Supplementary Material

A Systematic Review of Clinical Practice Guidelines for Alzheimer's Disease and Strategies for Future Advancements

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A1. INTRODUCTION

Theories of the Alzheimer's continuum have evolved recently. Management options may be changing from symptomatic care in those with mild to moderate dementia to earlier identification and disease-modifying therapies (DMTs). The late-stage clinical development and emerging DMTs call for a substantial paradigm shift in the diagnosis and management of the disease. While there exists several clinical assessment scores that can be used in primary care or specialist settings, these tests alone are not specific for Alzheimer's disease (AD) dementia or mild cognitive impairment (MCI) due to AD, as cognitive impairment may be attributed to several other causes. The biological hallmarks of AD, namely, amyloid plaques and intracellular neurofibrillary tangles, formed by accumulation of amyloid-β peptides and hyperphosphorylated-tau protein, respectively, can be detected years before the onset of cognitive impairment or dementia symptoms; therefore, the use of biomarker tests to detect amyloid and tau is a key development for the early detection of AD pathophysiology [1]. However, assessment of biomarkers via positron emission tomography (PET) imaging or detection in cerebrospinal fluid (CSF) are invasive, expensive, and time and resource consuming [2]. Positron emission tomography (PET)–based molecular imaging using specific radio ligands allows for the regional localization of pathological fibrillar amyloid and tau but is associated with a high cost and very limited global and regional accessibility of equipment. Fluid-based CSF tests [3] are more cost-effective and accessible than PET imaging and allow for the testing of multiple pathophysiological biomarkers, but do not allow brain localization, are still considered invasive procedures in many global healthcare systems, and can be accompanied by inconvenient side effects. These tests, as well as tests for blood-based biomarkers that are currently in development, are not used in the routine care for diagnosis of AD, as the validation and confidence of these methodologies need further strengthening [4]. The progressive establishment of blood-based biomarkers and the validation of

multidimensional diagnostic techniques have the potential to change the detection, diagnosis, and management of early AD.

The systematic literature review (SLR) reported in this article aims to summarize the current recommendations for clinical practice related to MCI or AD-related dementia and assess their continuing relevance given the changing paradigm of AD disease management, which is being driven by increased understanding of the biomarkers and other changes in brain structure that lead to AD dementia as well as the development of potential DMTs to slow or prevent disease progression. In this supplement, we present (1) the search strategies used to select clinical practice guidelines for those with MCI or AD-related dementia for review; (2) the screening strategies to identify clinical practice guidelines and detailed tables presenting the characteristics and recommendations for screening, diagnosis, treatment, and monitoring from the 53 identified clinical practice guidelines; (3) an overview of the recommendations for screening, diagnosis, treatment, and monitoring from the 4 most highly cited guidelines (based on Google Scholar data); and (4) an overview of the recommendations for screening, diagnosis, treatment and monitoring from guidelines published before 2018. The main article Results section presents a summary of the recommendations for screening, diagnosis, treatment, and monitoring from clinical practice guidelines published in 2018 or more recently; the Discussion section provides a brief summary of how these recommendations have changed pre-2018 and post-2018.

A2. SEARCH STRATEGIES

Table A-1. Embase Literature Search Strategy. Limits: Humans; No Comments, Letters, Editorials or Conference Abstracts: 3 March 2022

Search No.	Search Terms	No. of Articles
Disease		
#1	('dementia'/mj OR dementi*:ti OR amentia:ti,ab OR demention:ti,ab OR 'pre-dementia':ti) AND [embase]/lim	69,854
#2	('alzheimer disease'/exp/mj OR alzheimer*:ti OR alzeimer*:ti,ab OR 'cortical sclerosis':ti) AND [embase]/lim	120,762
#3	('cognitive defect'/exp/mj OR 'cognitive dysfunction*':ti OR 'cognition disorder*':ti OR 'cognitive disorder*':ti OR 'cognitive defect*':ti OR 'cognitive deficit*':ti OR 'cognitive disabilit*':ti OR 'mild cognitive impairment*':ti OR mci:ti OR 'cognitive decline*':ti OR 'mental deterioration*':ti) AND [embase]/lim	265,979
#4	#1 OR #2 OR #3	271,639
Management		
#5	('diagnosis'/exp/mj OR diagnos*:ti OR screen*:ti OR treat*:ti OR 'best clinical practice*':ti,ab OR 'disease management'/exp/mj OR manage*:ti OR 'principles of car*':ti,ab OR 'comprehensive car*':ti,ab) AND [embase]/lim	4,190,991
#6	#4 AND #5	39,607
Guidelines		
#7	('practice guideline'/mj OR guide*:ti OR guidance:ti OR 'road map':ti OR roadmap:ti OR recommend*:ti OR polic*:ti OR 'action plan*':ti OR 'task force*':ti) AND [embase]/lim	310,859
#8	#6 AND #7	744

Search No.	Search Terms	No. of Articles
Exclusions		
#9	‘animal’/exp NOT ‘human’/exp	5,743,928
#10	‘comment’:ti OR ‘letter’:it OR ‘editorial’:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim	7,073,328
Total		
#11	#8 NOT (#9 OR #10)	**573**

Table A-2. MEDLINE Literature Search Strategy. Limits: Humans; No Comments, Letters, Editorials or Conference Abstracts: 3 March 2022

Search No.	Search Terms	No. of Articles
Disease		
#1	"Dementia"[Majr:NoExp]OR dementi*[Title] OR amentia[Title/Abstract] OR demention[Title/Abstract] OR "pre-dementia"[Title]	68,399
#2	"Alzheimer Disease"[Majr] OR Alzheimer*[Title] OR alzeimer*[Title/Abstract] OR "cortical sclerosis"[Title]	100,203
#3	"Cognitive Dysfunction"[Majr] OR "Cognitive Dysfunction*"[Title] OR "cognition disorder*"[Title] OR "cognitive disorder*"[Title] OR "cognitive defect*"[Title] OR "cognitive deficit*"[Title] OR "cognitive disabilit*"[Title] OR "mild cognitive impairment*"[Title] OR MCI[Title] OR "cognitive decline*"[Title] OR "Mental Deterioration*"[Title]	38,930
#4	#1 OR #2 OR #3	183,134
Management		
#5	"Diagnosis"[Majr] OR diagnos*[Title] OR screen*[Title] OR treat*[Title] OR "best clinical practice*"[Title/Abstract] OR "Disease Management"[Majr] OR manage*[Title] OR "principles of car*"[Title/Abstract] OR "Comprehensive Car*"[Title/Abstract]	5,066,589
#6	#4 AND #5	29,115
Guidelines		
#7	"Guidelines as Topic"[Majr] OR "Practice Guidelines as Topic"[Majr] OR "Guideline"[Publication Type] OR guide*[Title] OR guidance[Title] OR "road map"[Title] OR roadmap[Title] OR recommend*[Title] OR polic*[Title] OR "action plan*"[Title] OR "task force*"[Title]	359,178
#8	#6 AND #7	535

Search No.	Search Terms	No. of Articles
Exclusions		
#9	“Animals”[Mesh] NOT “Humans”[Mesh]	4,966,357
#10	“Comment”[Publication Type] OR “Letter”[Publication Type] OR “Editorial”[Publication Type]	2,040.098
Total		
#11	#8 NOT (#9 OR #10)	**471**

A3. SCREENING AND EXTRACTION OF CLINICAL PRACTICE GUIDELINES

This section presents the screening approach used to identify clinical practice guidelines for MCI or AD-related dementia and the data extracted from the 53 MCI and national or international practices identified in the SLR of electronic databases: Embase, MEDLINE, MEDLINE In-Process, CINAHL, PsycINFO, Guideline International Network library, the INAHTA International HTA database; websites and other resources; National Institute for Health and Care Excellence; Scottish Medicine Consortium, Pharmaceutical Benefits Advisory Committee, Canadian Agency for Drugs and Technologies in Health, and Google; plus hand searches of reference lists of the most recent systematic reviews and meta-analyses identified in the review.

A3.1 Screening Method and Inclusion and Exclusion Criteria

- Practice guidelines for inclusion in the data extraction were selected after level 1 (titles and abstracts of studies) and level 2 (full texts of studies) screening. The identified guidelines were reviewed in terms of their level of influence (i.e., Google Scholar citations).
- A 2-phase screening process was independently undertaken by 2 reviewers, following a predefined protocol. In phase 1, titles and abstracts were double screened to determine whether to include or exclude them. Progressing to phase 2, two reviewers retrieved full-text articles to ascertain the inclusion or exclusion for data extraction based on the inclusion criteria, types of guidelines, and developing methods. In case of discrepancy, uncertain guidelines were reviewed by a third researcher.

Specifically, guidelines were eligible if they met all the following criteria:

- The guidelines were produced by national or international groups.

- The guidelines focused on MCI relating to AD, early AD, or AD-related dementia populations.
- The guidelines provided recommendations on at least 1 of these outcomes: screening to identify those with MCI or AD-related MCI or AD-related dementia, diagnosis of AD-related MCI or dementia using neuropsychiatric scales, elimination of other causes of MCI or dementia, testing for biomarkers or genes associated with AD, and treatment of those with a diagnosis of AD.
- The guidelines aimed to provide recommendations for clinical practice. Clinical practice guidelines should be developed in a systematic and transparent way and should reflect the strengths of recommendations and the quality of evidence [5]. In this review, the clinical practice guidelines were identified based on keyword searches in the full texts (e.g., practice guidelines) combined with developing process (e.g., systematic review, grading synthesis).

The guidelines were ineligible if they met at least 1 of the following exclusion criteria:

- The guidelines were published by regional groups.
- The guidelines produced recommendations for MCI due to other diseases or other types of dementia.
- No relevant outcomes were presented.
- The guidelines aimed to introduce recommendations for research contexts or long-term national strategies.
- The guidelines represented the consensus of an expert panel rather than national and international groups or were presented as position papers or scientific statements by the authors of the paper.

All inclusion and exclusion processes were fully documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

A3.2 Recommendations Extracted From 53 Clinical Practice Guidelines

Following identification of the clinical practice guidelines, guideline characteristics and recommendations for screening, testing and diagnosis, treatment, and monitoring of MCI and/or AD dementia were extracted from each of the 53 clinical practice guidelines identified. Extraction of the recommendations was performed by 1 researcher and quality control procedures included verification of all extracted recommendations with original sources by a researcher who did not perform the extraction. The extracted recommendations from the national or international practice guidelines are presented in this Supplement in the order of the number of Google Scholar citations (high to low number of Google Scholar citations).

A.3.3 Monitoring Recommendations from the Most Recently Published Guidelines

From the most recently published guidelines, six documents presented recommendations for monitoring MCI or AD dementia progression [6-11]. The Irish dementia guidelines recommended regular physical examination for people aged >65 years [10]. The Korean dementia guidelines suggested monitoring the clinical development of older adults with subjective memory complaints, subjective cognitive impairment, and subjective cognitive decline (SCD) by conducting periodic follow-ups every 1-2 years because those with SCD are more likely to develop dementia or AD dementia than those without SCD [9].

For MCI or dementia, frequent reviews of medications and cognitive status were recommended [8,10].

For patients with AD, NICE recommended that AChE inhibitors should not be stopped because of disease severity alone [11]. Deprescribing AChE inhibitors or memantine should be considered in some situations, with close periodic monitoring and re-initiation of medication if necessary [6,7].

A.3.4 Differences Between the Pre- and Post-2018 Clinical Practice Guideline Recommendations

The pre- and post-2018 practice guidelines share similar recommendations for screening, diagnosis and treatment. Screening is not generally recommended for the general public or asymptomatic population in both earlier and more recent guidelines. Both earlier and recent guidelines recommend screening for those at risk of AD, such as adults with intellectual disability [12], patients older than 75 years who complain of memory impairment or have a family history of memory disorders [13], and individuals suspected of cognitive impairment by a physician despite a lack of complaint [14].

Our review found both pre- and post-2018 guidelines recommend using neuropsychological testing as a complementary tool to detect AD dementia and MCI, although the more recent guidelines suggest more sensitive tests for those with MCI. However, biomarker testing was specifically not recommended in four earlier guidelines and two most recent guidelines, indicating a lack of support for its routine use. While two recent MCI guidelines considered offering biomarker testing to clarify the underlying cause of the cognitive impairment, they did not advocate its use for routine diagnosis [8,15].

The treatment guidelines for AD have remained unchanged over time. This SLR found that AChE inhibitors and memantine are still the standard care for treating AD cognitive symptoms, as recommended in the most recent guidelines [6,11,16,17], which is consistent with the pre-2018 guidelines.

The method to assess the severity of AD dementia in diagnosis or treatment was not clearly defined in both pre- and post-2018 guidelines. Different classification concepts were recommended by each guideline, such as MMSE scores, DSM (III to V) and ICD-10, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and staging instruments (e.g., Clinical Dementia Rating). The range of MMSE scores was not standardized across guidelines, and the DSM or NINCDS-ADRDA criteria were not frequently mentioned in recent guidelines.

A.3.5 Identified Published Systematic Literature Reviews

We identified two earlier systematic reviews (one that summarizes guidelines for AD diagnostic testing [18] and one for MCI screening, diagnosis, and treatment [19]) in our guidelines database searches. Unlike our SLR, the one by Chen and colleagues [19] included both guidelines and consensus statements. Arevalo-Rodriguez and colleagues [18] presented recommendations on the use of brief cognitive tests in the diagnosis of patients with suspected AD dementia. They also noted that there are limited clinical studies on biomarkers, and several guidelines identified in that review presented recommendations against their use [18]. In contrast to Arevalo-Rodriguez and colleagues' and our SLR, Chen and colleagues [19] stated that "neuropsychological testing and biomarker assessments are the most recommended tests for the diagnosis of MCI." The authors also identified biomarker assessment recommendations for the identification of prodromal AD in individuals with MCI. It should be noted that the SLR by Chen and colleagues included both English and Chinese language guidelines.

Table A-3. 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 [20]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
12299	2011	International	AD dementia	Workgroup	Unlikely	Not applicable

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	**"Probable AD dementia is diagnosed when the patient:** ▪ meets criteria for dementia, and in addition, has the following characteristics: – Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days; – Clear-cut history of worsening of cognition by report or observation; and – The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: (a) Amnestic presentation or (b) Non-amnestic presentations; ▪ in persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology ▪ in persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2), increases the certainty that the condition is caused by AD pathology. The workgroup noted that carriage of the ε4 allele of the apolipoprotein E gene was not sufficiently specific to be considered in this category." **"Possible AD dementia: Core clinical criteria:** ▪ atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline, or; ▪ etiologically mixed presentation." **"Probable AD dementia with evidence of the AD pathophysiological process:** ▪ in persons who meet the core clinical criteria for probable AD dementia, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time." **"Possible AD dementia with evidence of the AD pathophysiological process:** ▪ in the biomarker table, we indicate that both categories of biomarkers must be positive for an individual who presents clinically with a non-AD phenotype to meet criteria for possible AD" **"Considerations related to the incorporation of biomarkers into AD dementia criteria** ▪ to make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied; ▪ practical use of biomarkers must follow best-practice guidelines within laboratory-specific contexts, until standardization has been fully accomplished; ▪ a sequence of events has been described with Aβ pathophysiological processes becoming abnormal first and downstream neuronal injury biomarkers becoming abnormal later. This might imply a hierarchical ranking of Aβ biomarkers over downstream neuronal injury biomarkers for diagnostic purposes. However, at this time, the reliability of such a hierarchical scheme has not been sufficiently well established for use in AD dementia. Also, the data are insufficient to recommend a scheme that arbitrates among all different biomarker combinations."

	"Pathophysiologically proved AD dementia ▪ the diagnosis of pathophysiologically proved AD dementia would apply if the patient meets clinical and cognitive criteria for AD dementia, and the neuropathological examination, using widely accepted criteria, demonstrates the presence of the AD pathology."
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ "National Institute on Aging and the Alzheimer's Association charged a workgroup with the task of revising the 1984 criteria for AD dementia" ▪ "Conflicts of interest were presented, for example: – Guy McKhann serves on a Data Safety Monitoring Board for Merck. – David Knopman serves on a Data Safety Monitoring Board for Lilly Pharmaceuticals and is an investigator for clinical trials sponsored by Elan Pharmaceuticals, Forest Pharmaceuticals, and Baxter Healthcare – Howard Chertkow serves as a consultant to Pfizer Canada, Lundbeck Canada, Janssen Ortho, Novartis Canada, and Bristol Myers Squibb; he receives a research grant from Pfizer Canada – Richard Mohs is a full-time employee of Eli Lilly and Company and holds stock in Lilly"

AA = Alzheimer's Association; AD = Alzheimer's disease; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-4. 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 [21]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
8778	2011	International	MCI due to AD	Workgroup	Unlikely	Not applicable

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	**"MCI—Criteria for the clinical and cognitive syndrome** ▪ concern regarding a change in cognition: There should be evidence of concern about a change in cognition, in comparison with the person's previous level; ▪ impairment in one or more cognitive domains: There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background; ▪ preservation of independence in functional abilities: Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously; ▪ not demented: These cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning. It should be emphasized that the diagnosis of MCI requires evidence of intraindividual change." **"Cognitive characteristics of MCI:** ▪ cognitive assessment: impairment in episodic memory (i.e., the ability to learn and retain new information) is most commonly seen in MCI patients who subsequently progress to a diagnosis of AD dementia. Various tests are suggested for identifying those MCI who have a high likelihood of progressing to AD dementia, including the Free and Cued Selective Reminding Test, the Rey Auditory Verbal Learning Test, and the California Verbal Learning Test; ▪ Summary of clinical and cognitive evaluation; ▪ it is important to obtain longitudinal assessments of cognition, whenever possible; ▪ cautionary issues pertaining to cognitive assessment: It is important to emphasize that virtually all cognitive tests are sensitive to differences in age, education (i.e., literacy), and/or cultural variation among individuals; ▪ to meet the core clinical criteria for MCI, it is necessary to rule out other systemic or brain diseases that could account for the decline in cognition: – Consider role of autosomal genetic mutations for AD – Consider role of genes that increase risk for AD" **"Biomarkers and levels of certainty for the diagnosis of MCI due to AD** ▪ biomarkers indicating a high likelihood that the MCI syndrome is due to AD: A positive Aβ biomarker and a positive biomarker of neuronal injury; ▪ biomarkers indicating an intermediate likelihood that the MCI syndrome is due to AD: – A positive Aβ biomarker in a situation in which neuronal injury biomarkers have not been or cannot be tested; or – A positive biomarker of neuronal injury in a situation in which Aβ biomarkers have not been or cannot be tested. ▪ situations in which biomarker information is uninformative: Results fall within ambiguous ranges (neither clearly positive nor negative) or biomarkers conflict with one another. In this category are also individuals in whom biomarkers have NOT been obtained;

	▪ biomarkers that suggest that the MCI syndrome is unlikely to be due to AD: The definitive absence of evidence of either Aβ deposition or neuronal injury strongly suggests that the MCI syndrome is not due to AD. In such situations, search for biomarkers that reflect alternative pathological processes should be considered."
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ The National Institute on Aging and the Alzheimer's Association ▪ "Conflicts of interest were presented, for example: – Marilyn Albert serves as a consultant to Genentech and Eli Lilly and receives grants to her institution from GE Healthcare. – Steven DeKosky serves as a consultant to Eisai, Merck, Elan/Wyeth, Novartis, he serves on the advisory board of Pfizer and provides clinical services to United Healthcare – Bruno Dubois serves as a consultant to Affiris, Pierre Fabre, and Eisai, serving on a scientific advisory board for Bristol-Meyers Squibb, Roche, Pfizer, Eli Lilly, and GE Healthcare, and receives grants to his institution from Novartis, Roche, and Eisai"

AA = Alzheimer's Association; AD = Alzheimer's disease; MCI = mild cognitive impairment; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-5. Practice Parameter: Diagnosis of Dementia (an Evidence-Based Review). Report of the Quality Standards Subcommittee of the American Academy of Neurology [22]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
2253	2001	US	Suspected AD or suspected dementia	Panel selection + SLR + evidence evaluation	Unlikely	No

