of AD pathophysiology, as established in current research diagnostic criteria (3-5).

If disease modifying-therapies enter clinical practice, several issues must be overcome to achieve large-scale cognitive and biological screening of AD.

First, MCI is heterogeneous in its clinical spectrum and has historically been challenging to define, identify, and monitor in clinical practice. In addition, the currently qualified biomarkers for AD are assessed through invasive, expensive, and time- and resource-consuming investigations such as cerebrospinal fluid (CSF) analysis and positron-emission tomography (PET) imaging. The progressive establishment of blood-based biomarkers (6) and the validation of multi-dimensional diagnostic techniques have the potential to make the diagnosis and management of MCI-AD feasible in primary care, as is necessary for early screening and detection.

Primary care physicians (PCPs) currently lack technical support, infrastructure, training, and experience to efficiently detect and manage AD along its clinical continuum, from preclinical phases to MCI and dementia. A 2019 survey conducted among U.S. PCPs reported that short cognitive evaluations are assessed in only half of individuals 65 years of age and older and that cognitive evaluations are frequently omitted due to: i) subtle cognitive impairment, ii) lack of time, and iii) patient resistance to testing (7). In a parallel patient survey, only 16% of Americans aged 65 years and older reported receiving regular cognitive assessments during routine health visits (7). Less than half of older adults report ever having discussed their cognitive performance with a physician, and less than a third have ever been assessed for cognitive impairment. Additionally, a majority of surveyed PCPs reported uncertainty around which cognitive assessment to deploy, how to perform a brief cognitive assessment, and, importantly, what to do after assessing cognition (7). Referral to specialists (e.g., neurologists, psychiatrists, geriatricians, and neuropsychologists) is the default for evaluating cognition and diagnosing MCI-AD. However, with the expected AD (and other neurodegenerative disease) epidemic burden, access to specialists has been and will become even more challenging. PCPs will need to be fully involved in the process and equipped with the proper means to ensure timely and efficient detection and care.

In recognition of current challenges around the detection of MCI, a working group composed of international experts on MCI and AD convened in April 2019 to elaborate on existing frictions and barriers, in both clinical and non-clinical settings, that prevent widespread cognitive screening for early detection of MCI and particularly MCI-AD. We summarize potential solutions to overcoming those barriers in a series of three manuscripts, of which this is the first. The first manuscript focuses on advantages and disadvantages of early detection of MCI, the current MCI detection landscape, and data-driven hypothetical models on how

MCI-AD diagnosis and management may change in the future given recent technological advances and potential approval of disease-modifying therapies. In the second manuscript of this series, we offer recommendations around ways to meaningfully and rapidly implement MCI detection in primary care settings. The third manuscript of this series will focus on the potential for direct-to-consumer cognitive testing intended for use by adults or informants in an at-home setting without direct supervision by a healthcare provider. Given the critical importance of these topics, the recommendations outlined across this suite of manuscripts reflect careful consideration by this group of cognitive neuroscientists and physicians and extensive iteration and discussion from April 2019 through the present.

From the outset of this endeavor, the primary objective of this working group has been to identify actionable methods to improve detection of MCI, thereby providing developers and researchers of novel tools and tests with guidance and tangible recommendations to maximize their potential usability. To that end, the group agreed that the most feasible strategy to optimize early detection of MCI in the near-term will be to boost primary care capacity for detection by providing infrastructure and equipment that improve the accuracy and efficiency of tools for cognitive assessment without substantially increasing workload for primary care clinicians. Recommendations and strategies to facilitate this paradigm shift are described in detail in the second manuscript of this series.

Our group recognized that detection tools intended for use outside of clinical settings present unique challenges, yet they deserve critical future development, because they offer the potential to dramatically improve the scale of MCI detection. With dramatic increases in the use of consumer electronics by aging adults, digital approaches that leverage the capacities of mobile devices and Internet connectivity are a promising avenue for detection of MCI in non-clinical settings, if these consumer-directed resources can be suitably validated and linked to healthcare systems. The third manuscript in this series summarizes the challenges and opportunities relating to the detection of MCI in non-clinical settings, i.e., at an individual's home or in everyday settings such as pharmacies or community screening events, as has already been accomplished with brief paper and pencil tests (8, 9).

