

Clinical tools used to assess Alzheimer's disease in the early stages

This content is intended for health care professionals only for educational and informational purposes and does not substitute for sound medical judgement or clinical decision making in the context of medical treatment

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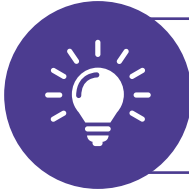
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Introduction to cognition, function and behavior

Domains of cognition



Cognition is not a unitary construct; it consists of different domains

Episodic memory

Recollection of past events and personal experiences^{1,2}

Language

Verbal expression, language interpretation, and communication¹

Visuospatial functions

Concerned with the integration of space and visual form

Attention

The capacity to focus and sustain concentration¹

Executive functions

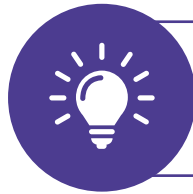
Thinking skills that assist with reasoning, planning, problem solving, and managing one's life³

Praxis

Monitor and process data in the surrounding environment to plan a motor action, eg imitate a hand gesture⁴

1. Harvey PD. Dialogues Clin Neurosci 2019;21:227–237; 2. Zilli EA, Hasselmo ME. Hippocampus 2008;18:193–209; 3. Blair C. Curr Dir Psychol Sci 2016;25:3–7; 4. Ward M, et al. Dement Neuropsychol 2015;9:71–75

Clinical features of behavior and functional ability



Behavior and functional ability are also important clinical features in AD¹⁻³

Functional ability

Ability to perform basic and complex activities³

Basic activities of daily living related to self-maintenance^{4,5}

- Bathing
- Dressing
- Grooming
- Mouth care
- Toileting
- Transferring from bed to chair
- Walking
- Climbing stairs
- Eating

Complex activities related to independent living^{4,6}

- Managing finances
- Driving / using public transport
- Shopping
- Cooking
- Managing medications
- Housework

Behavior

Social behavior and psychological status^{1,2}

Neuropsychiatric symptoms include^{7,8}:

- Depression
- Anxiety
- Irritability
- Apathy
- Disinhibition
- Agitation
- Aggression
- Psychosis
- Hallucinations
- Sleep disturbances

1. Fernández M, et al. BMC Neurol 2010;10:87; 2. Sachdev PS, et al. Nat Rev Neurol 2014;10:634–642; 3. Jutten RJ, et al. Alzheimers Dement (Amst) 2017;8:26–35; 4. Mlinac ME, Feng MC. Arch Clin Neuropsychol 2016;31:506–516; 5. Jekel K, et al. Alzheimers Res Ther 2015;7:17; 6. Book S, et al. BMC Psychiatry 2018;18:308; 7. Lanctôt KL, et al. Alzheimers Dement (N Y) 2017;3:440–449; 8. Eikelboom WS, et al. Neurology 2021;97:e1276–e1287

Definition of mild cognitive impairment (MCI)

Mild cognitive impairment (MCI)

MCI defines the state between normal aging and dementia and is defined **by three key features**:¹

1. Cognitive complaint, decline, or impairment: reported by the patient, care partner, or clinician¹
2. Objective evidence of impairment in ≥ 1 of the following domains: attention, executive function, visuospatial function, and episodic memory¹
3. No dementia: performs ADLs independently. However, cognitive difficulty may have a mild but detectable impact on more complex activities, either self-reported or corroborated by the care partner^{1,2}

- ✓ MCI can be caused by multiple underlying neurodegenerative pathologies (but also reversible causes)³
- ✓ Current DSM-5 nomenclature refers to MCI as mild neurocognitive disorder⁴