Screening	"Depression is a common, treatable comorbidity in patients with dementia and should be screened for: ▪ B12 deficiency is common in the elderly, and B12 levels should be included in routine assessments of the elderly ▪ Because of its frequency, hypothyroidism should be screened for in elderly patients ▪ Unless the patient has some specific risk factor or evidence of prior syphilitic infection, or resides in one of the few areas in the United States with high numbers of syphilis cases, screening for the disorder in patients with dementia is not justified"
Diagnosis and testing	▪ "The DSM-III-R definition of dementia is reliable and should be used routinely" ▪ "The NINCDS-ADRDA for the diagnosis of probable AD or DSM-IIIR criteria for DAT should be routinely used" ▪ "Linear or volumetric MR or CT measurement strategies for the diagnosis of AD and are not recommended for routine use at this time" ▪ "For patients with suspected dementia, SPECT cannot be recommended for routine use in either initial or differential diagnosis as it has not demonstrated superiority to clinical criteria" ▪ "PET imaging is not recommended for routine use in the diagnostic evaluation of dementia at this time" ▪ "Structural neuroimaging with either a non-contrast CT or MR scan in the routine initial evaluation of patients with dementia is appropriate" ▪ "Routine use of APOE genotyping in patients with suspected AD is not recommended at this time" ▪ "There are no other genetic markers recommended for routine use in the diagnosis of AD" ▪ "Testing for tau mutations or AD gene mutations is not recommended for routine evaluation in patients with FTD at this time" ▪ "There are no CSF or other biomarkers recommended for routine use in determining the diagnosis of AD at this time"
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ "The Quality Standards Subcommittee of the American Academy of Neurology (AAN) is charged with developing practice parameters for physicians" ▪ "This guideline has been endorsed by the American Association of Neuroscience Nurses and the American Geriatrics Society." ▪ "Conflict of interest information was not presented"

AA = Alzheimer's Association; AAN = American Academy of Neurology; AD = Alzheimer's disease; APOE = apolipoprotein E; CSF = cerebrospinal fluid; CT = computed tomography; DAT = "Dementia of the Alzheimer type"; DSM-IIIR= *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; FTD = frontotemporal dementia; MR = magnetic resonance; NIA = National Institute on Aging; NINCDS-ADRDA = National Institute of Neurologic, Communicative Disorders and Stroke–AD and Related Disorders Association; PET = positron emission tomography; SPECT= single-photon emission computerized tomography; US = United States.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-6. Practice Guideline Update Summary: Mild Cognitive Impairment Report of the Guideline Development, Dissemination, and Implementation (Subcommittee of the American Academy of Neurology) [8]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
1033	2018	US	MCI relating to AD	Panel selection+ SLR + evidence evaluation	Unclear	No

Screening	▪ "For patients for whom the patient or a close contact voices concern about memory or impaired cognition, clinicians should assess for MCI and not assume the concerns are related to normal aging (Level B)." ▪ "Clinicians should evaluate patients with MCI for modifiable risk factors, assess for functional impairment, and assess for and treat behavioral/neuropsychiatric symptoms (Level B). Cognitively impairing medications should be discontinued where possible and behavioral symptoms treated (Level B)."
Testing	▪ "Clinicians should assess for MCI with validated tools in appropriate scenarios (Level B)." "Various instruments have acceptable diagnostic accuracy for detecting MCI, with no instrument being superior to another." ▪ "For patients suspected to have MCI, clinicians who lack the necessary experience should refer these patients to a specialist with experience in cognition (level B)" for evaluation for underlying causes. ▪ "For patients diagnosed with MCI, clinicians should perform a medical evaluation for MCI risk factors that are potentially modifiable (Level B)" because MCI is associated with reversible causes of cognitive impairment, including medication side effects, sleep apnea, depression, and other medical conditions. ▪ "For interested patients, clinicians may discuss the option of biomarker research or refer patients, or both, if feasible, to centers or organizations that can connect patients to this research (e.g., ClinicalTrials.gov) (Level C)." ▪ "When performing a Medicare Annual Wellness Visit, clinicians should not rely on historical report of subjective memory concerns alone when assessing for cognitive impairment (Level B)." ▪ "For patients and families asking about biomarkers in MCI, clinicians should counsel that there are no accepted biomarkers available at this time (Level B)" because no biomarkers have been clearly shown to date to predict progression in patients with MCI. ▪ "This guideline does not review the rapidly evolving field of biomarker research in MCI; the guideline panel determined that this should be the subject of a future guideline or systematic review." ▪ "Clinicians need to distinguish between a diagnosis of MCI and one of dementia, although the boundary is not always clear."
Diagnosis	▪ "For patients who test positive for MCI, clinicians should perform a more in-depth clinical assessment for diagnosis of MCI (Level B)." ▪ "For patients suspected to have MCI, clinicians who lack the necessary experience should refer these patients to a specialist with experience in cognition (Level B)." ▪ "Clinicians should discuss diagnosis, prognosis, long-term planning, and the lack of effective medicine options (Level B)."
Monitoring	▪ "Clinicians should monitor cognitive status of patients with MCI over time (Level B)." ▪ "For patients diagnosed with MCI, clinicians should perform serial assessments over time to monitor for changes in cognitive status (Level B)."
Treatment	▪ "For patients diagnosed with MCI, clinicians should recommend regular exercise (twice/week) as part of an overall approach to management (Level B). Clinicians may recommend cognitive training (Level C)." This is because treatment with exercise training for 6 months is likely to improve cognitive measures, and cognitive interventions may be beneficial in improving measures of cognitive function.

	▪ "For patients diagnosed with MCI, clinicians should counsel the patients and families that there are no pharmacologic or dietary agents currently shown to have symptomatic cognitive benefit in MCI and that no medications are FDA-approved for this purpose (Level B)." ▪ "If clinicians choose to offer cholinesterase inhibitors, they must first discuss with patients the fact that this is an off-label prescription not currently backed by empirical evidence (Level A)."
Sponsorship/ Conflict of interest	"This practice guideline was developed with financial support from the American Academy of Neurology. Authors who serve as AAN subcommittee members, methodologists, or employees, past or present were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed." "There were several potential conflicts of interest listed, for example: ▪ R. Petersen, O. Lopez, D. Marson have served as a consultant for several pharmaceutical companies. ▪ M. Ganguli has served on advisory committee for Biogen ▪ G. Day holds stock in ANI pharmaceuticals"

AA = Alzheimer's Association; AAN = American Academy of Neurology; FDA = US Food and Drug Administration; MCI = mild cognitive impairment; NIA = National Institute on Aging; US = United States.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-7. Current Pharmacologic Treatment of Dementia: A Clinical Practice Guideline from the American College of Physicians and the American Academy of Family Physicians [23]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
458	2008	US	patients with dementia (specific for AD)	SLR-based	Likely	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ N/A					
Treatment	▪ "Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment. (Grade: weak recommendation, moderate-quality evidence.)" ▪ "Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia. (Grade: weak recommendation, low-quality evidence.)" ▪ "There is an urgent need for further research on the clinical effectiveness of pharmacologic management of dementia."					
Sponsorship/ Conflict of interest	▪ "This guideline was developed by the American College of Physicians and American Academy of Family Physicians" ▪ "Financial support for the development of this guideline comes exclusively from the American College of Physicians' and American Academy of Family Physicians' operating budgets." ▪ "Conflicts of interest: – Honoraria: P. Santaguida (American College of Physicians). – Grants received: V. Snow (Centers for Disease Control and Prevention, Novo Nordisk, Bristol-Myers Squibb, Robert Wood Johnson Foundation, Boehringer-Ingelheim, Endo Pharmaceuticals)"					

AA = Alzheimer's Association; N/A = not applicable; NIA = National Institute on Aging; US = United States.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-8. American Psychiatric Association Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. Second Edition [24]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
391	2007	US	Patients with AD	APA Guideline Development Process (literature review + evidence tables + workgroup)	No	No

Screening	▪ N/A
Testing	▪ "Neuropsychological testing may help to characterize the extent of cognitive impairment, to distinguish among the types of dementias, and to establish baseline cognitive function. It is particularly useful in the evaluation of individuals who present with mild cognitive impairment" ▪ "Biomarker techniques remain investigational, and there is insufficient evidence for their utility in routine clinical practice" ▪ "Testing for apolipoprotein E4 (APOE4) is not recommended for use in diagnosis" ▪ "Three genes associated with the disease have been identified in families with apparent autosomal dominant inheritance of early onset Alzheimer's disease; which are APP, PSEN1, PSEN2" ▪ "Genetic testing is best done in conjunction with experts familiar with Alzheimer's disease genetics, as test results require careful interpretation" ▪ "Genetic counseling and sometimes genetic testing may also be appropriate for some patients with other dementias and a family history of similar syndromes"
Diagnosis	▪ "The diagnosis of Alzheimer's disease should be made only when the patient exhibits the typical symptom profile of Alzheimer's disease and when other etiologies for the dementia have been ruled out by careful history, physical and neurological examinations, and clinical and laboratory tests" ▪ "Specific functional staging (FAST staging) has also been developed, is widely used, and can be very useful in tracking the course of Alzheimer's disease" ▪ "The Clinical Dementia Rating is a commonly used scale to stage dementia severity" ▪ "In DSM-IV-TR, Alzheimer's disease is subdivided into the subtypes 'With Early Onset' and 'With Late Onset,' as well as 'With and Without Behavioral Disturbance'." ▪ "Should determine if any treatable psychiatric or general medical conditions (e.g., major depression, thyroid disease, vitamin B12 deficiency, hydrocephalus, structural brain lesion) might be causing or exacerbating the dementia" ▪ "Functional neuroimaging using brain positron emission tomography (PET) scans may contribute to diagnostic specificity in certain instances and has been recently approved by Medicare for the indication of differentiating between Alzheimer's disease and frontotemporal dementia"
Monitoring	▪ "Ongoing assessment includes periodic monitoring of the development and evolution of cognitive and noncognitive psychiatric symptoms and their response to intervention [I]" ▪ "In order to offer prompt treatment, enhance safety, and provide timely advice to the patient and family, it is generally necessary to see patients in routine follow-up at least every 3-6 months [II]" ▪ "More frequent visits (e.g., up to once or twice a week) or even psychiatric hospitalization may be required for patients with acute, complex, or potentially dangerous symptoms or for the administration of specific therapies [I]"
Treatment	▪ "The treatment of patients with dementia should be based on a thorough psychiatric, neurological, and general medical evaluation of the nature and cause of the cognitive deficits and associated noncognitive symptoms, in the context of a solid alliance with the patient and family [I]"

	▪ "Three ChEIs—donepezil, rivastigmine, and galantamine—should be offered to patients with mild to moderate AD after a thorough discussion of their potential risks and benefits [I], and they may be helpful for patients with severe AD [II]." ▪ "The constructs of mild cognitive impairment and vascular dementia are evolving and have ambiguous boundaries with AD. The efficacy and safety of ChEIs for patients with these disorders are uncertain; therefore, no specific recommendation can be made at this time, although individual patients may benefit from these agents [II]." ▪ "Memantine may be considered in patients with moderate and severe AD (I) There is some evidence of its benefit in mild AD [III]" ▪ "Vitamin E (α-tocopherol) is no longer recommended for the treatment of cognitive symptoms of dementia because of limited evidence for its efficacy as well as safety concerns [II]." ▪ "NSAIDs, statin medications, and estrogen supplementation (with conjugated equine estrogens) have shown a lack of efficacy and safety in placebo-controlled trials in patients with AD and therefore are not recommended [I]" ▪ "Treatments of depression, psychosis and agitation, and sleep disturbances were discussed and recommended in the guideline"
Sponsorship/ Conflict of interest	▪ "The development of the APA Practice Guidelines is not financially supported by any commercial organization." ▪ "Conflicts of interest were presented, but the Executive Committee on Practice Guidelines has reviewed this guideline and found no evidence of influence from relationships between authors and other stakeholders."

AA = Alzheimer's Association; AD = Alzheimer's disease; APA = American Psychiatric Association; ChEI = cholinesterase inhibitor; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; NIA = National Institute on Aging; NSAID = nonsteroidal anti-inflammatory agent; US = United States.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-9. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines [25]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
375	2019	International	Adults with MCI	Panel selection+ SLR + evidence evaluation	No	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ N/A					
Treatment	▪ N/A					
Risk management	▪ "Physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline (QoE: Moderate, SoR: strong)" ▪ "Physical activity may be recommended to adults with MCI to reduce the risk of cognitive decline (QoE: Low, SoR: conditional)" ▪ "Interventions for tobacco cessation should be offered to adults who use tobacco since they may reduce the risk of cognitive decline and dementia in addition to other health benefits (QoE: Low, SoR: strong)" ▪ "The Mediterranean-like diet may be recommended to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia (QoE: moderate, Strength: conditional)" ▪ "A healthy, balanced diet should be recommended to all adults based on WHO recommendations on healthy diet (QoE: low to high, SoR: strong)" ▪ "Vitamins B and E, polyunsaturated fatty acids and multi-complex supplementation should not be recommended to reduce the risk of cognitive decline and/or dementia (QoE: moderate, SoR: strong)" ▪ "Interventions aimed at reducing or ceasing hazardous and harmful drinking should be offered to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia in addition to other health benefits. (QoE: moderate, SoR: conditional)" ▪ "Cognitive training may be offered to older adults with normal cognition and with mild cognitive impairment to reduce the risk of cognitive decline and/or dementia (QoE: very low to low, SoR: conditional)"					
Sponsorship / Conflict of interest	▪ "Funds received from Public Health England, United Kingdom; Centers for Disease Control and Prevention, United States of America; and the WHO Core Voluntary Contributions Account were used for the development of these guidelines."					

AA = Alzheimer's Association; MCI = mild cognitive impairment; N/A = not applicable; NIA = National Institute on Aging; QoE = Quality of Evidence; SoR = Strength of Recommendation; WHO = World Health Organization.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-10. Genetic Counseling and Testing for Alzheimer Disease: Joint Practice Guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors [26]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
346	2011	US	Suspected AD or patients with AD	NSGC and ACMG workgroup	Not discussed	No

Screening	▪ N/A
Testing	▪ "Pediatric testing for AD should not occur. Prenatal testing for AD is not advised if the patient intends to continue a pregnancy with a mutation" ▪ "Genetic testing for AD should only occur in the context of genetic counseling (in-person or through videoconference) and support by someone with expertise in this area." ▪ "DTC APOE testing is not advised" **"For families in which autosomal dominant AD gene mutation is a possibility:** Testing for genes associated with early-onset autosomal dominant AD should be offered in the following situations: ▪ a symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption); ▪ autosomal dominant family history of dementia with one or more cases of EOAD; ▪ a relative with a mutation consistent with EOAD (currently PSEN1/2 or APP)" **"For families in which autosomal dominant AD is unlikely:** ▪ genetic testing for susceptibility loci (e.g., APOE) is not clinically recommended due to limited clinical utility and poor predictive value; ▪ if a patient wishes to pursue testing despite genetic counseling and recommendations to the contrary, testing may be considered at the clinician's discretion. Testing performed should follow the HD genetic testing guidelines, with emphasis on genetic counseling with a qualified clinician. As such, DTC genetic testing is not advised."
Diagnosis	▪ "A ≥3-generation family history should be obtained, with specific attention to the age of onset of any neurologic and/or psychiatric symptoms, type of dementia and method of diagnosis, current ages, or ages at death (especially unaffected relatives), and causes of death." ▪ "Medical records should be used to confirm AD diagnosis when feasible. The history of additional relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia" ▪ "A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD or LOAD and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance." ▪ "Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression." ▪ "The potential genetic contributions to AD should be reviewed."
Monitoring	▪ N/A
Treatment	▪ N/A
	"The practice guidelines of the National Society of Genetic Counselors (NSGC) and the American College of Medical Genetics (ACMG) are developed by members of the NSGC and ACMG" "Conflict of interest was not reported"

AA = Alzheimer's Association; ACMG = American College of Medical Genetics; AD = Alzheimer's disease; APOE = apolipoprotein E; APP = amyloid beta A4 protein; DTC = direct to customer; EOAD = early onset AD; HD = Huntington disease; LOAD = Late onset AD; PSEN1/2 = presenilin 1/2; N/A = not applicable; NIA = National Institute on Aging; NSGC = National Society of Genetic Counselors; US = United States.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-11. Diagnosis and Treatment of Dementia: 2 Diagnosis [27]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
299	2008	Canada	Suspected AD or suspected dementia	SLR-based (grading evidence)	Unclear	No

Screening	▪ N/A
Testing	▪ "A range of brief cognitive tests, including the Montréal Cognitive Assessment, the DemTect, the 7-Minute Screen, the General Practitioner Assessment of Cognition and the Behavioural Neurology Assessment Short Form, may be more accurate than the Mini-Mental State Examination in discriminating between dementia and the normal state. There is insufficient evidence to recommend one test over the others (grade B, level 2; new recommendation)." ▪ "Brief cognitive tests have not been developed to differentiate between dementia subtypes and should not be used for this purpose (grade D, level 2; new recommendation)." ▪ "For all patients who have a clinical presentation consistent with Alzheimer disease with typical cognitive symptoms or presentation, only a basic set of laboratory tests should be ordered to rule out causes of chronic metabolic encephalopathy producing chronic confusion and memory loss (grade B, level 3; recommendation unchanged)" ▪ "Genetic testing, including screening for the apolipoprotein E gene, is not recommended for the purpose of diagnosing Alzheimer disease because the positive and negative predictive values are low (grade E, level 2; new recommendation)" ▪ "Cranial computed tomography scanning is recommended if one or more of the criteria shown in box 1 (in the guideline) are present (grade B, level 3; recommendation unchanged)" ▪ "There is fair evidence to support the use of structural neuroimaging with computed tomography or magnetic resonance imaging to rule in concomitant cerebrovascular disease that can affect patient management (grade B, level 2; new recommendation)." "The diagnosis and differential diagnosis of dementia is currently a clinically integrative one. Neuropsychological testing alone cannot be used for this purpose and should be used selectively in clinical settings (grade B, level 2; new recommendation)." "Neuropsychological testing may aid in: ▪ addressing the distinction between normal aging, mild cognitive impairment or cognitive impairment without dementia, and early dementia (grade B, level 2; new recommendation); ▪ addressing the risk of progression from mild cognitive impairment or cognitive impairment without dementia to dementia or Alzheimer disease (grade B, level 2; new recommendation); and ▪ determining the differential diagnosis of dementia and other syndromes of cognitive impairment (grade B, level 2; new recommendation)."
Diagnosis	▪ "The diagnosis of dementia remains clinical. There is good evidence to retain the diagnostic criteria currently in use (grade A, level 2; new recommendation)." ▪ "The sensitivity of clinical diagnosis for possible or probable Alzheimer disease based on the NINCDS–ADRDA criteria remains high. The specificity is lower. The continued use of the NINCDS–ADRDA criteria is recommended (grade A, level 1; new recommendation). ▪ "Mild" AD can be diagnosed with a high degree of specificity, when the presenting clinical picture is one of memory impairment (grade B, level 1; new recommendation)."
Monitoring	▪ N/A
Treatment	▪ N/A

Sponsorship / Conflict of interest	▪ "Conflicts of interest were presented: – Alain Robillard has been a member of the speaker's board, has served as a consultant to or has given lectures sponsored by Janssen-Ortho, Novartis, Pfizer and Lundbeck; he has received travel assistance to attend scientific meetings by Novartis, Pfizer and Janssen-Ortho; and he is the principal investigator for a number of clinical trials sponsored by the previously named companies – Tiffany Chow has served as a consultant to Janssen-Ortho and has received speaker fees or educational grants from Novartis and Lundbeck – Hyman Schipper has served as a consultant to Osta Biotechnologies, Teva Neurosciences and Caprion Pharmaceuticals; he holds equity in Molecular Biometrics and stock options in Osta Biotechnologies – Andrew Kertesz has served as a consultant and has received honoraria, speaker fees and travel assistance from Pfizer, Janssen-Ortho, Novartis and Lundbeck."

AA = Alzheimer's Association; AD = Alzheimer's disease; N/A = not applicable; NIA = National Institute on Aging; NINCDS–ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-12. Guidelines for Managing Alzheimer's Disease: Part I. Assessment...Part I of a Two-Part Article [28]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
197	2002	US	Patients with AD	Workgroup	No	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ "Discuss the diagnosis and progression of Alzheimer's disease with the patient and family in a manner consistent with their values and preferences, as well as the patient's abilities."					
Monitoring	▪ "Conduct and document assessments of the following: daily function, including feeding, bathing, dressing, mobility, toileting, continence, and ability to manage finances and medications; cognitive status, using a reliable and valid instrument such as the Mini-Mental State Examination; other medical conditions; behavioral problems, psychotic symptoms, and depression." ▪ "Reassess the patient every 6 months or more frequently if indicated." ▪ "Identify the primary caregiver and assess the adequacy of family and other support systems." ▪ "Assess the culture, values, primary language, and decision-making process of the patient and family."					
Treatment	▪ "Develop and implement an ongoing treatment plan, with defined goals that include the following: use of cholinesterase inhibitors, if clinically indicated, to treat cognitive decline; referral for appropriate structured activities such as exercise, recreation, and adult day care; appropriate treatment of comorbid medical conditions" ▪ "Treat behavioral problems and mood disorders using the following: nonpharmacologic approaches such as environmental modification, task simplification, and appropriate activities; referral to social service agencies or support organizations, including the Alzheimer's Association Safe Return Program for people who wander; medications, if clinically indicated"					
Sponsorship / Conflict of interest	"The authors indicate that they do not have any conflicts of interest ▪ Dr. Cummings has served as a consultant and conducted research for AstraZeneca L.P., Bayer Corporation, Janssen Pharmaceutica Products, L.P., Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Parke-Davis, and Pfizer Inc. ▪ Dr. Frank has served as a consultant for Novartis Pharmaceuticals. The work was supported in part by California's Department of Health Services and by grant from the Federal Health Resources and Services Administration's Bureau of Primary Health Care and Administration on Aging, and the Los Angeles chapter of the Alzheimer's Association."					