In this initial manuscript, we summarize existing guidelines and consensus statements to provide context around this set of recommendations. We also weigh the advantages and disadvantages of early detection of MCI, and we ultimately support the idea that detection of MCI is an important component of whole person care. Finally, we summarize our expectations of how the MCI detection landscape may continue to shift in the next 3 – 5 years to highlight the need for proactive changes and ongoing research and development.

Advantages and drawbacks of MCI detection

Consistent with previous guidelines and consensus statements (10), this panel recognized that early detection of MCI is associated with both advantages and disadvantages, and we acknowledge that the decision to assess an individual's cognitive function should be made on a case-by-case basis with each individual's best interests in mind. To support large-scale cognitive screening, the field would require a clinical consensus on the appropriate course of action for PCPs when an individual is identified as cognitively impaired. Additionally, large-scale cognitive screening algorithms were acknowledged as unlikely to become standard practice in the near-term, given the infrastructural challenges inherent to existing healthcare systems around the world. In this context, we have summarized the most critical benefits and drawbacks of early detection of MCI identified by this working group.

Benefits of Early Detection of MCI

If disease-modifying therapies for delaying or even halting AD at its MCI stage (also called prodromal stage) become available, the necessity of detecting MCI accurately, extensively, and in a timely manner is obvious. Moreover, the inability to robustly identify patients at prodromal stages remains a substantial limitation for developing AD therapies and may, at least in part, contribute to the series of drug failures. Accordingly, early MCI detection may optimize identification of patients eligible for future clinical trials and maximize the likelihood of successfully developing novel AD therapies.

However, even in the absence of a disease-modifying therapy, and regardless of the underlying etiology, multiple advantages remain associated with early detection of MCI. Individuals and healthcare systems can only benefit from an efficient algorithm for investigating MCI at a large-scale.

An early identification of MCI also increases the possibility of a timely diagnosis of the medical condition that may underlie a cognitive impairment (i.e., secondary cause of MCI), which are all potentially treatable or even reversible (e.g., metabolic and endocrine diseases, mood and sleep disorders, iatrogenicity) (11). In addition, growing evidence demonstrates that specific lifestyle habits and activities may slow down or even prevent cognitive decline. Early detection of MCI may provide subjects with greater motivation to implement lifestyle modifications and, at a minimum, will provide physicians with an additional opportunity to counsel individuals on lifestyle changes. In the current screening and diagnostic paradigm, the identification of MCI is likely to escape the therapeutic window where individuals may benefit from these non-pharmacological interventions to slow cognitive decline. Early identification of cognitive

impairment also can help individuals and their families better prepare for future care needs and address financial planning considerations, for example. In the absence of a disease-modifying therapy in the immediate future, early detection also can identify potential candidates for research and clinical trials for therapies in development that target individuals in the earlier stages of their cognitive decline and disease.

Emerging evidence also suggests that early detection of MCI may provide an economic benefit to healthcare systems. Although this has been investigated less extensively in individuals with MCI than in individuals with dementia, published literature suggests that the financial burden associated with caring for MCI patients is significant and that routine cognitive assessment may be cost effective (12-16). Tong et al. investigated screening for MCI and dementia by PCPs in England and reported that PCP use of the Mini-Mental State Examination (MMSE), 6-Item Cognitive Impairment Test and the General Practitioner Assessment of Cognition (GPCOG) led to more quality-adjusted life-years (QALYs) than informal PCP assessment alone (i.e., observing individual cognitive ability) (12). While additional research is needed to further understand the economic benefits of early detection of MCI, existing literature suggests that healthcare systems may derive significant benefits from implementing early detection practices.