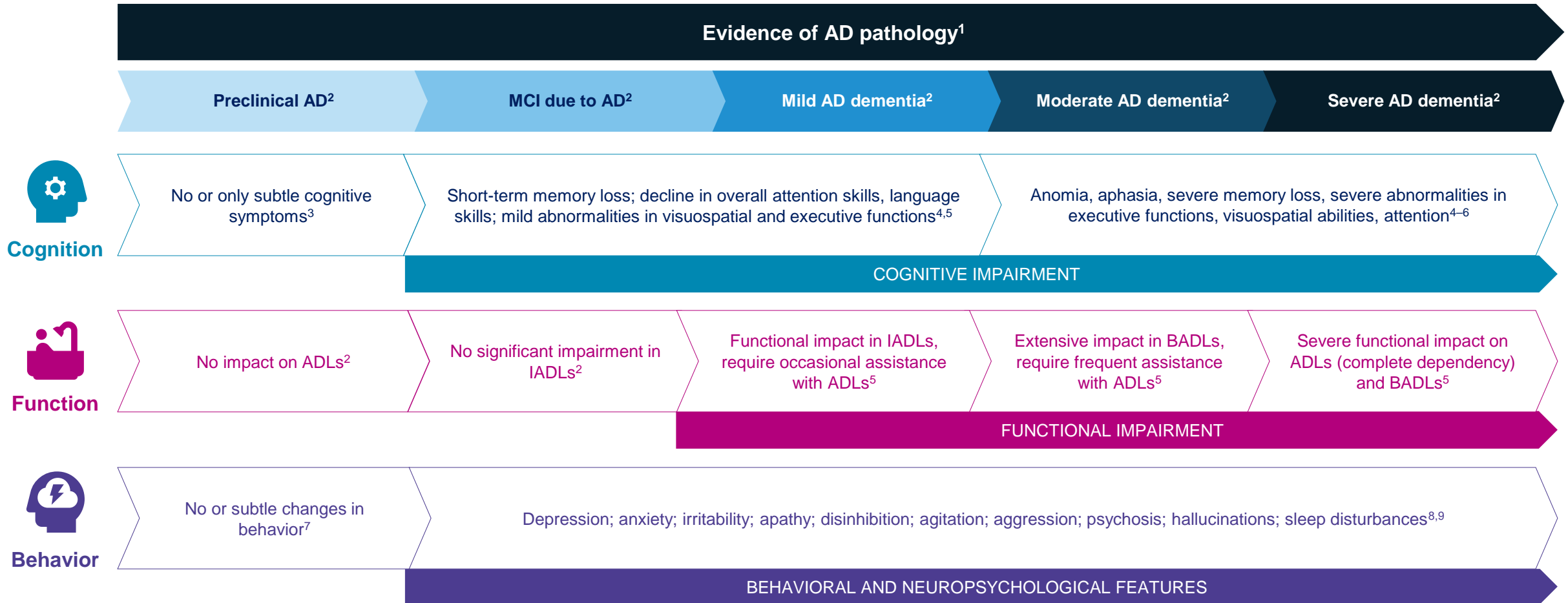
Some individuals with MCI remain stable for many years and may even revert to normal cognition. Other individuals progress to dementia; indeed, there is significant heterogeneity in the MCI population^{5,6}

AD, Alzheimer's disease; ADL, activities of daily living; DSM, Diagnostic and Statistical Manual of Mental Disorders; MCI, mild cognitive impairment

1. Alberts MS, et al. *Alzheimers Dement* 2011;7:270–279; 2. Mlinac ME, Feng MC. *Arch Clin Neuropsychol* 2016;31:506–516;
3. Dugger BN, et al. *BMC Neurol* 2015;15:146; 4. Hugo J et al. *Clin Geriatr Med* 2014;30:421–442; 5. Sugarman MA, et al. *J Alzheimers Dis* 2018;62:1841–1855;
6. Ganguli M, et al. *J Am Geriatr Soc* 2019;67:232–238

The Alzheimer's disease (AD) continuum and disease staging

The AD clinical continuum and disease staging



AD, Alzheimer's disease; ADL, activities of daily living; BADL, basic activities of daily living; IADL, instrumental activities of daily living;

MCI, mild cognitive impairment

1. Aisen PS, et al. *Alzheimers Res Ther* 2017;9:60; 2. Jack CR Jr, et al. *Alzheimers Dement* 2018;14:535-562; 3. Harada CN, et al. *Clin Geriatr Med* 2013;29:737-752; 4. Kazim SF, Iqbal K. *Mol Neurodegener* 2016;11:50

5. Mayo Clinic. Alzheimer's stages: How the disease progresses. <https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-stages/art-20048448> (Accessed April 2023); 6. Kipps CM, Hodges JR. *J Neurol Neurosurg Psychiatry* 2005;76(Suppl. 1):i22-i30;

7. Ismail Z, et al. *Alzheimers Dement* 2016;12:195-202; 8. Eikelboom WS, et al. *Neurology* 2021;97:e1276-e1287; 9. Lanctôt KL, et al. *Alzheimers Dement (N Y)* 2017;3:440-449.