AA = Alzheimer's Association; AD = Alzheimer's disease; N/A = not applicable; NIA = National Institute on Aging; US = United States.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-13. Guidelines for Managing Alzheimer's Disease: Part II. Treatment [29]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
193	2002	US	Patients with AD	Workgroup	No	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ "Beneficial response to a ChEIs (i.e., stabilization or delayed deterioration of cognitive or behavioral problems) can be determined from the physician's global assessment of the patient, the primary caregiver's report, a neuropsychologic assessment or mental status questionnaire, or evidence of behavioral or functional changes." ▪ "Brief mental status tests are relatively insensitive measures of the cognitive effects of ChEIs. Observation for 6 to 12 months is usually necessary to assess potential benefit." ▪ "ChEIs should be discontinued if side effects develop and do not resolve, adherence is poor, or deterioration continues at the pretreatment rate after 6 to 12 months of treatment. Patients who do not respond to one ChEI may respond to another."					
Treatment	▪ "Donepezil, rivastigmine, and galantamine are ChEIs that have been labeled for the treatment of Alzheimer's disease (AD)." ▪ "Tacrine is no longer considered first-line treatment for AD." ▪ "Current expert consensus recommends the use of vitamin E." ▪ "Insufficient evidence is currently available to recommend treatment with NSAIDs or nutraceutical products such as Ginkgo biloba in patients with AD." ▪ "Substantial evidence has shown that estrogens do not benefit cognitive function after the onset of AD." ▪ "Suggested nonpharmacologic interventions for use in patients with AD are presented in the guideline."					
Sponsorship/ Conflict of interest	▪ The authors indicated that they do not have any conflicts of interest.					

AA = Alzheimer's Association; AD = Alzheimer's disease; ChEI = cholinesterase inhibitor; N/A = not applicable; NIA = National Institute on Aging; NSAID = nonsteroidal anti-inflammatory drug; US = United States.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-14. Update on Appropriate Use Criteria for Amyloid PET Imaging: Dementia Experts, Mild Cognitive Impairment, and Education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging [30]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
167	2013	International	Patients with MCI, uncertain dementia/AD	Workgroup	No	No

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	▪ "The number of dementia experts would increase to serve the demand for amyloid PET referral if indeed amyloid PET can enable more effective management. ▪ "Any initial constraint on amyloid PET due to the limited availability of the dementia expert will gradually resolve and that requiring a dementia expert to order the scan is justified now to maximize the potential that it will be used only under appropriate circumstances." ▪ "Dementia expert and PET physician would be required to document checklist information, including age and date of onset of symptoms, in the medical record of each patient." ▪ "Amyloid PET is indicated only for those who, according to the dementia expert, carry a diagnosis of MCI that conforms to established consensus criteria (indication 1 in the AUC document)." ▪ "The scope of use of amyloid PET would be substantially limited by 2 prerequisites imposed by the AUC, the requirement for etiologic uncertainty and the requirement for a change in patient management." ▪ "Amyloid PET could be appropriately used "when knowledge of the presence or absence of [amyloid-ß] pathology is expected to increase diagnostic certainty and alter management" ▪ "Develop educational programs to increase awareness of the amyloid PET appropriate use criteria and providing instructions on how this test should be used in the clinical decision-making process."
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship/ Conflict of interest	No potential conflict of interest relevant to this article was reported

AA = Alzheimer's Association; AUC = appropriate use criteria; MCI = mild cognitive impairment; N/A = not applicable; NIA = National Institute on Aging; PET = positron emission tomography.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-15. Treatment of Alzheimer Disease [31]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
140	2011	US	Patients with AD	Literature review	No	Yes
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ N/A					
Treatment	▪ "Acetylcholinesterase inhibitors are modestly effective in patients with mild to moderate Alzheimer disease, although limited by their adverse effects (Evidence rating A)" ▪ "Combination therapy with an acetylcholinesterase inhibitor and memantine (Namenda) should be considered in patients with moderate to severe Alzheimer disease (Evidence rating B)." ▪ "Atypical antipsychotic agents can improve some behavioral manifestations of Alzheimer disease but are associated with increased mortality in older patients (Evidence rating B)." ▪ "Nonsteroidal anti-inflammatory drugs, vitamin E, testosterone, estrogen, statins, and insulin sensitizers are not recommended for the treatment of Alzheimer disease (Evidence rating B)." ▪ "Physicians should consider discontinuing treatment for Alzheimer disease in patients who continue to decline despite maximal therapy (Evidence rating C)."					
Sponsorship / Conflict of interests	No relevant financial affiliations to disclose					

AA = Alzheimer's Association; N/A = not applicable; NIA = National Institute on Aging; US = United States.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-16. SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain 1.0 [32]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
128	2016	International	Patients with MCI, probable AD, possible AD	SNMMI/EANM workgroup	Not discussed	No

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	"The use of amyloid PET is considered appropriate when any of the following is true: ▪ the patient has persistent or progressive unexplained MCI; ▪ the core clinical criteria for possible AD are satisfied but there is an unclear clinical presentation—either an atypical clinical course or an etiologically mixed presentation; ▪ The patient has progressive dementia, and the age of onset was atypically early (usually defined as ≤ 65 years old). The use of amyloid PET is considered inappropriate when any of the following is true: ▪ the patient meets the core clinical criteria for probable AD and had a typical age of onset, there is a need to determine the severity of dementia; ▪ the patient is asymptomatic and either has a family history of AD or has been shown to carry the e4 allele of apolipoprotein E; ▪ the patient has a cognitive complaint that has not been confirmed on clinical examination; ▪ a test in lieu of genotyping is needed for a patient who is a suspected autosomal dominant mutation carrier; ▪ The patient is asymptomatic, or the imaging is to be performed for nonmedical reasons (e.g., legal, insurance coverage, or employment screening)." "The above appropriate-use criteria have not been validated for patient outcome or for use of possible future anti-Aβ therapies, and further health services research is necessary to determine effective clinical use of amyloid PET."
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ A joint committee of The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and The European Association of Nuclear Medicine (EANM) ▪ Conflict of interest was not reported

AA = Alzheimer's Association; AD = Alzheimer's disease; anti-Aβ = a pathologic hallmark of Alzheimer disease; EANM = European Association of Nuclear Medicine; MCI = mild cognitive impairment; N/A = not applicable; NIA = National Institute on Aging; PET= Positron emission tomography; SNMMI = Society of Nuclear Medicine and Molecular Imaging.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-17. Practice Guidelines for the Clinical Assessment and Care Management of Alzheimer's Disease and Other Dementias Among Adults With Intellectual Disability [12]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
106	1996	International	people with intellectual disability who are at risk of AD, or with AD	Workgroup	Unlikely	No
Screening	▪ "Step 1: Understanding changes in normal ageing, being aware of risk factors and recognizing changes indicating the onset of dementia Adults with intellectual disability who are at risk of Alzheimer's disease include those over 50 years of age, those with Down's syndrome over 40 years of age, or those who are from families with a history of AD."					
Testing	▪ N/A					
Diagnosis	▪ "To make a distinction between possible and probable diagnosis of AD, it is necessary to observe a well-documented progression of symptoms substantiated by appropriate clinical test results."					
Monitoring	"Frequent review of all medications is necessary, with the goal of using the fewest number and lowest possible doses of effective medications." "Early signs and symptoms of Alzheimer's dementia do not mean that a change of familiar program or residence is necessary or even desirable."					
Treatment	▪ N/A					
Sponsorship / Conflict of interest	▪ "The Alzheimer disease and intellectual disability project (colloquium and reports) was funded by conference support grants from the National Institutes of Aging and Child Health and Human Development and the National Institute for Disability and Rehabilitation Research." ▪ "Additional support was also provided by the New York State Office of Mental Retardation and Developmental Disabilities, the New York State Institute for Basic Research in Developmental Disabilities, the Waisman Center at the University of Wisconsin-Madison, and the Rehabilitation Research and Training Center on Aging with Mental Retardation at the University of Illinois in Chicago" ▪ "Conflicts of interest were not presented"					

AA = Alzheimer's Association; AD = Alzheimer's disease; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-18. Clinical Practice Guidelines for Dementia in Australia [33]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
105	2016	Australia	Patients with dementia, patients with AD	Adapted from existing guidelines using ADAPTE methodology	No	No

Screening	▪ Clinical cognitive assessment should include examination with a screening tool with established reliability and validity ▪ The committee recommended review of people with MCI after 6-18 months
Testing	▪ A number of tools are recommended in the guidelines including the MMSE. The KICA tool for remote areas. ▪ People with dementia who develop behavioral and psychological symptoms should be offered a comprehensive assessment at an early opportunity by a professional skilled in symptom assessment and management ▪ The guidelines recommend the need to understand the person and symptoms via a comprehensive assessment and analysis of the behavior, behavior description and consequence (ABC approach)
Diagnosis	▪ "The guidelines recommend a systematic approach to diagnosing dementia; this includes patient and informant history taking, cognitive assessment, medication review, blood tests and computed tomography or magnetic resonance imaging to exclude other cerebral pathologies." ▪ "The use of single-photon emission computed tomography is not recommended." ▪ "More recent diagnostic techniques using biomarkers (including the use of positron emission tomography) are not recommended for routine use" ▪ "People with a possible diagnosis of dementia should be offered referral to memory assessment specialists or services for a comprehensive assessment" ▪ "The medical practitioner should be honest and respectful and use a gradual and individualized approach when communicating the diagnosis to the person with dementia and their carer(s) and family"
Monitoring	N/A
Treatment	▪ "Acetylcholinesterase inhibitors (AChE-Is) and memantine are routinely prescribed for people with mild to moderate Alzheimer's disease (AD) in order to delay functional decline, and the guidelines support their use." ▪ "The combination of an AChE-Is and memantine could be considered for managing the symptoms of functional decline for people with moderate to severe AD" ▪ "AChE-Is should not be prescribed for people with MCI" ▪ "People with AD, vascular dementia or mixed dementias with mild-to-moderate behavioral and psychological symptoms of dementia should not usually be prescribed antipsychotic medications because of the increased risk of cerebrovascular adverse events and death" ▪ "A number of pharmacological treatments are recommended to complement non-pharmacological approaches when the person with dementia is severely distressed or there is an immediate risk of harm"
Sponsorship/ Conflict of interest	"The National Health and Medical Research Council (NHMRC) Partnership Centre for Dealing with Cognitive and Related Functional Decline in Older People was established in 2013 with funding support from the NHMRC, HammondCare, Alzheimer's Australia, Brightwater Care Group and Helping Hand Aged Care. " "No relevant disclosures for competing interests."

AA = Alzheimer's Association; ABC = Antecedent-Behavior-Consequence; AChE-Is = acetylcholinesterase inhibitors; AD = Alzheimer's disease; ADAPTE = ADAPTE Collaboration; KICA = Kimberley Indigenous Cognitive Assessment; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; N/A = not applicable; NHMRC = National Health and Medical Research Council; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-19. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Alzheimer's Disease and Other Dementias [34]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
88	2011	International	Patients with dementia (including AD)	Literature review	No	No

Screening	N/A
Diagnosis and testing	▪ AD differential diagnosis excludes Creutzfeldt-Jakob disease, vascular dementia, Lewy body dementia in part due to increased tau and phosphotau, and decreased A β in the CSF ▪ Additional tests such as EEG, structural MRI/CT, and PET scans are listed
Monitoring	N/A
Treatment	▪ For the symptomatic treatment of AD, donepezil, galantamine, memantine, ginkgo biloba extract, rivastigmine show a modest, over a limited time, effect in a part of the patients (Level B). For symptomatic treatment of AD, these pharmaceuticals can be recommended (Grade 3) ▪ Memantine alone had inclusive evidence. Concomitant medication study groups differed. Memantine in AD compared with placebo showed superiority (Level D) ▪ Methodological inadequateness prohibits a systematic recommendation of pharmaceuticals related to specific severity levels (Level F) ▪ Methodological limitations of studies in the prevention of so called "MCI" do not allow conclusion on preventive effects. Thus, antidementia pharmaceuticals cannot be recommended in MCI. ▪ The treatment should start after diagnosis with clearly defined treatment goals (Level C3, Grade 4) ▪ End of treatment should depend on an individual decision (Level C3, Grade 4) ▪ Discontinue if there are significant adverse effects or after consensus with patients and relatives/caregivers/legal representatives (Level C3, Grade 4)
Sponsorship/ Conflict of interest	▪ The preparation of these guidelines has not been financially supported by any commercial organization ▪ These guidelines were developed by an international Task force of the World Federation of Societies of Biological Psychiatry (WFSBP) ▪ "Conflicts of interest were presented, for example: – Prof. Dr. Ralf Ihl received grants/research support or was involved as consultant, speaker or in advisory boards or received authors honoraria within the last three years from APK, Austroplant, BDI, Beltz Test, BOD, Caritas Siegen, Double Helix Development, Eisai, Friedrichverlag, GE Healthcare, Hogrefe, IFE, Janssen, KDA, Landesinitiative Demenz Service NRW, LVR Düren, Lundbeck, Medical Tribune, Med. Komm., Novartis, Pfizer, Pfrimmer Nutritia, Pierrel, Schwabe, Thieme, Urban & Vogel, Westermayer. – Prof. Dr. Moeller has received grants or is a consultant for and on the speakership bureaus of Astra-Zeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth."

AA = Alzheimer's Association; AD = Alzheimer's disease; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; N/A = not applicable; NIA = National Institute on Aging; PET = positron emission tomography.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-20. Clinical Practice Guidelines for Severe Alzheimer's Disease [35]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
86	2007	Canada	Patients with severe AD	Literature review (following rules of evidence developed by the Canadian Task Force)	Unlikely	No

Screening	N/A
Testing	N/A
Diagnosis	▪ "Severe AD can be defined as the stage in which the patient becomes totally dependent on a caregiver for survival. This will typically correspond to MMSE < 10 and GDS 6 to 7 (Grade B, Level 2)." ▪ "Assessment should include cognition (e.g., MMSE), function, behavior, medical status, nutrition, safety, and caregiver health (Grade B, Level 3)."
Monitoring	▪ "Patients with severe AD should be assessed at least every 4 months or if treated with pharmacotherapy at least every 3 months (Grade C, Level 3)."
Treatment	▪ "The goals for management are to improve the quality of life for patient and caregivers maintain optimal function and provide maximum comfort (Grade B, Level 3)." ▪ "Medical management includes treatment of intercurrent medical conditions (e.g., infections, parkinsonian symptoms, seizures, pressure ulcers) ameliorating pain improving nutritional status and optimizing sensory function (Grade B, Level 3)." ▪ "Patients with severe AD can be treated with ChEIs, memantine, or the combination. Expected benefits would include modest improvements or slower decline in cognition, function, and behavior (Grade A, Level 1)." ▪ "Treatment with ChEIs and/or memantine should persist until clinical benefit can no longer be demonstrated. Treatment should not be discontinued simply because of institutionalization (Grade C, Level 3)." ▪ "The management of BPSD should begin with appropriate assessments, diagnosis, and identification of target symptoms and consideration of safety of the patient, their caregiver, and others in their environment (Grade B, Level 3)." ▪ "Nonpharmacologic treatments should be initiated first. Approaches that might be useful for severe AD include behavioral management for depression and caregivers/staff education programs for a variety of behaviors. Music and multi-sensory intervention (Snoezelen) are useful during treatment sessions, but longer-term benefits have not been demonstrated (Grade B, Level 1)." ▪ "Pharmacologic interventions should be initiated concurrently with nonpharmacologic approaches in the presence of severe depression, psychosis, or aggression that puts the patient or others at risk of harm (Grade B, Level 3)." ▪ "Pharmacologic interventions for BPSD should be initiated at the lowest doses, titrated slowly, and monitored for effectiveness and safety (Grade B, Level 3)." ▪ "Attempts to taper and withdraw medications for BPSD after a period of 3 months of behavioral stability should occur in a standardized fashion (Grade A, Level 1)." ▪ "Risperidone and olanzapine can be used for severe agitation, aggression, and psychosis. The potential benefit of all antipsychotics must be weighed against the potential risks such as cerebrovascular adverse events and mortality (Grade A, Level 1)." ▪ "There is insufficient evidence to recommend for or against the use of trazodone in the management of nonpsychotic agitated patients (Grade C, Level 3)." ▪ "Benzodiazepines should be used only for short periods as prn agents (Grade B, Level 1)."

	▪ "Selective serotonin reuptake inhibitors can be used for the treatment of severe depression (Grade B, Level 3)." ▪ "If BPSD fails to improve after appropriate nonpharmacologic and pharmacologic interventions refer to a specialty service (Grade B, Level 3)."
Sponsorship / Conflict of interest	▪ "Conflicts of interest: Nathan Herrmann has received research support, honoraria, and/or consultant fees from Lundbeck, Janssen Ortho Inc, Pfizer, Novartis, and Eli Lilly. Serge Gauthier has been an investigator and/or consultant for Lundbeck, Pfizer, and Merz."

AA = Alzheimer's Association; AD = Alzheimer's disease; BPSD = behavioral and psychological symptoms of dementia; ChEI = cholinesterase inhibitor; GDS = Global Deterioration Scale; MMSE = Mini-Mental State Examination; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-21. Dementia: the NICE–SCIE Guideline on Supporting People With Dementia and Their Carers in Health and Social Care [36]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
78	2007	UK	Patients with MCI, dementia (including AD)	Workgroup	Unlikely	No

Screening	▪ "General population screening for dementia should not be undertaken."
Testing	▪ "Primary healthcare staff should consider referring people who show signs of MCI for assessment by memory assessment services to aid early identification of dementia, because more than 50% of people with MCI later develop dementia." ▪ "Memory assessment services that identify people with MCI (including those without memory impairment, which may be absent in the earlier stages of non-Alzheimer's dementias) should offer follow-up to monitor cognitive decline and other signs of possible dementia in order to plan care at an early stage." ▪ "Imaging techniques can identify early brain changes, both structural and metabolic, but no single technique if used as a screening test can accurately identify individuals with MCI who will subsequently develop AD or other dementias." ▪ "The means of identification of the early changes of dementia syndromes are developing more rapidly than the therapeutic options and so the usefulness of such very early pre-clinical diagnosis currently remains uncertain."
Diagnosis	▪ "Standardized and widely accepted criteria exist for the diagnosis of subtypes of dementia including AD, VaD, DLB and FTD" ▪ "A standardized cognitive assessment tool is a useful adjunct to cognitive testing." ▪ "CT scanning can detect most gross intracerebral pathology, but MRI has superior sensitivity and is preferred where available." ▪ "Neuropsychological assessment can be helpful, especially in early cases, to help determine whether dementia is present or not." ▪ "Blood-flow SPECT or FDG PET can detect functional changes in AD and be useful in differentiating AD, FTD and VaD." ▪ "Dopaminergic SPECT or PET can detect nigrostriatal degeneration in vivo and can differentiate DLB and Parkinson's disease from AD and VaD." ▪ "CSF examination shows changes in AD, including increased levels of tau and phosphorylated tau and reduced levels of Abeta 1-42, though the role of these measurements in diagnosis and monitoring of AD and other dementias remains to be determined." ▪ "The resting EEG shows non-specific abnormalities in most types of dementia." ▪ "Brain biopsy may be considered appropriate in highly selected cases and can contribute in a minority of cases to accurate diagnosis that alters management."
Monitoring	▪ "Patients who continue on the drug (AChE inhibitors) should be reviewed every 6 months by MMSE score and global, functional and behavioral assessment. Carers' views on the patient's condition at follow-up should be sought."