Drawbacks of Early Detection of MCI

While early detection of MCI offers many positive benefits, even in the absence of a disease-modifying therapy, we acknowledge that early detection efforts may not be universally beneficial. For example, false negatives may provide subjects with false reassurance that their cognitive function has not declined, thereby preventing them from seeking further care. Similarly, false positives may create undue stress for impacted individuals and their families. These potential drawbacks underscore the urgent need for an accurate assessment, with sensitivity and specificity sufficient to minimize the detrimental impact of an incorrect result. In the context of an accurate identification, MCI individuals and their families likely will experience distress upon learning of cognitive impairment. Anecdotally, this panel noted that MCI individuals might react to this distress by distancing themselves from their physician and/or the healthcare system in response to the societal stigma that exists for individuals with a known cognitive impairment.

Importantly, implementing widespread evaluation of MCI in the primary care setting may require significant time and resources, representing a burden that may be untenable for all PCPs. Similarly, as routine wellness exams tend to last fewer than twenty minutes, devoting time to cognitive assessment may limit time spent addressing other health concerns. Limited time in PCP visits is likely to be a particularly pressing issue for the

care of geriatric individuals, who are more likely to have cognitive performance issues but also often have more morbidities and preventative health needs that must be addressed during PCP visits. Additionally, expanding cognitive testing may create an administrative burden for medical personnel, although a digital tool can help minimize this impact. Finally, widespread cognitive assessment is likely to increase the burden on specialists, as greater identification of primary care patients with MCI likely will translate to more referrals to specialists for confirmatory diagnosis. However, if the quality of cognitive assessment in a primary care setting can be improved, this may help identify patients in whom a referral is appropriate, limiting referrals for patients with only a subjective memory complaint (i.e., a self-reported loss of memory performance without objective cognitive decline). Subjective memory complaint (SMC) represents a condition at-risk for AD (5, 17-21). Moreover, SMC may underlie the beginning of the AD clinical continuum (5, 17-21). Therefore, it will be even more imperative to provide physicians with the proper tools for timely detection of AD to allow initiation of appropriate care pathways.

Summary of previous guidelines and consensus statements

Numerous consensus statements and clinical guidelines have been published in the past to provide perspective and expert guidance on defining and detecting MCI through cognitive testing (3, 22). Previous guidelines have summarized the circumstances when cognitive testing becomes appropriate, examined the current testing landscape for MCI detection, and identified the challenges and uncertainties around the detection of MCI. However, an expert consensus with an updated view on the field of cognitive neuroscience in light of novel testing modalities that are now practical due to consumer digital technology, such as smartphone applications, online games and questionnaires, etc., does not currently exist in the literature. Increasing adoption of consumer digital technology and digital fluency, even among older adults, will allow for novel testing modalities that will improve whole patient care and pave the way for potential novel therapies for AD.

A controversy remains in the field of cognitive neuroscience on the appropriate frequency of cognitive testing, as advocates see the benefit of widespread use, while others are proponents of limited and targeted use of cognitive testing. In the U.S., the 2009 Affordable Care Act (ACA) federal legislature mandated an annual cognitive assessment to be conducted during Medicare Annual Wellness visits for seniors (7, 23). However, the ACA did not mandate or provide any guidance on what type of testing should be used to meet the ACA requirements, leaving this decision to the discretion of the clinical community. In the wake of the ACA mandate, the

controversy on the appropriateness of cognitive testing has continued. In 2014, the United States Preventive Services Task Force concluded that the available evidence was insufficient to assess the benefits (e.g., potential lifestyle interventions and better patient management) and drawbacks of screening for cognitive impairment (e.g., false positives and negatives, patient suspicion and alienation from physicians, etc.) and therefore, could not recommend universal screening (24). However, due to the ACA mandate, there was still a clear need for a consensus from the field on best practices for the development, validation, and use of cognitive testing. This view has been validated by the National Institute on Aging and the Alzheimer's Association AD Framework and the 2015 working group of the International Association of Gerontology and Geriatrics (IAGG) which concluded that early identification of MCI is essential to improving cognitive performance in older adults (25). The IAGG working group found that benefits can be derived from better management of the treatable components of cognitive impairment and lifestyle interventions that may slow cognitive decline (25). Finally, a 2017 Edinburgh consensus group focused on the implications of disease-modifying treatments for AD emphasized the crucial importance of identifying early cognitive impairment, given that therapies will likely be most efficacious early in cognitive decline (26).