Detecting the early stages of disease

Delays in early detection of AD

PCPs, neurologists, psychiatrists, and geriatricians play a crucial role in the detection, diagnosis, and treatment of AD¹⁻⁶

Detection of early stages of AD is challenging.¹⁻⁴

- **AD-related early cognitive decline is difficult to differentiate from normal aging^{1,5}**
- Comorbid medical conditions (e.g., stroke, depression) can impact cognitive and functional abilities¹
- Patients wait years for an accurate diagnosis and appropriate intervention⁶

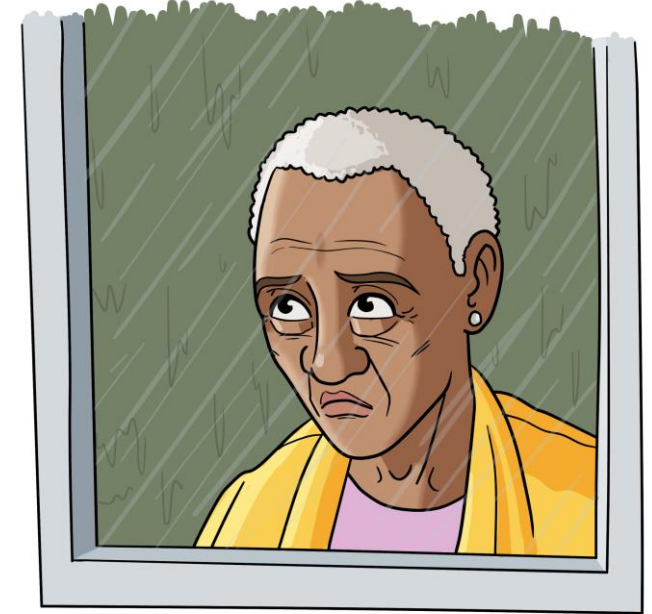
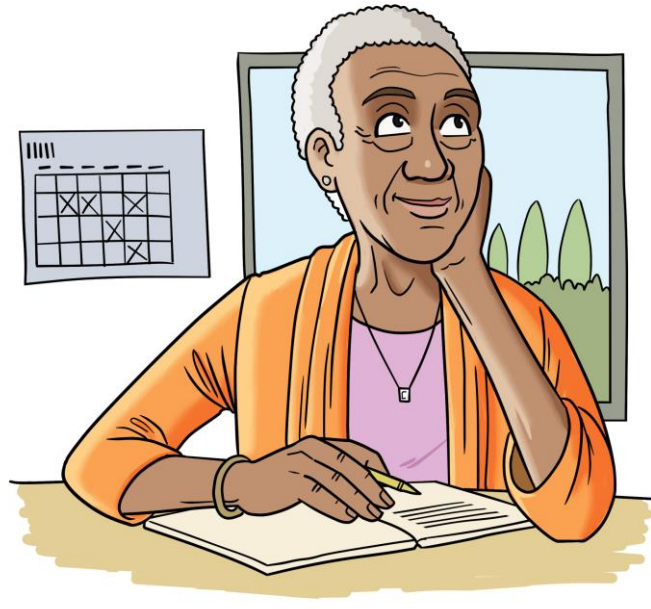
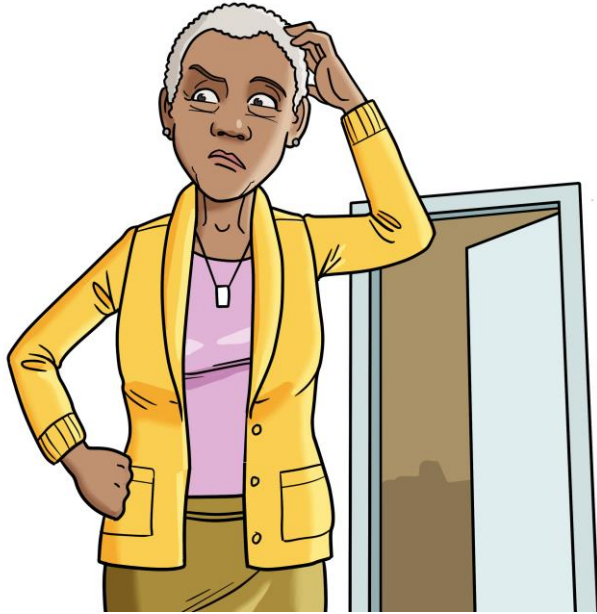


Cognitive impairment may remain unrecognized in up to 80% of affected patients in primary care⁷