Treatment	**Non-pharmacological interventions:** ▪ "People with mild-to-moderate dementia of all types should be given the opportunity to participate in a structured group cognitive stimulation program. This should be commissioned and provided by a range of health and social care staff with appropriate training and supervision and offered irrespective of any drug prescribed for the treatment of cognitive symptoms of dementia." **"Pharmacological interventions for the cognitive symptoms of AD:** ▪ the three AChE-Is donepezil, galantamine and rivastigmine are recommended as options in the management of people with AD of moderate severity only (that is, those with an MMSE score of between 10 and 20 points), and under the conditions; ▪ although it is recommended that AChE-Is should be prescribed only to people with AD of moderate severity, healthcare professionals should not rely on the MMSE score in certain circumstances, including in those with an MMSE score greater than 20, who have moderate dementia as judged by significant impairments in functional ability and personal and social function compared with premorbid abilities, etc.; ▪ when the decision has been made to prescribe an AChE-I, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost. However, an alternative AChE-I could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical comorbidity, possibility of drug interactions, and dosing profiles; ▪ memantine is not recommended as a treatment option for people with moderately severe to severe AD except as part of well-designed clinical studies; ▪ people with mild AD who are currently receiving AChE-Is and people with moderately severe to severe AD currently receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy until they, their carers and/or specialist consider it appropriate to stop; ▪ for people with MCI, AChE-Is should not be prescribed, except as part of properly constructed clinical studies." **Pharmacological interventions for non-cognitive symptoms and behaviors: Presented in the guideline.**
Sponsorship / Conflict of Interest	▪ "The Guideline Development Group was convened by the National Collaborating Centre of Metal Health and Social Care Institute for Excellence (SCIE) and supported by funding from the National Institute for Clinical Excellence (NICE) and SCIE." ▪ The interests of all the members were presented.

AA = Alzheimer's Association; AChE-I = acetylcholinesterase inhibitor; AD = Alzheimer's disease; CSF = cerebrospinal fluid; CT = computed tomography; DLB = dementia with Lewy bodies; EEG= electroencephalogram; FDG-PET = Fluorodeoxyglucose Positron Emission Tomography; FTD = frontotemporal dementia; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NIA = National Institute on Aging; NICE = National Institute for Clinical Excellence; SCIE = Social Care Institute for Excellence; SPECT = Single-Photon-Emission Computed Tomography; UK = United Kingdom; VaD = vascular dementia.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-22. Guidelines for the Treatment of Alzheimer's Disease From the Italian Association of Psychogeriatrics [37]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
76	2005	Italy	Patients with AD	Literature review (RCT, observational studies)	Unclear	No, published prior to 2011

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	▪ N/A
Monitoring	▪ N/A
Treatment	**"Treatment with AChEe- inhibitors** ▪ should be considered for the control of cognitive disturbances (Standard guideline strength); ▪ should be considered for the control of functional status (Standard guideline strength); ▪ should be considered for the control of BPSD (Standard guideline strength); ▪ should be considered in moderate to severe AD (Recommendation); ▪ start treatment as early as possible (Practical option); ▪ continue treatment, in patients who have derived benefit, even in those with MMSE score < 10 (Practical option); ▪ are not contraindicated in the presence of symptoms indicating cerebrovascular disease, or vascular risk factors, in patients with AD (Standard); ▪ can be used to control cognitive symptoms, without differentiation between specific compounds, and based on individual physician preferences (Standard); ▪ donepezil may be preferred to galantamine and rivastigmine because of a lower incidence of adverse events (Practical option); ▪ adverse events do not preclude the use of AChE inhibitors in clinical practice (Standard)" **"Treatment with memantine and other pharmacotherapies** ▪ memantine should be considered for the control of symptoms and cognitive impairment in moderate to severe AD (Standard); ▪ memantine should be considered for patients with moderate to severe AD who are already receiving donepezil (Standard); ▪ NSAIDs (nonsteroidal anti-inflammatory drugs) should not be considered for the treatment of AD (Standard); ▪ Gingko biloba should not be considered (Practical option); ▪ hormone replacement therapy should not be considered in women with AD (Standard); ▪ vitamin E can be considered as an adjunct to other treatments (Recommendation) ▪ selective serotonin reuptake inhibitors (SSRIs), particularly citalopram and sertraline, should be considered for depression (Standard); ▪ low dosages of olanzapine, quetiapine, risperidone, or even citalopram should be considered for BPSD (Standard); ▪ use atypical with caution after confirming that nonpharmacological intervention is ineffective (Standard); ▪ assess the potential for treatment withdrawal after 2 months (Standard)"

Sponsorship / Conflict of interest	▪ "A committee of experts from the Italian Association of Psychogeriatrics compiled these guidelines" ▪ "This work was made possible by an unconditional grant from Pfizer Italia Srl."

AA = Alzheimer's Association; AChE = acetylcholinesterase; AD = Alzheimer's disease; BPSD = behavioral and psychological symptoms of dementia; MMSE = Mini-Mental State Examination; NIA = National Institute on Aging; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-23. Guidelines for the Diagnosis of Dementia and Alzheimer's Disease. The Dementia Study Group of the Italian Neurological Society [38]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
60	2000	Italy	Patents with dementia (including AD)	Scientific evidence emerging from peer-reviewed journals	Likely	No

Screening	▪ "It is therefore inadvisable to use the existing instruments for screening asymptomatic populations insofar as they do not offer any public health advantages (I)."
Testing	▪ "Alongside the use of standardized neuropsychological test batteries, the patient's cognitive status should be further explored using tests that investigate particular functional areas (III)." ▪ "A lumbar puncture should be performed in the presence of known or suspected meningeal carcinomatosis, central nervous system infection, positive syphilitic serology, suspected central nervous system vasculitis, unusual or rapidly progressive dementia, or immunosuppression (I)." ▪ "The cerebrospinal fluid (CSF) levels of substances that may play a pathogenetic role in dementia (e.g., beta-amyloid, tau protein) are of great scientific interest. These should be measured in the context of research protocols which explicitly require that informed consent be obtained from the patient or caregiver (III)."
Diagnosis	▪ "The diagnosis should be based on the DSM-IV or ICD-10 criteria that assume the existence of a single syndromic picture (dementia) common to various diseases (III)." ▪ "It is reasonable to perform brain computed tomography (CT) or magnetic resonance imaging (MRI) at least at the time of first diagnosis, because this is often indispensable for a correct differential diagnosis (I)." ▪ "Other examinations, such as single photon emission computed tomography (SPECT) or positron emission tomography (PET), can provide information on brain function. These are of great interest for research purposes and should be used in the framework of research protocols (III)." ▪ "Although not strictly necessary for diagnosing dementia, at the time of first diagnosis (and particularly in the case of Alzheimer's disease), each patient should undergo a complete neuropsychological evaluation (II)." ▪ "In the case of Alzheimer's disease (the most frequent of all of the forms of dementia) and all of the other forms that are not clearly hereditary, there are still no biological or instrumental markers that can be definitively used for diagnostic purposes (I)." ▪ "The clinical diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA and DSM-III R criteria (almost identical to those of DSM-IV) is confirmed by neuropathological diagnosis in 89%-100% of cases (I)." ▪ "In cases in which familial investigations reveal a dominant autosomal transmission, a genetic examination is indicated with the aim of identifying amyloid precursor protein (APP) or preseniline 1 and 2 (PS1 and PS2) gene mutations (I)." ▪ "Other genetic investigations of factors potentially capable of modulating the clinical characteristics of the disease (e.g., ApoE, IL1α) are of great scientific interest. These should be performed within the context of specific research protocols (III)." ▪ "The anatomopathological finding of AD is useful confirmation in the case of clinically diagnosed dementia (I)."
Monitoring	▪ N/A
Treatment	▪ N/A

Sponsorship/ Conflict of interest	▪ These guidelines were prepared by the Dementia Study Group of the Italian Neurological Society (SIN). ▪ The work was partially supported by an Educational Grant from Novartis Italia

AA = Alzheimer's Association; AD = Alzheimer's disease; ApoE = Apolipoprotein E; APP = amyloid precursor protein; CSF = cerebrospinal fluid; CT = computed tomography; DSM-III = *Psychiatry Diagnostic & Statistical Manual of Mental Disorders–Third Edition Revised*; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ICD-10 = *International Statistical Classification of Diseases, Tenth Revision*; MCI = mild cognitive impairment; NIA = National Institute on Aging; NINCDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke; PET = positron emission tomography; SPECT = single photon emission computed tomography.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-24. Guideline Watch (October 2014): Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias [39]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
60	2017	US	Patients with AD	Workgroup	Unclear	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ N/A					
Treatment	▪ "Available evidence remains modest for the efficacy of the cholinesterase inhibitors for mild to severe Alzheimer's disease and of memantine for moderate to severe Alzheimer's disease." ▪ "New randomized controlled trials show effects that are, at best, slight or of unclear clinical significance when memantine is added to cholinesterase inhibitors. Evidence for the sustained benefit of either cholinesterase inhibitors or memantine is unclear." ▪ "Studies indicate that cholinesterase inhibitors and memantine have no clinically significant effects on disruptive behaviors." ▪ "New evidence indicates that antipsychotics provide weak benefits for the treatment of psychosis and agitation in patients with dementia. Adverse effects of antipsychotics reported include sedation, metabolic effects, and cognitive impairment."					
Sponsorship / Conflict of interest	▪ "Watches may be authored and reviewed by experts associated with the original guideline development effort and are approved for publication by APA's Executive Committee on Practice Guidelines. Thus, watches represent the opinion of the authors and approval of the Executive Committee but not APA policy." ▪ Conflicts of interest were presented and include financial support from pharmaceutical companies.					

AA = Alzheimer's Association; APA = American Psychological Association; N/A = not applicable; NIA = National Institute on Aging; US = United States.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-25. Clinical Practice Guidelines for Management of Dementia [17]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
55	2018	India	People with dementia (including AD), MCI	Literature review	Not discussed	No

Screening	▪ N/A
Testing	▪ "Brief screening tests can be useful. This can help in eliciting key information and by making brief cognitive assessments" ▪ "Shorter tests may confirm a cognitive problem that needs to be evaluated, whereas longer tests contribute more to the diagnosis"
Diagnosis	▪ "DSM 5 criteria may be used as a guide for clinical diagnosis of MCI" ▪ "Cognitive assessment can be made as part of detailed examination of higher functions. Commonly used instruments like Mini-Mental State Examination (MMSE) can be used. Addenbrooke's Cognitive Examination (ACE) is a more detailed test battery for assessing cognitive functions" ▪ "Simple instruments like the Clinical Dementia Rating Scale can help in assessing the severity of dementia in routine clinical practice" ▪ "Two commonly used scales for assessment of BPSD symptoms are the Neuropsychiatric Inventory (NPI) and the BEHAVE-AD" ▪ "The clinicians might choose any standard criteria for making clinical diagnosis of dementia, especially common sub-types, i.e., ICD-10 and DSM-5 for AD" ▪ "Assessment of the activities of daily living is very important to formulate the individualized plan of intervention (e.g., Everyday Activities Scale for India [EASI])"
Monitoring	▪ N/A
Treatment	▪ "ChEIs (Donepezil, Rivastigmine and Galantamine) can be used for all the stages of Dementia due to Alzheimer's disease" ▪ "There is no clear evidence regarding the benefit of cholinesterase inhibitors for the management of behavioral and psychological symptoms in Alzheimer's dementia" ▪ "The efficacy of cholinesterase inhibitors is established clearly in the short term randomized controlled trials lasting for 3 to 6 months for the cognitive domains and global functioning" ▪ "Few studies have indicated continued benefit of cholinesterase inhibitors in the long term (up to 1 year). But there are limitations in the quality of this evidence." ▪ "The benefit of cholinesterase inhibitors in the long term is suggested through the observation of deterioration of cognitive function and global functioning after the withdrawal of cholinesterase inhibitors" ▪ "Memantine alone or in combination with ChEIs is useful in moderate to severe Dementia due to Alzheimer's disease" ▪ "Despite the minor differences in the mechanism of action of Donepezil, Rivastigmine and Galantamine, there is no clear evidence to support choosing any specific cholinesterase inhibitor over other drugs" ▪ "Low dose atypical antipsychotics (Risperidone, Aripiprazole, Quetiapine) can be considered for severe agitation, aggression and psychotic symptoms" ▪ "Disease modifying drugs for dementia are expected to be more effective in the stage of MCI compared to the stage of dementia. However, no effective medication has been identified for MCI" ▪ "ChEIs and Memantine have not been found to be effective in delaying the conversion of MCI to dementia. Routine use of ChEIs or Memantine for the treatment of MCI is not recommended"

Sponsorship / Conflict of interest	▪ Conflict of interest information was not presented.

AA = Alzheimer's Association; ACE = Addenbrooke's Cognitive Examination; AD = Alzheimer's disease; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; BPSD = behavioral and psychological symptoms of dementia; ChEI = cholinesterase inhibitor; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ICD-10 = *International Statistical Classification of Diseases, Tenth Revision*; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; N/A = not applicable; NIA = National Institute on Aging; NPI = Neuropsychiatric Inventory.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-26. Practice Guidelines for the Diagnosis and Treatment of Alzheimer's Disease in a Managed Care Setting: Part II--Pharmacologic Therapy [40]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
48	2000	US	Patients with AD	Evidence-based + expert panel	Likely	Not applicable

Screening	▪ N/A
Testing	▪ "A baseline assessment global, cognitive, functional, and behavioral status should be undertaken"
Diagnosis	▪ N/A
Monitoring	▪ "Patients should be reassessed periodically to determine if the symptoms of AD are improved or stabilized or if the rate of decline has been reduced". ▪ "Any of these beneficial responses to donepezil warrant continued therapy". ▪ "Failure to improve, stabilize or reduce the rate of decline in a patient adhering to the regimen indicates that donepezil therapy is not efficacious in this patient, and the agent should be discontinued". ▪ "Any residual, non-urgent or emerging behavioral disturbances that impair patient function or produce distress should be treated with the appropriate psychotropic medicine". ▪ "Maintenance donepezil therapy may be reevaluated when the patient reaches a stage of severe dementia". ▪ "If cognitive, functional or behavioral deterioration occurs with discontinuation of donepezil, re-initiation and continued therapy are indicated".
Treatment	▪ "Patients with urgent behavioral problems should be treated appropriately with antidepressants for major depressive symptoms or with antipsychotic mood stabilizers, or other appropriate symptom-based agents for behavioral disturbances" ▪ "Patients who do not have behavioral problems are candidates for treatment with donepezil, those have mild-to-moderate AD (e.g., often defined as a MMSE evaluation score ≥ 10). Donepezil is introduced at a dose of 5 mg and should be reassessed after 3 to 4 therapies. Patients tolerating 5 mg should be advanced at 10-mg dose and reassessed. Patients unable to consume 10-mg dose should be returned to the 5-mg doses and the rechallenged with 10 mg after four to six weeks". ▪ "After the introduction of donepezil, many clinicians would add vitamin E to the patient's therapeutic regimen at a dose of 2,000 IU daily".
Sponsorship/ Conflict of interest	▪ "The Work of the Alzheimer's Disease Managed Care Advisory Council has been funded, in part, with an unrestricted educational grant from Pfizer Inc, and Eisai Inc". ▪ "Conflicts of interest were presented: – Dr Fillit was Corporate Medical Director for Medicare at NYLCare Health Plans, now a subsidiary of Aetna U.S. Healthcare, during the initial development of these guidelines. – Dr Cummings is supported by several grants"

AA = Alzheimer's Association; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; N/A = not applicable; NIA = National Institute on Aging; US = United States.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-27. Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine in People with Dementia [7]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
44	2018	Australia and Canada	Patients with AD	Expert panel + SLR + grading evidence	No	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ N/A					
Treatment and deprescribing	▪ "A proportion of people who have used these medications for over 12 months or outside an approved indication may be able to stop the medication with minimal clinically relevant negative consequences." ▪ "Discontinuation of ChE-Is and/or memantine may lead to a worsening of cognitive function in certain populations of users." ▪ "The limited data on person-important outcomes, such as quality of life and function, suggests that these outcomes may not be altered by discontinuation. However, there is considerable uncertainty in the benefits and harms of both prescribing and deprescribing in the individual." ▪ "It is important to consider the values, preferences and experiences of the person with dementia and/or their carer/family when determining if trial deprescribing is appropriate." ▪ "ChE-Is and memantine have been found to be cost-effective in treating approved indications in some populations and settings, based on the data from short-term studies." ▪ "There are numerous clinical considerations when deprescribing ChE-Is and/or memantine, including how to assess for ongoing benefit, how to conduct withdrawal and monitoring (plus actions to follow monitoring) and implementation of non-pharmacological management strategies."					
Sponsorship / Conflict of interest	▪ "The development, publication and dissemination of this guideline were funded through an NHMRC-ARC Dementia Research Development Fellowship awarded to Dr Emily Reeve (APP1105777). Guideline Development Team members generously contributed their time to developing this guideline."					

AA = Alzheimer's Association; ChE-I = cholinesterase inhibitor; N/A = not applicable; NHMRC-ARC = National Health and Medical Research Council - Australian Research Council; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-28. Deprescribing Cholinesterase Inhibitors and Memantine in Dementia: Guideline Summary [6]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
43	2019	Australia and Canada	Patients with AD	Expert panel + SLR + grading evidence	Unclear	No

Screening	N/A
Testing	N/A
Diagnosis	N/A
Monitoring	▪ "Deprescribing a ChEI or memantine should be a trial discontinuation, with close periodic monitoring (e.g., every 4 weeks) and re-initiation of the medication if the individual shows clear worsening of condition after withdrawal (Practice Point)"
Treatment	▪ "For individuals taking a ChEI for Alzheimer's disease, PDD, LBD or vascular dementia for > 12 months, we recommend trial discontinuation if: (Strength: strong; LoE: Low) – cognition and/or function has significantly worsened over the past 6 months (or less, as per the individual) – no benefit (improvement, stabilization or decreased rate of decline) was seen at any time during treatment; or – the individual has severe or end-stage dementia" ▪ "For individuals taking memantine for AD, PDD or LBD for > 12 months, we recommend trial discontinuation if: (Strength: Strong, LoE: very Low) – cognition and/or function has significantly worsened over the past 6 months (or less, as per the individual) – no benefit (improvement, stabilization or decreased rate of decline) was seen at any time during treatment. – the individual has severe/end-stage dementia" ▪ "The dose of the ChEIs or memantine should be tapered prior to discontinuation by halving the dose (or by stepping down through available dose formulations) every 4 weeks to the lowest available dose, followed by discontinuation (Practice Point) ▪ Other situations in which trial deprescribing of ChEIs or memantine can be considered include (Practice Point): – a decision by a person with dementia and/or their family/carer to discontinue the medication – a person with dementia's refusal or inability to take the medication – non-adherence that cannot be resolved – drug–drug or drug–disease interactions that make treatment risky – severe agitation/psychomotor restlessness and non-dementia terminal illness"
Sponsorship / Conflict of interest	▪ "The guideline development, publication, dissemination and implementation were funded through an Australian National Health and Medical Research Council (NHMRC) - ARC Dementia Research Development Fellowship awarded to Emily Reeve (APP1105777). The funding body had no involvement in guideline development and, as such, the views and/or interests of the funding body have not influenced the final recommendations." ▪ There was a description of author's engagement, but no declaration of conflict was made.