In addition to assessing the scenarios in which testing is appropriate, select organizations have published recommendations and advisories on preferred methods for MCI detection. As noted above, the ACA declined to recommend a specific methodology for cognitive assessment in the U.S. given that noconsensus has been reached on a universally accepted screening methodology, and formal guidance has yet to be issued on this topic by federal health authorities (e.g., Centers for Medicare & Medicaid Services, (CMS)).

In response to the "call to arms" that the ACA mandate represents, an Alzheimer's Association working group outlined specific recommendations for the detection of cognitive impairment in the primary care setting. The expert consensus highlighted that in other countries, such as Canada, the national consensus guidelines have detailed primary care as preferred site for evaluation (https://alzheimer.ca/sites/default/files/files/national/for-hcp/for_hcp_recos_cccdtd4_en.pdf). Moreover, the group recommended that both structured (e.g., use of a formal cognitive test) and unstructured (e.g., informal physician questions about memory) cognitive assessments should be utilized for testing and tracking cognitive function by PCPs (23). A 2018 clinical practices guideline from the American Academy of Neurology noted that relying on subjective cognitive complaints alone is an insufficient assessment criterion for MCI because of the significant potential for over or under-identification (27). The guideline instead recommended that physicians use a validated tool for cognitive

assessment and solicit patient history along with informant input (27). The 2015 IAGG working group also recommended utilizing both patient and informant assessments of cognitive function along with physician testing to evaluate subjects for early cognitive impairment (25). The group urged the use of validated tests that take only three to seven minutes to conduct, limiting the time burden for patients and providers. Similarly, the Gerontological Society of America workgroup recommended screening tests that take five or fewer minutes to administer, are free of charge, assess multiple cognitive domains, and are validated in a community-based sample (25). Unfortunately, despite this past guidance, specific and up-to-date recommendations grounded in currently available tools do not yet exist, potentially resulting in uncertainty among PCPs about how best to detect MCI.

In addition to considering when testing is appropriate and what battery of tests is most appropriate, previous groups have also elaborated on how an optimal care pathway may be achieved for early detection of cognitive impairment. This is a critical unmet need in the field, as the uncertainty toward the methodology of assessing for cognitive impairment is compounded by the lack of consensus on what physicians should do in the event of a positive result. Uncertainty about an assessment returns a positive result may de-motivate PCPs from broaching the topic of cognitive impairment or testing with their patients in the first place. In contrast to this PCP-directed recommendation, the 2015 Edinburgh Consensus working group noted that the UK healthcare system would be unable to accommodate the strain on PCPs and specialists if a disease-modifying therapy becomes available, noting that the current role of the PCP in controlling patient access to specialists is unclear (26). This group emphasized that restructuring cognitive healthcare to allow patients to receive care across disciplines may optimize efficiency and improve patient care (26).

Similarly, despite published insight on select aspects of an “ideal” cognitive assessment (25), it remains unclear which specific tools, particularly digital assessments, are best suited for widespread use and how new assessments could be improved to allow higher detection rates of MCI. This panel sought to provide further clarity on technologies that can improve early detection of MCI, including noting how potential modification or validation of existing tools could contribute to enhanced patient care.

Anticipated changes to the MCI landscape

The late-stage development of some compounds with a putative disease-modifying effect support optimism that a disease-modifying therapy may become available within the next 3 – 5 years (28). Among these Phase 3 agents, monoclonal antibodies targeting amyloid- β have

recently gaining momentum. Several clinical studies indicate that targeting the early phases of AD, including MCI or even preclinical populations, can increase the likelihood of clinical success (28). This recent focus on early intervention in cognitive decline underscores the value of identification of MCI before the onset of more severe cognitive decline to maximize the potential for intervention and minimize the personal, clinical, and economic costs of cognitive decline.