AA = Alzheimer's Association; AD = Alzheimer's disease; ChEIs = cholinesterase inhibitors; LBD = dementia with Lewy Body; LoE = level of evidence; N/A = not applicable; NIA = National Institute on Aging; PDD = Parkinson's disease dementia.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-29. Clinical Practice Guidelines and Principles of Care for People With Dementia in Australia [41]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
37	2016	Australia	Patients with dementia (including AD), MCI	Expert panel + SLR + grading evidence	Unclear	No
Screening and testing	"Guidelines state that there is insufficient evidence on the relative benefits and harms to support general population screening (CBR). Nevertheless, GPs should look out for symptoms of cognitive decline, particularly in those aged ≥75 years (CBR), and investigate symptoms when they are first raised" "A basic dementia screen should be performed at the time of presentation, including routine hematology, biochemistry tests (e.g., electrolytes, calcium, glucose, renal and liver function), thyroid function tests, serum vitamin B12 and folate levels" "Offer referral to memory assessment specialists or services (EBR low)" "Occupational therapy interventions, including assistive technologies, tailored interventions to improve independence, and environmental assessment and modification are useful for those living in the community (EBR-low)"					
Diagnosis	▪ N/A					
Monitoring	▪ "The Guidelines recommend regular medication review that includes considering discontinuation (PP)." ▪ "Symptoms should be measured using objective, validated tools so that the behaviors and effectiveness of any treatments can be monitored (PP)."					
Treatment	"There is evidence that ChEIs can improve cognitive function and independence in activities of daily living in those with mild to moderately severe dementia (EBR, low)." "Recent evidence has also shown benefits of ChEIs in people who have dementia with Lewy bodies, Parkinson's disease dementia, vascular dementia and severe AD (EBRs, low)" ▪ "The combination of a ChEI plus memantine has been shown to improve cognition and reduce symptoms such as distress and agitation (EBR, low)" ▪ "ChEIs are not recommended for MCI (EBR, low)" ▪ "Non-pharmacological approaches, such as engaging the person with dementia in activities that are interesting and meaningful, should be implemented first (PP)" ▪ Approaches to manage symptoms were recommended in the guidelines					
Sponsorship/ Conflict of interest	▪ This work was supported by the NHMRC Partnership Centre on Dealing with Cognitive and Related Functional Decline in Older People ▪ Conflicts of interest were presented in the full guideline document					

AA = Alzheimer's Association; AD = Alzheimer's disease; CBR = consensus-based recommendations; ChEI = cholinesterase inhibitor; EBR = evidence-based recommendations; GP = general practitioner; MCI = mild cognitive impairment; NHMRC = National Health and Medical Research Council; N/A = not applicable; NIA = National Institute on Aging; PP = practice point.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-30. Recommendations from the Italian Interdisciplinary Working Group (AIMN, AIP, SINDEM) for the Utilization of Amyloid Imaging in Clinical Practice [42]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
24	2015	Italy	Patients with MCI due to AD, patients with possible, or probable AD	Literature search from peer-reviewed	Unclear	Yes

Screening	▪ N/A
Testing and diagnosis	**" Before considering the exam and performing it, the presence of all three following conditions is necessary:** ▪ The patient must have a cognitive impairment objectively confirmed by means of a standardized neuropsychological battery. Normative reference values for these tests must be based on the Italian population. ▪ The cause of the cognitive impairment remains uncertain despite an extensive clinical evaluation performed by an expert in dementia and related Cognitive Disorders. AD must be one of the possible causes in the differential diagnosis. ▪ The expert believes that knowing whether cerebral amyloidosis is present or not could increase diagnostic accuracy. This information may substantially modify the patient clinical/therapeutic management, consisting not only in pharmacological approaches, but also in a globally considered planning of non-pharmacological supports" **"Amyloid PET is recommended in the following cases:** ▪ Subjects affected by a persistent or progressive (for at least 6 months) Mild Cognitive Impairment (MCI), defined according to the NIA-AA criteria, when the expert's diagnosis based on morphological and/or functional neuroimaging is still uncertain. ▪ MCI subjects (a) when the clinical onset is either atypical or uncertain without a clear diagnosis, (b) when the etiology may be mixed due to a concomitant cerebrovascular disease or (c) when there are potentially misleading clinical conditions, i.e., pharmacological effects or not properly controlled systemic diseases (e.g., diabetes). ▪ Patients with a diagnosis of possible AD, defined according to the NIA-AA criteria when the final diagnosis is still uncertain after the diagnostic procedures involving morphological and possibly functional neuroimaging. ▪ Patients with cognitive decline or progressive dementia and an early age at onset (≤ 65) when the expert's diagnosis is still unclear at the end of the diagnostic procedure involving morphological and functional neuroimaging. ▪ Patients affected by focal syndromes (e.g., progressive aphasia, agnosia and apraxia; cortico-basal syndrome) when the expert's diagnosis is still unclear after structural and functional neuroimaging and with the aim to exclude AD pathology." **"Amyloid PET is not recommended in the following conditions:** ▪ Patients who met the criteria for probable AD and with a typical age at onset, probable DLB, probable PDD and amyloid angiopathy (given that positivity of amyloid PET does not discriminate the specific pathology). ▪ For the definition of the severity and for the follow-up of the cognitive impairment ▪ For asymptomatic individuals, even in the presence of a familiarity for dementia and/or with one or two of the e4 alleles of the apolipoprotein E ▪ For patients reporting deficits not confirmed by the objective neuropsychological evaluation. ▪ As an alternative to genetic testing in suspected carriers of dominant autosomal gene mutations causing AD.

	▪ For non-medical use (legal and insurance purposes, screening for employment).”
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ “The guideline was developed by experts on behalf of three scientific associations: the Italian Neurological Society for the Study of Dementia (SINDEM), the Italian Association of Psychogeriatrics (AIP) and the Italian Association of Nuclear Medicine (AIMN)” ▪ “Conflict of interest: – Alessandro Padovani has received honoraria for speaking at Symposia from General Electrics-Health, Lundbeck, and Novartis – Flavio Mariano Nobili has received honoraria for speaking at Symposia from Eli Lilly & Co and Piramall. – Ugo Paolo Guerra, Daniela Perani, Sandro Sorbi, Alberto Pupi and Marco Trabucchi declared that they have no conflict of interest.”

AA = Alzheimer’s Association; AD = Alzheimer’s disease; AIMN = Italian Association of Nuclear Medicine; AIP = Italian Association of Psychogeriatrics; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; N/A = not applicable; NIA = National Institute on Aging; NIA-AA = National Institute on Aging – Alzheimer’s Association; PDD = Parkinson’s disease dementia; PET= positron emission tomography; SINDEM = Italian Neurological Society for the Study of Dementia.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-31. Italian Neurological Society Guidelines for the Diagnosis of Dementia: Revision l [43]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA Guidelines
20	2004	Italy	Patients with dementia (including AD), MCI relating to AD	Workgroup + scientific evidence from peer-reviewed + expert consensus	Likely	No

Screening	▪ "Some screening instruments can highlight cognitive or functional deficits in asymptomatic subjects. However, they are not sufficiently specific, and they would lead to a high number of false positive results (I)" ▪ "The use of the currently available screening instruments is therefore not recommended insofar as it would not offer any public health advantages (I)" ▪ "It should involve GPs in the first screening phase, and neurologists in the second and third (diagnostic confirmation and the differential diagnosis of the various forms of dementia) (III)." ▪ "In the case of all of the forms or situations attributable to MCI, a neurologist should draw up a complete diagnostic picture (III)" ▪ "One of the most widely used screening instruments is Folstein's Mini Mental State Examination, and another instrument validated is the Milan Overall Dementia Assessment, which was constructed on the basis of the paradigm of AD (I)."
Testing	▪ "A careful assessment should be made of the presence of severe non neurological diseases that may give rise to encephalopathies, such as hyper- or hypothyroidism; hepatic, renal or respiratory insufficiency; diabetes and arterial hypertension (I)" ▪ "Conditions that may cause folic acid or vitamin B12 deficiency should also be considered because they are known to cause, or contribute to the manifestation of reduced cognitive capacities (I)" ▪ "The existence of the abuse of alcohol other substances, and an evaluation should be made of the presence of psychiatric diseases, previous cranial traumas and, particularly, other neurological diseases (I)." ▪ "It is also essential to investigate the presence of dementia in other members of the same family (I)" ▪ "The physical examination should be performed on the basis of general medical principles and must necessarily include a complete neurological examination (I)." ▪ "We recommend the use of the Instrumental Activities of Daily Living (AIDL) scale, which investigates 16 activities of everyday life (I)" ▪ "Although it is not strictly necessary for the diagnosis of dementia, every patient should undergo a complete neuropsychological assessment at the time of the first diagnosis, particularly in the case of AD (II)." ▪ "Specific scales should be used, such as the Neuropsychiatric Inventory of which there is an Italian version that makes it possible to measure the frequency and severity of the disorders common to AD and, to a lesser extent, other dementias; the Behavioral Pathological Rating Scale for Alzheimer Disease, which concentrates on the specific psychological symptoms of AD; or the Behavioral Scale of the Consortium to Establish a Registry in AD, which analyzes both behavioral and psychological symptoms (III)."
Diagnosis	▪ "The diagnosis must be based on the DSM-IV or ICD-10 criteria, which foresee the existence of a single syndromic picture (dementia) shared by different diseases (III)" ▪ "In the case of Alzheimer's disease, and the other forms that are not clearly hereditary, there is currently a lack of biological and/or instrumental markers that can safely be used for diagnostic purposes (I)" ▪ "It has been found that the clinical diagnosis of probable AD according to the criteria of the NINCDS-ADRDA and those of the DSM III R is confirmed by the neuropathological diagnosis in 89%-100% of cases (I)."

	▪ "The neuropathological markers of AD can also be encountered in non-demented elderly subjects; anatomopathological findings are useful for confirming AD in the presence of clinically diagnosed dementia (I)" ▪ "Anatomic cerebral neuroimaging examinations (CT, MRI) are mandatory, at least at the time of first diagnosis (if only to ensure a correct differential diagnosis and assess the possible vascular component), and whenever there are particularly important variations in the patient's clinical course. Volumetric studies of the hippocampus are currently restricted to research protocols, as are MR-spectroscopy studies (I)." ▪ "Functional cerebral neuroimaging examinations such as SPECT and PET, which provide information concerning the status of cerebral function and metabolism, are indicated in the case of dementias with an atypical presentation or evolution (III)." ▪ "Cerebral neuroimaging examinations should be considered on the basis of the clinical characteristics at presentation (III)."
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship / Conflict of interest	▪ This paper was partially supported by an Educational Grant from Novartis Italy

AA = Alzheimer's Association; AD = Alzheimer's disease; AIDL = Instrumental Activities of Daily Living; CT = computerized tomography; DSM III R = *Psychiatry Diagnostic & Statistical Manual of Mental Disorders, Third Edition Revised*; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; GP = general practitioner; ICD-10 = *International Statistical Classification of Diseases, Tenth Revision*; MCI = mild cognitive impairment; MR = magnetic resonance; MRI = magnetic resonance imaging; N/A = not applicable; NIA = National Institute on Aging; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke; PET = Positron emission tomography; SPECT = single-photon emission computerized tomography.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-32. Dementia, Disability and Frailty in Later Life – Mid-Life Approaches to Delay or Prevent Onset [44]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
19	2015	UK	People who are at risk of dementia, Diagnosed with dementia	Reviews, expert reports and economic modelling reports + recommendations developed by Public Health Advisory Committee	Unlikely	Not applicable

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	▪ N/A
Monitoring	▪ N/A
Treatment	▪ N/A
Risk management	▪ "Encouraging healthy behaviors ▪ Integrating dementia risk reduction prevention policies ▪ Raising awareness of risk of dementia, disability and frailty ▪ Producing information on reducing the risks of dementia, disability and frailty ▪ Preventing tobacco use ▪ Improving the environment to promote physical activity ▪ Reducing alcohol-related risk ▪ Supporting people to eat healthily ▪ Delivering services to promote behavior change ▪ Providing advice on reducing the risks of dementia, disability and frailty at every appropriate opportunity ▪ Providing accessible services ▪ Providing physical activity opportunities ▪ Provide training ▪ Providing support in the workplace ▪ Leading by example in the public sector"
Sponsorship / Conflict of interest	▪ This guideline was developed by NICE

AA = Alzheimer's Association; N/A = not applicable; NIA = National Institute on Aging; NICE = National Institute for Health and Care Excellence; UK = United Kingdom.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-33. ACR-ASNR Practice Parameter for Brain PET/CT Imaging Dementia [45]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
15	2016	US	Patients with AD, patients with MCI relating to AD	ACR-ASNR workgroup	No	No

Screening	"Clinical amyloid-PET imaging has not been validated for screening asymptomatic subjects with genetic or other risk factors for developing AD"
Testing	▪ N/A
Diagnosis	▪ "FDG-PET can identify the underlying characteristic brain regional patterns of cerebral hypometabolism and can thereby distinguish AD from other degenerative processes such as FTD." ▪ "Although the use of FDG-PET has not been determined to be useful for screening of asymptomatic patients who may ultimately be at risk of developing dementia, the modality can be useful in patients who meet the criteria for MCI" ▪ "Pathological depositions of fibrillar Aß-amyloid are requisite for the pathological diagnosis of AD" ▪ "It is anticipated that Aß-amyloid imaging may be more specific than FDG-PET in differentiating among degenerative dementias, but it may not necessarily provide evidence of a specific neurodegenerative cause of early cognitive complaints in nondemented patients" ▪ "The use of amyloid imaging is recommended to determine presence (or absence) of pathological fibrillar Aß-amyloid deposition in patients with progressive cognitive decline or dementia of uncertain etiology in whom AD is a possibility" ▪ "Detection of Alzheimer pathology in cognitively impaired adults: Subjects with progressive cognitive decline who demonstrate features atypical of AD and suggestive of another neurodegenerative process such as FTD (e.g., early age of onset, prominent behavioral dysregulation, or primary progressive aphasia) may have atypical AD presentations or may have FTD"
Monitoring	▪ "Amyloid PET cannot be used to establish the diagnosis of AD or monitor the response to therapy for AD in terms of disease progression or improvement"
Treatment	▪ N/A
Sponsorship / Conflict of interest	▪ This guideline was developed collaboratively by the American College of Radiology (ACR) and the American Society for Neuroradiology (ASNR) ▪ Conflicts of interest and sources of funding: none declared.

AA = Alzheimer's Association; ACR = American College of Rheumatology; AD = Alzheimer's disease; ASNR = American Society for Neuroradiology; ACR = American College of Rheumatology; FDG-PET = fluorodeoxyglucose (FDG)-positron emission tomography; FTD = frontotemporal disorders; MCI = mild cognitive impairment; NIA = National Institute on Aging; PET = positron emission tomography; US = United States.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-34. EANM Procedure Guidelines for Brain PET Imaging Using [^{18}F]FDG, Version 3 [46]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
13	2022	International	Patients with MCI, with AD	EANM Neuro-Imaging Committee workgroup	Unclear	No

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	▪ "[18F] FDG-PET is viewed as a marker of neurodegeneration and progression, and currently included — with hippocampal volume measured with MRI (N) — in the amyloid-ß (A), tau (T), and neurodegeneration (ATN) classification scheme" ▪ "[18F] FDG-PET is an independent biomarker to predict AD conversion in patients with mild cognitive impairment (MCI) along with amyloid-β and tau, independently of hippocampal volume and of amyloid PET status." ▪ "The use of [18F] FDG-PET is complementary to other biomarkers, such as amyloid PET, CSF Aβ42, CSF Aβ42/Aβ40 ratio, CSF phosphorylated tau, and MRI" ▪ "[18F] FDG-PET is recommended to support early diagnosis of AD in MCI" ▪ "FDG-PET is also recommended to support the differential diagnosis between (i) AD and FTLD, (ii) AD and DLB, (iii) FTLD and DLB; (iv) AD and vascular dementia when clinical and MRI data are inconclusive" ▪ "[18F] FDG-PET can also be used to help distinguish between cognitive impairment of degenerative diseases from nondegenerative origin, such as in traumatic brain injury (in correlation to MRI using PET/MRI device or fusion)."
Monitoring[b]	▪ "Continuous supervision of patients during the whole scanning procedure is required. This is particularly important for patients with cognitive impairment." ▪ "In patients with limited ability to cooperate (e.g., due to their cognitive/behavioral disorders) and in whom no contraindications against medical sedation exist, it may be useful to apply conscious sedation (e.g., by a short-acting benzodiazepine such as i.v. midazolam)." ▪ "Sedation should be used with caution and rather be avoided if dynamic acquisitions are performed for quantification of rCMRglc, because of the effects of the sedative on glucose metabolism and thus also on brain uptake of [18F] FDG. The dose of sedation should be reduced in elderly patients" ▪ "Appropriate monitoring by pulse oximetry should be performed to prevent cardiopulmonary depression, and appropriate antidote/emergency backup should be foreseen"
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ Conflict of interest was reported, for example: – "BvB received research support from ZON-MW, AVID radiopharmaceuticals, CTMM, IXICO, Springer and Janssen Pharmaceuticals. He is a trainer for Piramal and GE. He receives no personal honoraria.EG has received consultant and speaker honoraria from GE Healthcare and CIS Bio International, and consultant honoraria from Advanced Accelerator Applications. HB has received speaker honoraria from AAA/Novartis, etc."

AA = Alzheimer's Association; AD = Alzheimer's disease; CSF = cerebrospinal fluid; DLB = dementia with Lewy bodies; EANM = European Association of Nuclear Medicine; FTLD = frontotemporal lobar degeneration; i.v. = intravenous; MCI = mild cognitive impairment; rCMRglc= regional metabolic rate of glucose consumption; [18F]FDG-PET = 2-[18F] fluoro-2-deoxy-D-glucose - positron emission tomography; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 11, 2022.

[b] These are general monitoring recommendations and are not AD/MCI specific.

Table A-35. Periodic Health Examination, 1991 Update: 1. Screening for Cognitive Impairment in the Elderly. Canadian Task Force on the Periodic Health Examination [47]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
5	1991	Canada	People over 65 years	Scientific evidence-based+ developed by Canadian Task Force	Not discussed	No

Screening	▪ "Insufficient evidence to include routine screening for cognitive impairment in or exclude it from periodic health examination of people over 65 years of age (level C)"
Testing	▪ N/A
Diagnosis	▪ N/A
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ The work of the task force is supported by the Department of National Health and Welfare ▪ Conflict of interest information was not presented

AA = Alzheimer's Association; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-36. Recommendations for the Neuropsychological Assessment Supporting the Diagnosis of Dementia in the Luxembourgish Context (NP-DiaDem) [48]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
4	2016	Luxembourg	Suspected MCI	Workgroup	Not discussed	Yes

Screening	▪ N/A
Testing and Diagnosis	▪ "A qualified neuropsychological evaluation is defined – by using appropriate, objective and well standardized testing instruments – by interpreting the test results in the context of all other potentially intervening factors (e.g., affectivity, social factors, comorbidities, professional background, educational attainment level) – in providing clinically sound and coherent recommendations for further diagnostic and/or therapeutic care." ▪ "The neuropsychological assessment is complementary to the other exams (e.g., imaging, blood tests, biomarkers) prescribed by medical doctors and is supportive to the medical diagnosis of neurodegenerative cognitive disorders." ▪ "The following core diagnostic criteria are assessed during neuropsychological evaluations: – Concern of cognitive decline emanating from the patient and/or a knowledgeable other – Impairment in at least one cognitive domain (moderate or severe) – Interference with or independent in activities of daily living – Deficits are not better explained by other mental health issues" ▪ "The taskforce recommends the Montreal Cognitive Assessment scale (MoCA) as a first gatekeeper that can be used to trigger further, more detailed assessments." ▪ "The taskforce considers the focus of the neuropsychological evaluation to be the detection of very early signs of neurocognitive disorders (i.e., MCI); and thus, to inform about the degree of degradation" ▪ "The taskforce recommends a geriatric/dementia assessment for patients with MoCA scores of 18 and below – MoCA < 19 usually goes along with major cognitive drawbacks; the necessity of detailed and thorough cognitive assessments is in this case challenged. The neuropsychologist's role should be focused on the identification of neuropsychiatric deficiencies along with the global repercussions on activities of daily living (e.g., ADLs). In addition, special attention should be given to potential family burdens. – MoCA ≥ 19 an MCI assessment is strongly recommended. This more thorough and detailed neuropsychological assessment aims at determining the characteristics of the perceived cognitive decline and the potential influences of psychological factors, such as depression." ▪ "If on the MCI assessment, results are below z <−2, the geriatric/dementia assessment should be realized ad hoc, by exploring in more detail ADLs and behavior."
Monitoring	▪ "If the patient's performances (i.e., test results) are within the norms and correspond to none or minor cognitive impairments, a retest should be offered 6-12 months later"
Treatment	▪ N/A
Sponsorship / Conflict of interest	▪ "The guideline was developed on behalf of the Taskforce Neuropsychologie Démence of the Luxembourg Society of Psychology (SLP)" ▪ Conflict of interest information was not presented

AA = Alzheimer's Association; ADL = activity of daily living; MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment scale; NIA = National Institute on Aging; SLP = Luxembourg Society of Psychology.

z < -2 = z score lower than −2 are indicative of major neurocognitive disorders (American Psychiatric Association, 2013)

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-37. Clinical Practice Guidelines and Care Pathways for People with Dementia Living in the Community [49]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
4	2008	Australia	Patients with dementia (including AD)	Review and synthesis existing guidelines + multidisciplinary panel + rating evidence following NHMRC	No	No

Screening	▪ N/A
Testing	▪ N/A
Diagnosis and screening	▪ Health professionals are responsible for: – Diagnosis of dementia and where possible identification of the sub-type of dementia – Assessing the functional abilities of the person with dementia using validated tools – Assessing the cognitive function of the person with dementia using validated tools (e.g., MMSE, GPCOG, GDS, CDR, and KICA-Cog.) – Assessment of informant's history using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) – Assessing and planning treatment for any co-morbidities – Understanding the knowledge of the person with dementia and their carer with respect to the diagnosis of dementia and its implications" – Identifying services required to meet the needs of the person with dementia and their carer – Assessing the understanding of advance care directives of the person with dementia and their carer
Monitoring	▪ N/A
Treatment	Assess and treat appropriately ▪ Pharmacological following the RACGP guidelines or NICE guidelines – The three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended as options for managing mild to moderate AD – Memantine is used for moderate to severe AD – Combination therapy is recommended option – Do not stop AChE inhibitors in people with Alzheimer's disease because of disease severity alone ▪ Nonpharmacological interventions include music, behavioral management, and reminisce therapy, etc." ▪ Specific interventions are presented to support the caregiver ▪ In advanced phase provide the caregivers appropriate support, information, institutional support if appropriate. No other pharmacological recommendations are presented
Sponsorship / Conflict of interest	▪ These Guidelines and Pathways have been prepared from information based on a collaborative research project between Queensland University of Technology and Queensland Health ▪ This project was funded by a grant from the J.O. and J.R. Wicking Trust which is managed by ANZ Trustees

AA = Alzheimer's Association; AChE = acetylcholinesterase; AD = Alzheimer's disease; CDR = Clinical Dementia Rating; GDS = Global Dementia Scale; GPCOG = General Practitioner Assessment of Cognition; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; KICA-Cog = Kimberley Indigenous Cognitive Assessment tool; MMSE = Mini-Mental Status Examination; NHMRC = National Health and Medical Research Council; NIA = National Institute on Aging; NICE = National Institute for Health and Care Excellence; RACGP = Royal Australian College of General Practitioners.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-38. Taiwan Dementia Treatment Guideline [16]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2021	Taiwan	Patients with MCI, patients with AD	Literature review	Unlikely	No

Screening	▪ N/A
Testing	▪ N/A
Diagnosis	▪ N/A
Monitoring	▪ N/A
Treatment	**Pharmacological treatment** ▪ "Regardless of severity, the use of 5 or 10mg of donepezil for dementia due to Alzheimer's disease (AD) can improve cognitive function, overall performance, and daily function and even ameliorate psychobehavioral symptoms in moderate and severe cases. Although a dose of 10 mg/day donepezil is slightly more effective in improving cognitive function compared with a dose of 5 mg/day, it might lead to more side effects." ▪ "The oral administration of 6-12 mg/day of rivastigmine or the use of a 9.5-cm rivastigmine patch for 24 h can improve cognitive function, daily living, and overall assessment in patients with mild and moderate AD. In addition, the long-term use (26 weeks) of low dose oral capsules (1-4 mg) is beneficial. Patches have the same effect as oral capsules but result in fewer adverse drug reactions. High-dose patches can be used in patients with severe AD, with the same risk of side effects as low-doses patches." ▪ "Continuous use of 16-24 mg of galantamine for more than 6 months can significantly improve the cognitive and daily function of patients with mild and moderate AD. The safety of galantamine is similar to that of other ChEIs." ▪ "Patients with MCI using galantamine should be aware of the increased mortality risk." ▪ "No valid evidence supporting the use of rivastigmine in adults with MCI exists" ▪ "Memantine can improve overall performance, cognitive function, daily function, and behavior in patients with moderate to severe AD. In patients with mild AD, treatment with memantine for 6-7 months is not effective." ▪ "ChEIs are still the first choice for treatment and should be used early after the diagnosis of dementia due to AD. Moreover, ChEIs should be used in combination with memantine if brain deterioration continues after treatment." ▪ "The effectiveness of monoclonal antibodies remains to be confirmed; therefore, they are not yet available in the market." ▪ "The inhibition of Aβ42 production and the condensation of oligomers are the focus of current drug development for AD, and combination therapy remains a possible treatment option for the future." ▪ Principles and clinical considerations that should be followed when prescribing psychotropic drugs for treating BPSD were presented in the guideline. **Nonpharmacological treatments** ▪ "Recent studies have demonstrated that exercise could improve cognitive performance in people with AD." ▪ "For people with MCI, aerobic exercise and resistance training were more effective in improving executive function than stretching and balance training." ▪ "For patients with mild-to-moderate AD, excessive vitamin B intake is not beneficial. Folic acid supplementation can improve global cognition. Vitamin C and E are not beneficial for overall cognition." ▪ "Omega-3 fatty acids can delay the decline in overall cognitive function in patients with MCI and mild dementia."

	▪ "Dietary recommendations for preventing or reducing dementia are as follows: high, but not moderate, adherence to the Mediterranean diet (MeDi) can reduce the risks of cognitive impairment and dementia in healthy individuals and can delay the progression of AD, and MeDi combined with antihypertensive diet involving eating more foods that are beneficial for the brain and eating less unhealthy foods was significantly positively correlated with the delay of cognitive decline and could reduce the risk of AD." ▪ "(I)n patients with mild to moderate AD dementia, acupuncture for 12 weeks three times per week could improve the AD Assessment Scale-Cognitive Subscale."
Sponsorship/ Conflict of interest	▪ This guideline was developed by a working group established by the Taiwan Dementia Society. ▪ This work was supported partly by grants from Ministry of Science and Technology. ▪ Conflict of interest was not reported.

AA = Alzheimer's Association; AD = Alzheimer's disease; BPSD = behavioral and psychological symptoms of dementia; ChEIs = cholinesterase inhibitors; MCI = mild cognitive impairment; MeDi = Mediterranean diet; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-39. International Clinical Practice Guideline of Chinese Medicine Alzheimer [50]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2021	International	Patients with AD, at risk of AD	Literature review + experts' experience	No	No

Testing and Screening	▪ "For those with family history of illness, genetic tests should be taken as early as possible for early detection, prevention and treatment, and regular screening for people over 65 years old is recommended."
Diagnosis	N/A
Monitoring	N/A
Treatment	▪ "Combination of Chinese Materia Medica and acupuncture is chosen for the early stage, while the focus should be placed on combination of both TCM and western medicine in the middle stage, and intensive care should be adopted in the late stage." ▪ **"Syndrome treatment** – Syndrome of marrow deficiency: Bushen Yisui Decoction (Evidence level: II; Recommendation level: C). – Spleen-kidney Yang deficiency syndrome: Bupi Yishen Decoction in Ancient and Modern Classic Recipes (Evidence level: III; Recommendation level: C). – Liver-kidney Yin deficiency syndrome: Zuogui Decoction in Jing-yue's Complete Works (Evidence level: III; Recommendation level: D). – Syndrome of Yin deficiency and effulgent fire: Huanglian Jiedu Decoction in Arcane Essentials from the Imperial Library and Tianwang Buxin Pills in Proofread Effective Prescriptions for Women's Diseases (Evidence level: II; Recommendation level: C)." ▪ "Acupuncture – Acupuncture prescription (Evidence level: III; Recommendation level: D). – Seven needles on the neck (Evidence level: III; Recommendation level: D). – Sanjiao acupuncture (Evidence level: II; Recommendation level: C). – Implanting catgut in acupoints (Evidence level: II; Recommendation level: C)." ▪ Prevention (recommendation level: D) ▪ Nursing (recommendation level: D) – "Psychotherapy: For those AD patients in the early stage who still have consciousness, attention should be paid to emotional adjustment to keep a good mood and to avoid emotional injury." – "Behavior therapy: Appropriate participation in activities and exercises, such as walking, Taijiquan, finger exercises, tongue exercises, and head massage is recommended to delay the process of dementia." – "Before going to bed, to reduce sleep disorder, AD patients should neither watch stimulating programs, nor drink refreshing drinks, and drugs can help when necessary." – "Cognitive training: For those with cognitive disorder, especially those who are in the middle and late stages, the training of cognitive function under the guidance of professional rehabilitation personnel is recommended." – Nursing of sleep disorder, medication ▪ Diet therapy (recommendation level: IIID)
Sponsorship/ Conflict of interest	There was no financial support and sponsorship. There were no conflicts of interest

	This guideline is jointly issued by World Federation of Chinese Medicine Societies and the China Association of Chinese Medicine

AA = Alzheimer's Association; AD = Alzheimer's disease; NIA = National Institute on Aging; TCM = traditional Chinese medicine.

[a] Google Scholar citation count recorded as of July 12, 2022.

Table A-40. Clinical Practice Guideline for Dementia (Diagnosis and Evaluation): 2021 Revised Edition [9]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2022	Korea	Patients with dementia (including AD), with MCI due to AD, subjective cognitive decline	SLR-based and meta-analysis methods	No	No

Screening	▪ "Performing MMSE in patients with neurocognitive disorders is recommended for screening dementia and evaluating cognitive function. (Level High, grade Strong)"
Testing	▪ "CSF Aβ, total tau, and phosphorylated tau tests can increase the accuracy of the diagnosis of AD in patients with MCI or dementia. These tests can be considered for differential diagnosis of AD. (Level High, grade Weak)" ▪ "APOE genotyping can be considered as a diagnostic tool since it can be helpful in the diagnosis and prognostic evaluation of dementia due to AD in patients with MCI or dementia. (Level Moderate, grade Weak)" ▪ "Brain MRI (structural brain imaging) examination in patients with MCI or dementia is recommended since it can increase the sensitivity and accuracy of the diagnosis of AD by evaluating the degree of MTL atrophy as well as by excluding other causative diseases. (Level Moderate, grade Strong)" ▪ "Results of amyloid PET scans in patients with MCI or dementia can increase the diagnosis accuracy of AD. This test can be considered for the diagnosis of AD. (Level High, grade Weak)"
Diagnosis	▪ "Performing CDR in patients with neurocognitive disorders is useful in diagnosing dementia by distinguishing it from cognitively normal and MCI. It is recommended to perform CDR for dementia diagnosis. (Level Moderate, grade Strong)" ▪ "In the process of diagnosing dementia, performing MMSE may be considered to determine whether overall cognitive function of patients has reached the level of dementia. (Level High, grade Weak)" ▪ "The neurological examination is recommended for the differential diagnosis of dementia in patients with MCI or dementia. (Level Moderate, grade Strong)"
Monitoring	▪ "The elderly with SCD have a higher risk of progression to dementia (or AD dementia) in the future compared to those without SCD. Therefore, it is recommended to evaluate their clinical progress through periodic follow-ups every 1 or 2 years. (Level Moderate, grade Strong)"
Treatment	▪ N/A
Sponsorship/ Conflict of interest	▪ "The Executive Committee for Guideline Development of the Korean Dementia Association updated recent changes related to the diagnosis and evaluation of dementia in this revised guideline" ▪ The authors have no financial conflicts of interest

AA = Alzheimer's Association; Aβ = amyloid-beta; AD = Alzheimer's disease; APOE = apolipoprotein E; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; MTL = medial temporal lobe; NIA = National Institute on Aging; PET = positron emission tomography; SCD = subjective cognitive decline.

[a] Google Scholar citation count recorded as of July 13, 2022.

Table A-41. Practice Guidelines for the Diagnosis and Treatment of Alzheimer's Disease in a Managed Care Setting: Part I -- Early Detection and Diagnosis [13]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	1999	US	Patients with dementia (including AD)	Evidence-based approach (previous and existing guidelines), managed care experience, and experts' opinions	Likely	No

Screening	▪ "Screening for dementia will vary among MCOs and might include all patients ≥75, patients who complain of memory impairment, patients whose caregivers have observed memory impairment, or the screening questions suggested by the Agency for Health Care Policy and Research guidelines" ▪ "Patients with dementia are particularly prone to delirium, and some patients will continue to exhibit cognitive decline after successful treatment of a delirious episode, these patients should be evaluated for a dementia syndrome" ▪ "Depression may produce cognitive impairment or complaints of cognitive compromise and should be assessed as part of the evaluation of a patient with a potential dementia syndrome" ▪ "Treatment of depression in elderly individuals typically involves using a selective serotonin-reuptake inhibitor or a tricyclic antidepressant with few anticholinergic side effects, Patients may present with both dementia and depression and cognition may not improve following successful treatment of the depression syndrome; these patients should be further assessed for the etiology and management of their dementing disorder." ▪ "Identification of systemic abnormalities, such as hypothyroidism or vitamin B12 deficiency. should be followed by appropriate medical therapy. Many patients continue to decline despite these interventions and have the systemic disorder as a comorbid condition with AD" ▪ "Use the Mini-Mental State Examination (MMSE)" or equivalent mental status questionnaire to evaluate patients who are cognitively impaired" ▪ "Patients with abnormally low scores on the MMSE or who fail the expanded dementia screen should be evaluated to determine if they meet criteria for a dementia syndrome. These include the presence of a memory abnormality, and impairments in at least one additional cognitive domain that are acquired and produce occupational or social disability. Patients who perform normally on these exams, or who fail to meet criteria for dementia syndrome, but who are regarded as at risk because of positive responses on the initial screen should be reassessed annually"
Testing	▪ "Use the MMSE or equivalent mental status questionnaire to evaluate patients who are cognitively impaired – Some patients with suspected dementia syndromes may not score in the impaired range on the MMSE, The MMSE is particularly insensitive to mental status changes in patients with high premorbid intellectual function or high educational levels. An expanded examination with additional cognitive tests, such as the clock drawing test," or functional assessments such as the FAQ or PS-MS, may reveal abnormalities consistent with dementia syndrome. Neuropsychological assessment may assist in distinguishing mild dementia from changes associated with normal aging – Laboratory studies to detect potential etiologies of dementia and common comorbidities of dementia in the elderly should be obtained on all patients with dementia syndromes. Routine laboratory tests Include a complete blood count, serum electrolytes including calcium, liver function test, blood urea nitrogen and creatinine, thyroid stimulating hormone, serum vitamin B12 level, and a serological test for syphilis." ▪ "Patients meeting criteria for dementia without laboratory abnormalities should be evaluated for the diagnostic criteria for AD. These include the presence of a dementia syndrome that has been insidious in onset, gradual in progression, and present for greater than six months. In addition, there must be no focal neurological signs and no seizures or gait disturbances early in the clinical course. Patients with

	neurological or behavioral features suggestive of alternative diagnoses should not be given a diagnosis of AD." ▪ "Identification of a patient with AD should be followed by initiation of appropriate treatment (see accompanying treatment guidelines)." ▪ "Those who do not meet criteria for AD, particularly because they have focal neurological signs, gait disturbances, or seizures, should be assessed for other causes of dementia." ▪ "Patients who do not meet criteria for AD and do not meet criteria for neuroimaging, or whose brain imaging is normal or shows nonspecific brain atrophy, have an atypical dementia or an atypical form at AD" ▪ "Some patients with cerebrovascular disease have mixed AD and ischemic brain injury. This will likely be manifested by a progressive clinical syndrome consistent with AD, plus focal neurological dysfunction and a steadily progressive course. These patients may be candidates for AD pharmacotherapy."
Diagnosis	▪ N/A
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship / Conflict of interest	"The work of the Alzheimer's Disease Managed Care Advisory Council has been funded, in part, with an unrestricted educational grant from Pfizer Inc and Eisai Inc. Conflicts of interest were presented: ▪ Dr. Fillit was Corporate Medical Director for Medicare at NYLCare Health Plans, now a subsidiary of Aetna U.S. Healthcare, during the initial development of these guidelines. ▪ Dr. Cummings is supported by a NIA Alzheimer's Disease Research Center grant, an Alzheimer's Disease Research Center of California grant, and the Sidell-Kagen Foundation."

AA = Alzheimer's Association; AD = Alzheimer's disease; FAQ = Functional Activity Questionnaire; MCO = Managed Care Organization; MMSE = Mini-Mental State Examination; N/A = not applicable; NIA = National Institute on Aging; PS-MS = Physical Self-Maintenance Scale; US = United States.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-42. Clinical Practice Guideline on the Comprehensive Care of People with Alzheimer's Disease and other Dementias [51]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2011	Spain	Patients with AD, with MCI, suspected dementia (including AD)	Panel selection + SLR + evidence evaluation and grading + external reviewers	Unclear	Not applicable

Screening	▪ "The use of the Spanish standardized version of the MMSE or the MEC is recommended to screen dementia in individuals with cognitive complaints or advanced age in our medium (Grade A)" ▪ "Other short screening tests, such as the Pfeiffer test, the MIS, the 7-minute test, the clock test, the Eurotest or the T@M can also be recommended to screen dementia in individuals who are suspected of having cognitive impairment. (Grade B)" ▪ "The performance of a detailed neuropsychological assessment via specific tests is recommendable when there are differences between the clinical impression and the screening tests, diagnostic doubts or else when the complaints are limited to just one cognitive domain or evolve over a short period of time. (Grade D)"
Testing	▪ "Different biological and neuroimaging markers can be used to help predict the progression of MCI to dementia in a research context, but they cannot be recommended for use yet in normal clinical practice (Grade C)" ▪ "Performing genetic analyses to detect causal mutations is indicated in patients with AD and an autosomal, dominant family history of pre-senile onset (Grade C)"
Diagnosis	▪ "The determination of homocystein as a risk factor associated with cognitive impairment or AD is not recommended. (Grade D)" ▪ "The determination of the APOE genotype is not recommended in healthcare practice to diagnose AD (Grade A)" ▪ "The ^{123}I-FP-CIT SPECT is recommended to support the diagnosis for the differential diagnosis between DLB/ PDD and AD (Grade B)"
Monitoring	▪ N/A
Treatment	▪ "The use of AChE inhibitors to avoid or delay the progression of MCI to dementia is not currently recommended (Grade A)" ▪ "The use of NSAID, replacement therapy with estrogens, ginkgo biloba or vitamin E to avoid or delay the progression of MCI to dementia is not currently recommended. (Grade A)" ▪ "There is not enough evidence to recommend cognitive stimulation or physical exercise to avoid or delay the progression of MCI to dementia (Grade C)" ▪ "Treatment is recommended with ACE inhibitors (donepezil 5-10 mg/day, galantamine 16-24 mg/day or rivastigmine 6-12 mg/day oral/4.6-9.5 mg/day transdermal) in patients with mild or moderate AD (Grade A)" ▪ "Treatment with ACE inhibitors is recommended in patients with mild to moderate AD, to manage the cognitive and functional symptoms, and to manage behavioral alterations (Grade A)" ▪ "The addition of memantine to donepezil is not recommended to treat patients with mild to moderate AD. (Grade B, good clinical practice)" ▪ "Hormonal therapies are not recommended as treatment of AD (Grade A)" ▪ "Neither ibuprofen, indometacine nor low doses of naproxen are recommended to treat AD (Grade A)" ▪ "Piracetam, Selegiline, Ibedenone, or propentofylline are not recommended to treat AD (Grade A)" ▪ "Dihydroergotoxine mesylate is not recommended to treat AD or VD (Grade B)"

Sponsorship / Conflict of interest	▪ "Declaration of interest was presented in Appendix 5 and includes financial support from pharmaceutical companies"

AA = Alzheimer's Association; ACE = angiotensin-converting enzyme; AChEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; APOE = apolipoprotein E; DLB = dementia with Lewy bodies; ^{123}I-FP-CIT SPECT= iodine I 123–radiolabeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single-photon emission computerized tomography; MCI = mild cognitive impairment; MIS = Memory Impairment Screen; MMSE = Mini-Mental State Examination; NIA = National Institute on Aging; NSAID = nonsteroidal anti-inflammatory drug; PDD = Parkinson's disease dementia; VD = vascular dementia.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-43. Dementia: Assessment, Management and Support for People Living With Dementia and Their Carers [11]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2018	UK	Suspected AD, Patients with AD	Multidisciplinary guideline committee + research evidence reviews	No	No

Screening	▪ N/A
Diagnosis and testing	▪ "When using cognitive testing, use a validated brief structured cognitive instrument such as: the 10-point cognitive screener (10-CS), the 6-item cognitive impairment test (6CIT), the 6-item screener, the Memory Impairment Screen (MIS), the Mini-Cog, and Test Your Memory (TYM)" in initial assessment or if dementia is still suspected. ▪ "If AD is suspected, include a test of verbal episodic memory in the assessment" ▪ "If the diagnosis is uncertain, and Alzheimer's disease is suspected, consider either: - FDG-PET (fluorodeoxyglucose-positron emission tomography-CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable; or - Examining cerebrospinal fluid for either total tau or total tau and phosphorylated-tau 181; and either amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40." ▪ "Do not rule out dementia solely because the person has a normal score on a cognitive instrument" ▪ "Diagnose a dementia subtype (if possible) if initial specialist assessment (including an appropriate neurological examination and cognitive testing) confirms cognitive decline and reversible causes have been ruled out" ▪ "Offer structural imaging to rule out reversible causes of cognitive decline and to assist with subtype diagnosis, unless dementia is well established and the subtype is clear" ▪ "Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans" ▪ "Do not use Apolipoprotein E genotyping or electroencephalography to diagnose Alzheimer's disease" ▪ "Be aware that young-onset Alzheimer's disease has a genetic cause in some people" ▪ "When taking a history from someone who knows the person with suspected dementia, consider supplementing this with a structured instrument such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or the Functional Activities Questionnaire (FAQ)" ▪ "When assessing the severity of Alzheimer's disease and the need for treatment, healthcare professionals should not rely solely on cognition scores in circumstances in which it would be inappropriate to do so" ▪ "Amyloid imaging techniques have been licensed for use in the UK, and new evidence is available for cerebrospinal fluid examination"
Monitoring	▪ "Do not stop AChE inhibitors in people with Alzheimer's disease because of disease severity alone" ▪ "Memory services and equivalent hospital- and primary-care-based multidisciplinary dementia services should offer a choice of flexible access or prescheduled monitoring appointments"