Approval of a novel therapy for MCI-AD is expected to dramatically increase both patient and physician involvement in cognitive screening. In the absence of proactive preparation, demand for cognitive assessment will likely present a significant strain on global healthcare systems around the world, with PCPs shouldering a significant portion of the burden. Specialists are also likely to be strained by a large volume of referrals, likely including a minority of patients with MCI-AD and a majority of individuals with MCI due to other etiologies, or even intact cognition (e.g., misdiagnosed or “worried well” individuals with an SMC). It is in the best interest of patients, physicians, and healthcare systems to implement large-scale cognitive screening and to develop and refine technological solutions that can optimize early and accurate detection of MCI and MCI-AD. Going hand in hand with improved detection will also be better patient-physician alignment on the appropriate care pathways once MCI-AD is observed. For example, prior studies evaluating the impact of cholinesterase inhibitors on cognitive symptoms in patients with mild – moderate AD suggest rivastigmine and galantamine may provide statistically significant symptomatic benefits in patients treated earlier in the disease trajectory, which were not achieved for patients in whom treatment was initiated later in the disease course (29, 31). Though clinical data to support early initiation of cholinesterase inhibitors in individuals with MCI at risk of developing AD is mixed (27, 29, 32), data from clinical trials investigating anti amyloid- β drugs have further supported the importance of early diagnosis and treatment in AD.

Conclusion

Current neuroscientific discoveries point toward a compelling need to optimize and harmonize clinical protocols for the timely and accurate detection and diagnosis of MCI-AD, also in light of late-stage clinical development of disease-modifying therapies. In subsequent manuscripts, we will outline potential methods to enhance MCI detection in individuals at risk and across clinical and non-clinical settings, focusing on cognitive, functional, and interview-based approaches. However, we acknowledge the potential for the detection of AD pathology, regardless to the clinical stage, to undergo a substantial change due to technological advances in the future, including blood-based biomarker assays to detect AD. In this case, it may become necessary

to compare the utility of various screening modalities in parallel through subsequent clinical trials.

The present working group has identified actionable methods to improve cognitive and functional assessment tools, recognizing that reassessing the optimal care pathway upon the availability of a blood-based biomarkers test with high clinical utility will be necessary for screening and diagnostic purposes. Consequently, blood-based biomarkers should be integrated into the design of studies evaluating the accuracy of cognitive and functional algorithms to detect MCI-AD. Additionally, both biomarkers and cognitive algorithms remain critical components of inclusion criteria and endpoints in clinical trials designed to evaluate MCI-AD therapies.

In this suite of publications, we hope to promote thoughtful but dramatic changes to the existing management plan for adults with MCI, inclusive of cognitive screening for the early detection of MCI. In subsequent articles, we will provide guidance for designing and validating cognitive assessment tools to enhance their real-world utility, which represents a “call to action” for our colleagues in the cognitive evaluation field.

In summary, this task force seeks to support MCI diagnosis and detection of underlying pathophysiology as a public health imperative, in parallel with other major organizations such as the World Health Organization (WHO) and the Alzheimer’s Association, in order to improve clinical outcomes for aging individuals - not just in preparation for a novel AD therapy but also in the current context of this field.

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References

1. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Lond Engl* 2017;390:1084–1150
2. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Lond Engl* 2018;392:1859–1922
3. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement J Alzheimers Assoc* 2011;7:270–279
4. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med* 2014;275:214–228
5. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease. *Alzheimers Dement J Alzheimers Assoc* 2018;14:535–562
6. Hampel H, O’Byrne SE, Molinuevo JL, et al. Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic. *Nat Rev Neurol* 2018;14:639–652
7. 2019 Alzheimer’s disease facts and figures. *Alzheimers Dement J Alzheimers Assoc* 2019;15:321–387
8. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–699
9. De Roeck EE, De Deyn PP, Dierckx E, Engelborghs S. Brief cognitive screening instruments for early detection of Alzheimer’s disease: a systematic review. *Alzheimers Res Ther* 2019;11:21
10. Borson S, Frank L, Bayley PJ, et al. Improving dementia care: The role of screening and detection of cognitive impairment. *Alzheimers Dement J Alzheimers Assoc* 2013;9:151–159
11. Morley JE. Anticholinergic medications and cognition. *J Am Med Dir Assoc* 2011;12:543–543.e1