Treatment	▪ "The three AChE inhibitors—donepezil, galantamine, and rivastigmine—as monotherapies are recommended as options for managing mild to moderate Alzheimer's disease" ▪ "Memantine monotherapy is recommended as an option for managing Alzheimer's disease" ▪ "Combination therapy is a consideration" ▪ "Do not offer cognitive training to treat mild to moderate Alzheimer's disease" ▪ "Do not offer interpersonal therapy to treat the cognitive symptoms of mild to moderate Alzheimer's disease" ▪ "Do not offer non-invasive brain stimulation (including transcranial magnetic stimulation) to treat mild to moderate Alzheimer's disease, except as part of a randomized controlled trial" ▪ "Do not offer the following specifically to slow the progress of Alzheimer's disease, except as part of a randomized controlled trial: diabetes medicines, hypertension medicines, statins, non-steroidal anti-inflammatory drugs, including aspirin"
Caregiver policies	▪ "Offer carers of people living with dementia a psychoeducation and skills training intervention" ▪ "Additional NICE guidelines are available on the transition to different care settings"
Sponsorship / Conflict of interest	▪ This guideline was developed by NICE

AA = Alzheimer's Association; AChE = acetylcholinesterase; AD = Alzheimer's disease; CSF = cerebrospinal fluid; FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography; MIS = Memory Impairment Screen; N/A = not applicable; NIA = National Institute on Aging; NICE = National Institute for Health and Care Excellence; SPECT = single-photon emission computerized tomography; TYM = Test Your Memory; UK = United Kingdom.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-44. National Clinical Guideline on Dementia and Medicine [52]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2018	Denmark	Persons with dementia (including AD)	Workgroup	Not discussed	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ N/A					
Treatment	▪ "It is good practice to consider a break in treatment in terms of discontinuation of dementia drugs during clinical observation for persons with very severe dementia. (Good practice)" ▪ "Discontinue antipsychotic medication (as a general rule with tapering) in persons with dementia in long-term (> 3 months) treatment (Strong recommendation)" ▪ "Consider offering melatonin to persons with dementia in the event of significant difficulty sleeping and/or circadian rhythm disorders. The treatment must be in addition to the non-pharmacological measures (Weak recommendation)" ▪ "Consider offering low-dose mirtazapine or mianserine to persons with dementia in the event of significant difficulty sleeping and/or circadian rhythm disorders, where treatment with approved drugs is inappropriate. The treatment must be in addition to the non-pharmacological measures. (Weak recommendation)" ▪ "Consider discontinuing use of antidepressants in persons with dementia without any known affective disorder who have been undergoing treatment for > 6 months. (Weak recommendation)" ▪ "It is good practice to refrain from or discontinue treatment with urological antispasmodics with an anticholinergic effect in persons with dementia (Good practice)" ▪ "It is good practice to consider reducing (e.g., in the form of fewer administrations) or pausing treatment with paracetamol with a view to discontinuation under clinical observation if it is uncertain whether the patient is experiencing pain and/or an effect of ongoing paracetamol treatment. (Good practice)" ▪ "It is good practice to consider reducing the dose of opioids with a view to discontinuation under clinical observation if it is uncertain whether the patient is experiencing pain and/or an effect of ongoing opioid treatment (Good practice)" ▪ "It is good practice to pursue the existing recommended treatment targets for persons with dementia aged > 80. (Good practice)"					
Sponsorship / Conflict of interest	▪ "The guideline was prepared under the auspices of the Danish Health Authority"					

AA = Alzheimer's Association; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-45. National Clinical Guideline for Diagnosis of Mild Cognitive Impairment and Dementia [15]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2018	Denmark	Patients with MCI or dementia	Workgroup	Not discussed	No

Screening	▪ N/A
Diagnosis and testing	▪ "Use a brief cognitive test as part of a basic clinical assessment of MCI or dementia in order to achieve a systematic, structured assessment of the level of cognitive functioning (Strong recommendation)" ▪ "Offer structural imaging of the brain in connection with the basic clinical assessment of suspected MCI or dementia – both to exclude other causes of cognitive impairment and to help to establish the subtype dementia (Strong recommendation)" ▪ "Consider a systematic assessment of activities of daily living as part of a basic clinical assessment of MCI or dementia. Where appropriate, choose an ADL (IADL) scale (Weak recommendation)" ▪ "Only after careful consideration use biomarkers for Alzheimer's disease as part of an assessment of suspected MCI, as the specificity of these biomarkers is relatively low, entailing many false positive cases. Biomarkers may be used in situations where in consultation with a patient with MCI it is considered crucial to identify the underlying cause of the cognitive problems. (Weak recommendation)" ▪ "In the event of continued uncertainty regarding a dementia diagnosis following a basic clinical assessment involving structural imaging of the brain, consider offering an examination of biomarkers for Alzheimer's disease based on analysis of the cerebrospinal fluid or amyloid imaging in order to clarify whether AD may be the cause of dementia (Weak recommendation)" ▪ "The working group recommends that a neuropsychological assessment be carried out by neuropsychologists or equivalent professionals with relevant training (Strong recommendation)" ▪ "In the event of continued uncertainty regarding the subtype of dementia following a basic clinical assessment and possibly neuropsychological assessment, offer functional imaging (18F-FDG PET) in order to clarify whether AD may be the cause of dementia (Strong recommendation)"
Monitoring	▪ N/A
Treatment	▪ N/A
Sponsorship / Conflict of interest	▪ "The guideline was prepared under the auspices of the Danish Health Authority."

18F-FDG-PET = 18F-fluorodeoxyglucose-Positron emission tomography; AA = Alzheimer's Association; AD = Alzheimer's disease; ADL = activity of daily living; IADL = Instrumental Activities of Daily Living; MCI = mild cognitive impairment; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-46. Japanese Society of Neurology. Dementia Disease Treatment Guidelines – Clinical Practice Guideline for Dementia 2017 [53]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2017	Japan	Patients with dementia (AD), with MCI, suspected MCI/AD	Expert committee + SLR + evidence evaluation + external reviewers	No	Discussed

Screening	▪ "As a useful scale for evaluating cognitive impairment in dementia, the Mini Mental State Examination (MMSE) is widely used internationally in clinical setting and in research. It is desirable to add necessary tests according to the subject evaluated, the purpose and the environment, and interpret the results taking into account the background and condition of each patient (Level C)"
Testing	▪ "Many large-scale prospective studies have provided evidence for decreased Aβ42 level and increased total tau or phosphorylated tau level in cerebrospinal fluid (CSF) as biomarkers for the diagnosis and prediction of onset of Alzheimer's disease dementia. The NIA-AA criteria recommend use of these biomarkers for research in AD dementia and MCI, while the IWG-2 advancing research diagnostic criteria for AD dementia include these markers as tests required for diagnosis (Level A)" ▪ "Routine testing APOE gene polymorphism is not recommended. Explanations to patients and obtaining consent, support by genetic counseling, and conducting genetic testing at specialized facilities are recommended for genetic testing (Level C)" ▪ "DSM-5 is recommended for clinical diagnosis of AD dementia. (Level A)" ▪ "Abnormal cerebrospinal fluid levels of Aβ42, phosphorylated tau, and total tau; presence of APOE gene ε4 polymorphism; and abnormal findings on amyloid PET and 18FDG-PET have been considered to be useful biomarkers for predicting conversion from mild cognitive impairment (MCI) to dementia. (Level B)" ▪ "MMSE is not adequate to detect mild cognitive impairment (MCI). Therefore, the MoCA-J is recommended. Instead of MMSE alone, adding slightly complex memory tasks such as sentence memorization facilitates the diagnosis of amnestic MCI (Level C)"
Diagnosis	▪ "MCI is originally a concept centered on memory impairment. Similar concepts are also found in Clinical Dementia Rating (CDR) 0.5; mild neurocognitive disorder in DSM-5; and mild cognitive disorder in ICD-10." ▪ "The characteristic image findings of AD dementia are as follows: (1) CT and MRI depicting atrophy in medial temporal lobe, especially the hippocampus; (2) SPECT and FDG-PET showing decreased blood flow and glucose metabolism in bilateral temporal/parietal lobes and posterior cingulate gyrus, (3) amyloid PET indicating amyloid deposition in frontal lobe, posterior cingulate gyrus, and anterior wedge (Level A)" ▪ "The positive rates of amyloid PET examination are approximately 98% for AD dementia, approximately 68% for MCI, and 33% in healthy older persons. Amyloid PET negativity is useful for differentiating non-AD dementia. In the NIA-AA criteria and IWG-2 advancing research diagnostic criteria for AD dementia, amyloid PET examination is required as a biomarker of brain amyloid deposition. Participation in clinical studies requires consent, and general clinical use should conform to appropriate guidelines. Amyloid PET examination is not covered by health insurance in Japan (Level A)"
Monitoring	▪ N/A
Treatment	▪ "The currently available drugs for improving cognitive function in AD dementia are the 3 ChEIs: donepezil, galantamine, and rivastigmine, as well as the NMDA receptor antagonist memantine. Scientific evidence of efficacy has been demonstrated for both classes of drugs, and their use is recommended (Level 1A)" ▪ "In patients with AD dementia, if hallucination and delusion, symptoms do not improve by anti-dementia drugs and the above methods, consider using atypical antipsychotics such as risperidone, olanzapine, quetiapine, and aripiprazole. Yokukansan may also be considered (Level 2C)"

	▪ "The therapeutic effects of non-pharmacological therapies depend largely on the patient's preference and the capability of the practitioner. Therefore, it is not meaningful to decide whether a therapy is superior or inferior. It is important that the patient participate willingly in therapy, and it is desirable to use multiple therapies as needed (Level C)"
Risk management	▪ "Control of hypertension, diabetes, dyslipidemia and other risk factors, as well as continued practice of moderate exercise are recommended. There is no sufficient evidence that anti-dementia drugs should be used for the purpose of preventing progression to dementia in MCI (Level 2C)."
Sponsorship / Conflict of interest	▪ "Funds necessary for preparation of this guideline were borne by the Japanese Society of Neurology." ▪ "This guideline was prepared based on appropriate conflict of interest management according to the "Regulations related to preparation of Japanese Society of Neurology clinical practice guideline", "Guide to preparation of Japanese Society of Neurology clinical practice guideline" and "Rules for establishment and operation of Japanese Society of Neurology conflict of interest committee." ▪ "Enterprises that declared conflict of interest were provided."

AA = Alzheimer's Association; AD = Alzheimer 's disease; APOE = apolipoprotein E; CDR = Clinical Dementia Rating; ChEI = cholinesterase inhibitor; CSF = cerebrospinal fluid; CT = computed tomography; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; FDG-PET = Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography; ICD-10 = *International Statistical Classification of Diseases, Tenth Revision*; IWG-2 = International Working Group; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MoCA- J = Montreal Cognitive Assessment-Japanese version; MRI = Magnetic Resonance Imaging; N/A = not applicable; NIA = National Institute on Aging; NIA-AA = National Institute on Aging and Alzheimer's Association; NMDA = *N*-Methyl-D-aspartate; PET = positron emission tomography; SPECT = Single-Photon Emission Computed Tomography.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-47. Appropriate Prescribing of Psychotropic Medication for Non-Cognitive Symptoms in People with Dementia [54]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2019	Ireland	People with AD	Search of existing guidelines + SLR developed by a workgroup	Not discussed	No

Screening	▪ N/A
Testing	▪ "Prior to considering any psychotropic medication in a person with dementia, a comprehensive assessment should be performed, by an appropriately trained healthcare professional. (QoE: Low; SoR = Strong)"
Diagnosis	▪ N/A
Monitoring	▪ N/A
Treatment	▪ "Non-pharmacological interventions should be used initially to treat non-cognitive symptoms in a person with dementia, unless there is severe distress, or an identifiable risk of harm to the person and/or others (QoE: High, SoR: Strong)" ▪ "Antipsychotic medication should be used with caution and only in cases where there is aggression, agitation or psychosis that either causes an identifiable risk of harm to the person with dementia and/or others or causes severe distress to the person (QoE: High; SoR: Strong)" ▪ "People with AD, vascular dementia or mixed dementias with mild to moderate non-cognitive symptoms should NOT be prescribed antipsychotic medication due to the increased risk of cerebrovascular adverse events and death (QoE: High; SoR: Strong)" ▪ "People with AD, VD, mixed dementias, dementia with Lewy bodies, or PD dementia, with severe non-cognitive symptoms, causing severe distress, or an identifiable risk of harm to the person and/or others, may be offered antipsychotic medication, where appropriate (QoE: Moderate; SoR: Conditional)" ▪ "Acetylcholinesterase inhibitors are indicated for cognitive enhancement in people with mild to moderate AD but are NOT recommended solely for the treatment of non-cognitive symptoms in a person with AD. (QoE: High; SoR: Strong)" ▪ "Memantine is indicated as a cognitive enhancer in people with moderate to severe AD, Parkinson's disease dementia and dementia with Lewy bodies, but it is NOT recommended to be prescribed solely for the treatment of non-cognitive symptoms in a person with dementia. (QoE: Moderate; SoR: Strong)" ▪ "In people with mild to moderate dementia, and mild to moderate depression and/or anxiety, psychological treatments should be considered. Antidepressants may be considered to treat severe comorbid depressive episodes in people with dementia, or moderate depressive episodes that have not responded to psychological treatment (QoE: Moderate, SoR: Conditional)"
Sponsorship / Conflict of interest	▪ "This National Clinical Guideline has been developed by a guideline development group convened by the National Dementia Office, to fulfil a priority action point of the National Dementia Strategy Implementation plan"

AA = Alzheimer's Association; AD = Alzheimer's disease; N/A = not applicable; NIA = National Institute on Aging; PD = Parkinson's disease; QoE = quality of evidence; SoR = strength of recommendation; VD = vascular dementia.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-48. Clinical Practice Guidelines: Management of Dementia [55]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2021 (update 2009 version)	Malaysia	Adults with dementia or MCI	SLR-based, developed by a multidisciplinary team	No	No

Screening	▪ "The evidence on routine screening for cognitive impairment among asymptomatic community-dwelling adults age 65 and older is insufficient to determine the balance of its benefits and harms" ▪ "The evaluation of dementia should be targeted at patients who present with memory complaints (by patients themselves and/or carer), have clinical suspicion of cognitive impairment or are at increased risk for dementia as well as elderly patients who have questionable mental capacity" ▪ "Laboratory tests for basic dementia screening are indicated to exclude dementia-mimicking conditions"
Testing	▪ N/A
Diagnosis	▪ "The diagnosis ▪ ▪ ▪ t of dementia should be based on detailed history and physical examination, and supported by cognitive, functional and behavioral evaluation." ▪ Common cognitive assessment tools in clinical practice: AD8 Dementia Screening Interview, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Mini–Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Mini-Cog, etc. ▪ "Structural neuroimaging (computed tomography or magnetic resonance imaging) should be done in evaluation of dementia to exclude reversible causes of cognitive decline and other intracranial pathology." ▪ "Electroencephalogram should be considered in rapidly progressive cognitive decline and atypical features of dementia." ▪ "Diagnosis of dementia should be made based on DSM-5 or ICD-10."
Monitoring	▪ "Follow-up of patients with MCI is done with serial assessment to monitor their cognitive status"
Treatment	▪ "Donepezil should be offered in AD of all severity." ▪ "Rivastigmine is an option in mild to moderate AD." ▪ "Memantine may be considered in moderate to severe AD as monotherapy or in combination with AChEIs." ▪ "Antipsychotics may be considered for behavioral and psychological symptoms in people with dementia (PWD) where there is a risk of harming themselves or others." ▪ "Antidepressants: – may be considered for PWD who have agitation – may be prescribed for PWD with pre-existing severe mental health problem" ▪ "The use of anticholinergic medications in dementia should be done cautiously with regular review of indication and deprescribed whenever possible." ▪ "To improve cognitive function in mild to moderate dementia, cognitive stimulation therapy and physical activity should be offered." ▪ "In people with dementia having behavioral and psychological symptoms: – explore and address possible clinical or environmental causes/triggering factors – offer psychosocial and environmental interventions as initial and ongoing treatment: ▪ psychological intervention for depressive symptoms and/or anxiety

	▪ personalized and tailored activities for agitation and aggression” ▪ “There is insufficient evidence to recommend the use pharmacological intervention in MCI” ▪ “There is insufficient evidence to recommend the use of traditional and complementary medicine in the treatment of dementia”
Risk reduction	▪ “Risk reduction strategies should be advocated to reduce the risk of developing cognitive decline and/or dementia. These include: – Physical activity – Tobacco cessation – Interventions for alcohol use disorders – Management of hypertension – Management of diabetes”
Sponsorship / Conflict of interest	▪ “The development of the CPG on Management of Dementia (Third Edition) was supported financially in its entirety by the Ministry of Health Malaysia” ▪ “None held shares in pharmaceutical firms or acts as consultants to such firms”

AA = Alzheimer’s Association; AChEI = acetylcholinesterase inhibitor; AD = Alzheimer’s disease; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ICD-10 = *International Statistical Classification of Diseases, Tenth Revision*; N/A = not applicable; NIA = National Institute on Aging; PWD = people with dementia.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-49. Singapore Ministry of Health. Functional Screening for Older Adults in the Community [56]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2010	Singapore	Asymptomatic older adults	Existing evidence-base	Not discussed	No
Screening	▪ "Currently, community screening or routine screening in the primary care setting for dementia in asymptomatic older persons is not recommended. (Grade C, level 2+)"					
Testing	▪ N/A					
Diagnosis	▪ N/A					
Monitoring	▪ N/A					
Treatment	▪ N/A					
Sponsorship / Conflict of interest	▪ Not discussed					

AA = Alzheimer's Association; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-50. A Guide to Dementia Diagnosis and Treatment [57]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2011	US	Suspected AD, with AD	Two acclaimed American Geriatrics Society guidelines - based	No	No

Screening	▪ N/A
Diagnosis and testing	"Evaluation: ▪ History and comprehensive physical and neurologic examination ▪ Assess functional status ▪ Evaluate mental status for attention, immediate and delayed recall, remote memory, executive function, depression. Useful screening tests are the Mini-Cog, number of animals named in 1 minute (18 is average; less than 10 markedly abnormal), MMSE, Geriatric Depression Scale, Patient Health Questionnaire-9. If Mini-Cog is positive, use MMSE (www.minimental.com) or Montreal Cognitive Assessment." "Neuroimaging (MRI or CT of the brain): ▪ May detect the 5% of patients with clinically significant structural lesions that otherwise would be missed. ▪ FDG-PET scans approved by Medicare for atypical presentation of AD. Clinical features distinguishing AD: ▪ Memory, language, visual-spatial disturbances, indifference, delusions, agitation"
Monitoring	▪ N/A
Treatment	▪ "Nonpharmacologic approaches: music, light exercise, pet therapy" ▪ "Pharmacologic approaches: – Mild to moderate AD treatment with cognitive enhancer: cholinesterase inhibitors – Memantine (Namenda) demonstrated modest efficacy compared with placebo in moderate to severe AD as monotherapy and when combined with donepezil – Stopping medication can lead to rapid decline – Treatment of agitation: antipsychotic options"
Cognitive test information	▪ "Information to describe the mini-Cog screen for Dementia, Geriatric Depression Scale, Reisburg Functional Assessment Staging Scale"
Sponsorship/ Conflict of interest	▪ The American Geriatrics Society (AGS) makes this convenient guide. The AGS is a nationwide, non-profit association of healthcare professionals.

AA = Alzheimer's Association; AD = Alzheimer's disease; CT = computed tomography; FDG = 18fluorodeoxyglucose; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; N/A = not applicable; NIA = National Institute on Aging; PET = positron emission tomography; US = United States.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-51. Singapore Ministry of Health. Dementia [14]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2013	Singapore	Suspected cognitive impairment or dementia, patients with AD	Workgroup	Unlikely	No

Screening	▪ "Individuals who should be evaluated for dementia include those with progressive cognitive or behavioral complaints suggestive of dementia, as well as patients who arouse the physician's or caregiver's suspicion of cognitive impairment despite absence of complaints. (Grade C, level 2+).
Testing	▪ "Assessment of dementia should be done via a comprehensive evaluation. This approach will aim to diagnose dementia early, assess complications of dementia and establish the cause of the dementia. (GPP)" ▪ "In individuals with suspected cognitive impairment, diagnosis should be made using the DSM-IV criteria for dementia with history from a reliable informant. This should be supplemented by an objective approach with bedside cognitive tests and/or neuropsychological assessment (Grade B, level 2++)" ▪ "Genetic testing should not be routinely carried out in the clinical evaluation of dementia (GPP)" ▪ "Routine testing of APOE gene is not recommended in dementia diagnosis and in tailoring dementia risk reduction (Grade B, Level 2++)"
Diagnosis	▪ "Clinicians should make a diagnosis of a specific type of dementia based on available criteria. A number of well-validated clinical criteria may be used for the various types of dementia (Grade B, level 2++)"
Monitoring	▪ N/A
Treatment	▪ "AChE-Is (donepezil, galantamine or rivastigmine) should be considered for the management of patients with mild to moderate AD (Grade A, level 1++)" ▪ "AChE-Is may be considered for the management of moderately severe to severe AD (Grade A, level 1+)" ▪ "Where tolerated, AChE-Is should be titrated to recommended doses (5-10 mg/day donepezil; 16-24 mg/day galantamine; 6-12 mg/day oral and 4.6-9.5 mg/24 hr transdermal rivastigmine), which have been shown to confer greater benefit compared with lower doses (Grade A, level 1++)" ▪ "N-methyl-d-aspartate antagonists (memantine) may be considered for the management of moderately severe to severe Alzheimer's disease, either alone or in combination with AChE-Is (Grade A, Level 1+)" ▪ "Memantine may be considered for treatment of mild to moderate AD, if AChE-I therapy is contra-indicated, not tolerated or if there is disease progression despite an adequate trial of AChE-I (Grade A, level 1+)" ▪ "Prednisolone is not recommended for the prevention of cognitive decline in AD (Grade B, Level 1+)" ▪ "Estrogen is not recommended for the prevention of cognitive decline in women with AD (Grade A, Level 1++)" ▪ "Selegiline is not recommended for the treatment of core or associated symptoms in AD (Grade A, Level 1+)" ▪ "High dose vitamin E (in excess of 400 IU per day) is not recommended for the prevention or treatment of AD (Grade B, Level 1+)" ▪ "Statin therapy is not recommended for the prevention or routine treatment of ad (Grade A, Level 1++)" ▪ "Rosiglitazone is not recommended as monotherapy or as adjunctive therapy to AChE-Is in mild to moderate AD (Grade A, Level 1+)"
Sponsorship / Conflict of interest	▪ These guidelines have been produced by a committee appointed by the Ministry of Health Singapore. ▪ Conflict of interest was not discussed.

AA = Alzheimer's Association; AChE-I = acetylcholinesterase inhibitor; AD = Alzheimer's disease; APOE = apolipoprotein E; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; GPP = good practice point; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-52. Dementia. Diagnosis and Treatment Guideline [58]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2012	US	Suspected AD or MCI, patients with dementia (including AD), patients with MCI	Systematic literature search, critical appraisal, and evidence synthesis by a workgroup	Not discussed	No

Screening	▪ "Universal screening for dementia is not recommended"
Testing	▪ "Three of the studies used a clinical diagnosis and one used neuropsychological testing as the gold standard for diagnosing Alzheimer's and MCI. Results from these studies suggest that the MoCA has a higher sensitivity and lower specificity than the MMSE for detecting MCI and Alzheimer's"
Diagnosis	▪ "A diagnosis of dementia should be made only after a thoughtful assessment to exclude other causes. Such an assessment includes detailed history taking, cognitive- and mental-state examination, physical examination, and a review of medications." ▪ "A diagnosis of dementia cannot be made solely on the basis of the results of any of the cognitive assessment tools, and it requires that functional status correlates well with the results" ▪ "For the majority of cases, a dementia diagnosis can be made from the patient's history, so imaging is not necessary. If a patient has memory loss plus warning signs, then imaging is indicated"
Monitoring	▪ Medication monitoring: "6–8 weeks after initiating medications, and every 6 months thereafter" ▪ Progression monitoring: – "Every 6 months, to assess progression with patient and caregiver. These visits can be by phone or e-mail" – "Patients should be seen in person at least annually"
Treatment	▪ "MCI: Medications are not recommended. Meticulous review of current medication list is recommended to determine any medications that may be clouding cognition or may be eligible for a trial "holiday"." ▪ "Results from several RCTs suggest that in patients with MCI, acetylcholinesterase inhibitors do not significantly improve cognitive function or reduce the rate of progression from MCI to dementia" ▪ "Early to mid-stage dementia: 1st line: Donepezil. 2nd line: Galantamine, Rivastigmine" ▪ "Treatment for behavioral and psychological symptoms of dementia were recommended"
Sponsorship / Conflict of interest	▪ "The Dementia Guideline development team included representatives from the following specialties: behavioral health, family medicine, neurology, nursing home and hospice services, and pharmacy."

AA = Alzheimer's Association; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; N/A = not applicable; NIA = National Institute on Aging; RCT = randomized controlled trial; US = United States.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-53. Dementia: Diagnosis & Management in General Practice [10]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2019	Ireland	Suspected or with dementia (including AD)	Evidence-based, SLR review	Unlikely	No

Screening	▪ N/A
Diagnosis and Testing	▪ "Investigations in Primary Care – Bloods – FBC, ESR, U&E, TFTs, Glucose, Lipids, Calcium & B12: to detect co-morbid conditions such as anemia due to B12 deficiency or renal disease and to exclude reversible causes. – General Medical Investigations: Chest X-Ray and MSU if clinically indicated; ECG (Cholinesterase inhibitors may induce sinus bradycardia and aggravate pre-existing sinus node disease and AV block)" ▪ "Investigations in Secondary Care – CT Scan (to exclude intracranial lesions, cerebral infarction and hemorrhage, extra and subdural hematoma, normal pressure hydrocephalus) – MRI Scan (a sensitive indicator of cerebrovascular disease) – Single-photon emission tomography (to assess regional blood flow) and dopamine scan to detect Lewy Body disease. – Carotid ultrasound (if large vessel atherosclerosis suspected) – EEGs are not part of routine workups. – The use of positron emission tomography (PET) and other functional neuroimaging techniques, to assist in the differential diagnosis and subtyping of dementia, is an area of investigation occasionally utilized by specialists assessing complex cases." ▪ "Review medications associated with an increased risk of confusion" ▪ "Cognitive function testing adds further evidence to the clinical assessment and investigations"
Monitoring	▪ "Regular physical examination should focus on hearing, vision, nutrition, bowel and bladder function. In the later stages of dementia dental hygiene may be poor, leading to gum disease, tooth decay, infection and difficulty eating. Dental review both early and throughout the illness may help to address these problems (level 5)." ▪ "Immunization guidelines recommend flu vaccine administration for residents of nursing homes and long stay institutions, as well as in persons aged 65 years and over (level 5)." ▪ "Along with this regular review, a risk assessment should be performed, to detect risk to self or others."
Treatment	▪ "Acetylcholinesterase Inhibitors (AChEIs): options for managing mild to moderate AD. Evidence has shown that AChEIs are of some benefit in terms of improvements in cognition and ADLs (Level 5). Effect sizes are modest." ▪ "Memantine: may be considered as the person's dementia progresses. It is recommended for the management of moderate AD for patients who are intolerant of or have a contraindication to AChEIs and for severe AD. It may be used alone or in combination with cholinesterase inhibitors (Level 1)." ▪ "Guidelines recommend that non-pharmacological strategies be used first-line for BPSD, unless the person with dementia poses a significant risk to themselves or others (level 1)."
Sponsorship / Conflict of interest	▪ The work was developed by ICGP Quality and Safety in Practice Committee ▪ Conflict of interest was not reported

AA = Alzheimer's Association; AChEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; ADL = activity of daily living; AV = atrioventricular; BPSD = behavioral and psychological symptoms of dementia; CT = computed tomography; ECG = electrocardiogram; EEG = electroencephalogram; ESR = erythrocyte sedimentation rate; FBC = full blood count; MRI = magnetic resonance imaging; MSU = mid-stream urine; N/A = not applicable; NIA = National Institute on Aging; PET = positron emission tomography; TFT = thyroid function test; U&E = urea and electrolytes.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-54. Haute Autorité de Santé. Alzheimer's Disease and Related Conditions: Management of Behavioral Disorders [59]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2009	France	Patients with AD	Workgroup	Not clear	No
Screening	▪ N/A					
Testing	▪ N/A					
Diagnosis	**"The recommended approach is as follows:** ▪ Assess the degree of urgency, danger or functional risk in the short term for the patient and for others; ▪ Talk to and examine the patient and talk to family and friends (how long the behavior has been going on, circumstances in which it occurs); ▪ Investigate an environmental cause, somatic cause (urine retention, infection, acute pain, fecaloma, etc.) or psychiatric cause (severe anxiety) to be treated as a priority, together with iatrogenic factors; ▪ Undertake a more in-depth clinical assessment of the behavior, the extent to which it occurs and its implications; ▪ Repeat this etiological review at different points of the patient's management if the problem persists ▪ In the event of any problems persisting after several days, they should be assessed using a tool such as the neuropsychiatric inventory (NPI)."					
Monitoring and preventing	"The prevention of BDs should be based on a strategy developed and adjusted to suit each individual patient. General preventive action includes: ▪ Providing information and support to family carers; ▪ Training of health professionals; ▪ Ensuring that the patient's environment is as well-suited as possible to his condition."					
Treatment	▪ "Priority areas for investigation are somatic and psychiatric causes, trigger factors and predisposing factors." ▪ "Appropriate non-pharmacological methods should be used as the first-line treatment for BDs." ▪ "Psychotropic agents are not effective in preventing the onset of BDs." ▪ "Treatment with psychotropic agents must not be prescribed unless an assessment has been carried out in cases of refusal to cooperate, shouting and wandering."					
Sponsorship / Conflict of interest	The guideline was developed by the French Health Authority					

AA = Alzheimer's Association; BD = behavior disorder; N/A = not applicable; NIA = National Institute on Aging.

[a] Google Scholar citation count recorded as of July 14, 2022.

Table A-55. Practical Guide for Alzheimer Professionals (Reina Sofia Foundation) [60]

Google Scholar citations[a]	Year published	Country	Target population	Method of developing guidelines	Manufacturer engagement	Cites 2011 NIA and AA guidelines
None	2012	Spain	Patients with AD, suspected AD	Workgroup	Unclear/Indirect	Yes

Screening	▪ Pfeiffer Questionnaire (Short Portable Mental Status Questionnaire, SPMSQ), Clock Drawing Test (CDT), 7 Minute Screen (7MT)
Diagnosis and testing	▪ "Cognitive assessments: Global Deterioration Scale (GDS), MMSE, Severe MMSE, Clock Drawing Test (CDT), Pfeiffer Questionnaire Short Portable Mental Status Questionnaire (SPMSQ), 7 Minute Screen (7MT), cognitive Alzheimer's Disease Assessment Scale (ADAS), CAM-COG (subtest of the CAMDEX-R Cambridge exploration test, reviewed for the evaluation of old age mental disorders), and Hopkins Verbal Learning Test (HVLT)." ▪ "Behavioral evaluation: Neuropsychiatric Inventory (NPI), non-cognitive Alzheimer's Disease Assessment Scale (ADAS)." ▪ "Emotional evaluation: Geriatric Depression Scale, Cornell Scale for Depression in Dementia." ▪ "Evaluation of other components: Alzheimer's Disease–Related Quality of Life (ADRQL)." ▪ "Detailed list of trials regarding biomarker investigation."
Monitoring	▪ "…Changing treatments as applicable. ▪ Informing the infirmary of changes to medication for immediate application" ▪ "Prepare and update his or her clinical record" ▪ "Refer residents to a hospital when deemed necessary" ▪ "Carry out control and monitoring activities with each resident…"
Treatment	▪ Non-pharmacological therapies suggested from the neuropsychology area, occupational therapy area, social work area ▪ "Pharmaceutical: cholinesterase inhibitors: donepezil, rivastigmine, galantamine, and memantine."
Sponsorship / Conflict of interest	"This guide has been prepared by professionals working in the Care Unit at the Reina Sofia Foundation's Alzheimer Centre." Conflict of interest information was not presented.

7MT = 7 Minute Screen; AA = Alzheimer's Association; ADAS = Alzheimer's Disease Assessment Scale; ADRQL = Alzheimer's Disease–Related Quality of Life; CAM-COG = Cambridge Cognition Examination; CDT = Clock Drawing Test; GDS = Global Deterioration Scale; HVLT = Hopkins Verbal Learning Test; MMSE = Mini-Mental State Examination; N/A = not applicable; NIA = National Institute on Aging; NPI = Neuropsychiatric Inventory; SPMSQ = Short Portable Mental Status Questionnaire.

[a] Google Scholar citation count recorded as of August 2, 2022.

A4. GUIDELINES SUMMARY FOR HIGHLY CITED GUIDELINES AND GUIDELINES PUBLISHED BEFORE 2018

The 2 sections below present summaries of the recommendations for screening, diagnosis, treatment, and monitoring in the clinical practice guidelines identified in the systematic searches performed for this review for 2 subsets of guidelines: (1) the recommendations from the most highly cited guidelines using Google Scholar and (2) the recommendations from clinical practice guidelines published before 2018. A summary of the recommendations from the clinical practice guidelines published in 2018 and more recently is presented in the Results section of this article's main text. In addition, changes in guidelines that were observed between the pre-2018 guidelines and the post-2018 guidelines are summarized in the Discussion section of this article's main text.

A4.1 Most Highly Cited Guidelines

Four guidelines have been cited more than 1,000 times in Google scholar [8,20-22] as a metric for reach and influence. It should be noted that, while the number of Google scholar citations is 1 metric to assess potential impact and reach of a given guideline, this number does not necessarily reflect the actual usage in the real world. The practice guidelines with the highest Google Scholar citations are 2 publications from National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines, with 12,299 and 8,778 Google Scholar citations for AD dementia and MCI due to AD, respectively [20,21]. Both of NIA-AA guidelines were developed by the NIA-AA Workgroups (panelists from United States, United Kingdom, France, Canada) on Diagnostic Guidelines for Alzheimer's disease [20,21]. Both of American Academy of Neurology (AAN) guidelines were from the United States, following the AAN's guideline development process, including panel selection, systematic review, and evidence analysis based on the quality and

strengths of evidence [8,22]. The AAN guideline published by Knopman et al. [22], was developed for suspected AD or suspected dementia focusing on diagnosis; whereas, the AAN guideline published by Petersen et al. [8] was developed for MCI relating to AD and covered all aspects of disease management.

A4.1.1 Screening Recommendations Presented in the Most Highly Cited Guidelines

Of the most highly cited guidelines, recommendations for screening were discussed in the AAN dementia 2001 and AAN MCI 2018 guidelines [8,22]. The AAN MCI 2018 guidelines advised clinicians to assess for MCI (particularly relating to AD) and not assume that concerns about memory or impaired cognition were due to normal aging for patients or those with close contact who expressed concerns about memory or impaired cognition [8]. The rationale for this recommendation was justified by the fact that a proper assessment of MCI was imperative to determine whether there were any reversible causes of cognitive impairment and that subjective complaints might indicate changes in cognitive function [8]. The AAN MCI 2018 also mentioned that clinicians should not rely solely on historical reports of subjective memory concerns when assessing for cognitive impairment during a Medicare Annual Wellness Visit in order to reduce overdiagnosis or underdiagnosis of MCI relating to AD [8]. For patients who are appropriate for MCI screening or assessment, it was advised to screen for MCI using brief, validated screening instruments; patients who test positive for MCI should then undergo additional formal assessments since the brief tests may be insufficient [8]. The AAN dementia 2001 guidelines recommended screening for comorbidities that could occur in patients with suspected dementia (e.g., depression, B12 deficiency, hypothyroidism) [22].

A4.1.2 Testing and Diagnosis Recommendations Presented in the Most Highly Cited Guidelines

All of the most highly cited guidelines presented testing and diagnosis recommendations [8,20-22]. Excluding other systemic or brain diseases causing the impaired cognition before giving a diagnosis of MCI due to AD is recommended in 2 guidelines [8,21]. Cognitive tests have been recommended, but not specified in all guidelines [8,20-22]. The 2011 NIA-AA guidelines emphasized that biomarkers increased the certainty of an AD diagnosis only [20,21]. Biomarkers were not recommended for routine diagnosis of AD in the most highly cited guidelines [8,20,22]. The NIA-AA AD dementia recommendations indicated that the limitations in standardization and accessibility of biomarkers, the lack of sufficient evidence to support incorporating biomarker use into current criteria, and the ability of the core clinical criteria to provide good diagnostic accuracy precluded the use of biomarkers in routine diagnosis [20]. According to AAN MCI guidelines, clinicians could refer patients who are interested in testing for biomarkers to research organizations [8]. NIA-AA guideline documents noted that testing of AD genes might increase the certainty of diagnosis, but those tests were not sufficient to be lone predictors [20,21]. Cerebrospinal fluid (CSF) testing, amyloid-focused imaging of AD, and fluorodeoxyglucose (FDG) uptake and brain structural atrophy may also be used to confirm an AD diagnosis [20,21]. According to NIA-AA AD dementia guidelines, positive PET amyloid imaging and low CSF Aβ42 protein levels both indicate brain amyloid beta (Aβ) protein deposition [20]. Indicating tau protein, the 3 major biomarkers were elevated CSF tau, total tau, and phosphorylated tau (p-tau); decreased FDG uptake on PET in the temporoparietal cortex; and disproportionate atrophy on structural MRI in the medial, basal, and lateral temporal lobes and medial parietal cortex [20].

A4.1.3 Treatment Recommendations Presented in the Most Highly Cited Guidelines

Only the AAN 2018 guidelines from the list of the most highly cited guidelines provided recommendations on treatment [8]. This practice guideline targeted the AD-related MCI population and recommended that nonpharmacological interventions such as regular exercise and cognitive training should be used in MCI patients in the context of the absence of pharmacologic or dietary agents approved by the US Food and Drug Administration for symptomatic cognitive benefit [8].

A4.1.4 Monitoring Recommendations Presented in the Most Highly cited Guidelines

Only the AAN 2018 guidelines provided recommendations on monitoring from the list of most highly cited guidelines [8]. Frequent reviews of medications and cognitive status were recommended.

A4.2 Guidelines Published Before 2018

A4.2.1 Screening

Several guidelines released prior to 2018 offered recommendations for the general or asymptomatic population, despite the fact that the most highly cited and recently published guidelines did not cover these target populations. Those guidelines published before 2018 indicated that screening for the general or asymptomatic population should not be undertaken due to insufficient evidence or unclear benefits/harms [36,38,41,43,56]. One Australian practice guideline published in 2016 encouraged general practitioners to investigate symptoms of cognitive decline, particularly in people aged over 75 years, and examine the symptoms when they are first raised [41]. Consistent with the most highly cited and recently published guidelines, some guidelines recommended that screening should be considered for persons at risk of AD, such as adults with intellectual disability [12], patients older than 75 years who complain of

memory impairment, or patients with a family history of memory disorders [13], and individuals whom the physician or family suspects of having a cognitive impairment despite a lack of complaint [14]. A basic dementia screen including blood, biochemistry, and functional tests was recommended in the Australian 2016 guidelines [41]. Other screening instruments suggested were Folstein's Mini-Mental State Examination (MMSE) and the Milan Overall Dementia Assessment in the Italian Neurological Society Guidelines 2004 [43] and the MMSE and a range of short tests (e.g., the Pfeiffer test, the Memory Impairment Screen, the 7-minute test, the clock test) in the Spanish 2011 guidelines [51].

A4.2.2 Testing and Diagnosis

Similar to the most highly cited and recently published guidelines**,** neuropsychological testing was recommended as a complementary tool to detect AD and MCI. Other tests were proposed; in particular, the Montreal Cognitive Assessment (MoCA) was encouraged in some guidelines because of its high sensitivity and accuracy [48,58]. A Japanese guideline indicated that the MoCA-Japanese version should be used to detect MCI rather than the MMSE [53]. Other recommendations on testing and diagnosis from guidelines published before 2018 were consistent with the most highly cited and recently published guidelines.

A4.2.3 Treatment

These guidelines recommended nonpharmacological interventions for MCI and acetylcholinesterase (AChE) inhibitors and memantine for AD symptom treatment, in accordance with the recommendations for treatment from the most highly cited and recently published guidelines.

A4.2.4 Monitoring

Several guidelines advocate for a frequent follow-up or re-assessment at least every 3-6 months for patients with AD dementia on pharmacologic treatment to manage safety and treatment efficacy [24,28,36]. The Luxembourgish 2016 guidelines for suspected MCI indicated that individuals who were within the norms and correspond to noncognitive or minor cognitive impairments should undergo a retest 6-12 months later [48]. The American 2002 guidelines for patients with AD recommended considering the culture, language, and decision-making processes of the patients and caregivers during the monitoring period [28].

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