12. Tong T, Thokala P, McMillan B, Ghosh R, Brazier J. Cost effectiveness of using cognitive screening tests for detecting dementia and mild cognitive impairment in primary care: Cost effectiveness of cognitive screening tests in primary care. *Int J Geriatr Psychiatry* 2017;32:1392–1400
13. Ton T, DeLeire T, May S, et al. Assessing the Financial Burden Associated with Mild Cognitive Impairment. 2015
14. Ton TGN, DeLeire T, May SG, et al. The financial burden and health care utilization patterns associated with amnesic mild cognitive impairment. *Alzheimers Dement J Alzheimers Assoc* 2017;13:217–224
15. Pennington M, Gomes M, Chrysanthaki T, et al. The cost of diagnosis and early support in patients with cognitive decline. *Int J Geriatr Psychiatry* 2018;33:5–13
16. Gomes M, Pennington M, Black N, Smith S. Cost-effectiveness analysis of English memory assessment services 2 years after first consultation for patients with dementia. *Int J Geriatr Psychiatry* 2019;34:439–446
17. Choe YM, Byun MS, Lee JH, Sohn BK, Lee DY, Kim JW. Subjective memory complaint as a useful tool for the early detection of Alzheimer's disease. *Neuropsychiatr Dis Treat* 2018;14:2451–2460
18. Brailean A, Steptoe A, Batty GD, Zaninotto P, Llewellyn DJ. Are subjective memory complaints indicative of objective cognitive decline or depressive symptoms? Findings from the English Longitudinal Study of Ageing. *J Psychiatr Res* 2019;110:143–151
19. Wanrooij LL van, Richard E, Jongstra S, Charante EPM van, Gool WA van. Associations of Subjective Memory Complaints and Simple Memory Task Scores With Future Dementia in the Primary Care Setting. *Ann Fam Med* 2019;17:412–418
20. Buckley RF, Maruff P, Ames D, et al. Subjective memory decline predicts greater rates of clinical progression in preclinical Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc* 2016;12:796–804
21. van Harten AC, Mielke MM, Swenson-Dravis DM, et al. Subjective cognitive decline and risk of MCI: The Mayo Clinic Study of Aging. *Neurology* 2018;91:e300–e312
22. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. *Lancet Lond Engl* 2006;367:1262–1270
23. Cordell CB, Borson S, Boustani M, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. *Alzheimers Dement* 2013;9:141–150
24. Moyer VA. Screening for Cognitive Impairment in Older Adults: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2014;160:791
25. Morley JE, Morris JC, Berg-Weger M, et al. Brain Health: The Importance of Recognizing Cognitive Impairment: An IAGG Consensus Conference. *J Am Med Dir Assoc* 2015;16:731–739
26. Ritchie CW, Russ TC, Banerjee S, et al. The Edinburgh Consensus: preparing for the advent of disease-modifying therapies for Alzheimer's disease. *Alzheimers Res Ther* 2017;9:85
27. 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;90:126–135
28. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement N Y N* 2019;5:272–293
29. Hampel H, Mesulam M-M, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain J Neurol* 2018;141:1917–1933
30. Farlow MR, Cyrus PA. Metrifonate therapy in Alzheimer's disease: a pooled analysis of four randomized, double-blind, placebo-controlled trials. *Dement Geriatr Cogn Disord* 2000;11:202–211
31. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* 2000;54:2261–2268
32. Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. *Cochrane Database Syst Rev* 2012;CD009132