AD, Alzheimer's disease; MCI, mild cognitive impairment; PCP, primary care provider

1. Galvin JE. *Curr Geriatr Rep* 2018;7:19-25; 2. Dubois B, et al. *J Alzheimers Dis* 2016;49:617-631; 3. Sabbagh MN, et al. *J Prev Alz Dis* 2020; 4. Porsteinsson AP, *J Prev Alzheimers Dis*. 2021;8:371-386; 5. Liss JL, et al. *J Intern Med*. 2021;290(2):310-334; 6. Galvin JE, et al. *Front Neurol* 2021;11:592302; 7. Cordell CB, et al. *Alzheimers Dement*. 2013;9(2):141-150

Identifying key symptoms in the early stages and how they differ from typical aging



Cognition^{1,2}

- Experiencing short-term memory loss?
- Struggling to learn new things?
- Experiencing word-finding difficulties or communication difficulties?
- Repeating him/herself?

Function³

- Starting to need support with complex activities related to independent living, such as managing finances?

Behavior/psychological¹

- Struggling to participate in meaningful social situations?
- Signs of impulsivity?
- Signs of apathy or depression?

Is the family member/care partner sharing/communicating concerns?⁴

1. Porsteinsson AP, et al. J Prev Alzheimers Dis 2021;8:371–386; 2. National Institute on Aging. What Are the Signs of Alzheimer's Disease?: <https://www.nia.nih.gov/health/what-are-signs-alzheimers-disease> (Accessed April 2023); 3. National Institute on Aging. Managing Money Problems in Alzheimer's Disease: <https://www.nia.nih.gov/health/managing-money-problems-alzheimers-disease> (Accessed April 2023); Centers for Disease Control and Prevention. 10 Warning Signs of Alzheimer's: <https://www.cdc.gov/aging/healthybrain/ten-warning-signs.html> (Accessed April 2023)

Distinguishing Alzheimer's disease from normal aging

Typical aging brings about changes to several cognitive abilities, such as **increased forgetfulness** and **difficulty multi-tasking**,¹ therefore it is important to establish whether changes are due to AD or to normal aging processes.

The table below displays some differences between AD-related and normal aging-related changes:²

Signs of AD and dementia	Typical age-related changes
Poor judgement and decision-making	Making a bad decision once in a while
Inability to manage a budget	Missing a monthly payment
Losing track of the date or the season	Forgetting which day it is and remembering it later
Difficulty having a conversation	Sometimes forgetting which word to use
Misplacing things and being unable to retrace steps to find them	Losing things from time to time

AD, Alzheimer's disease

1. Harada CN, et al. Clin Geriatr Med 2013;29(4):737-752; 2. Alzheimer's Association. Alzheimers Dement. 2023;19(4):1598-1695

Key considerations when selecting a test

What makes a suitable test?

Assessments must be:^{1,2}

- Reliable¹

- Sensitive¹

- Valid¹

- Cross-culturally valid²

Brief assessments should be:³

- Ideally, less than 10 mins to complete

- Achieve at least 80% specificity and sensitivity for detecting MCI or mild dementia

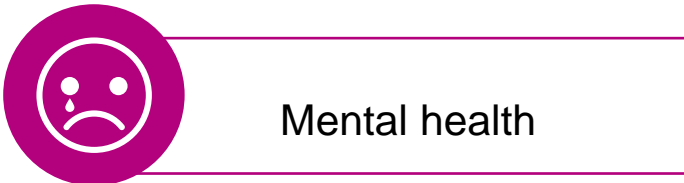
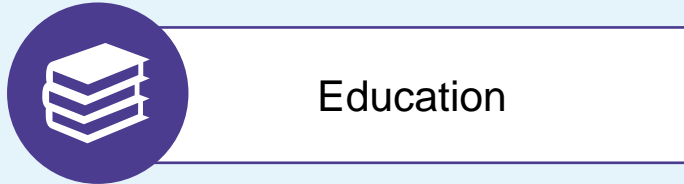
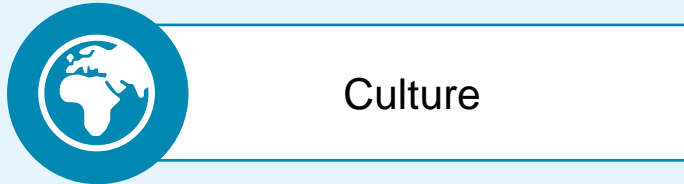
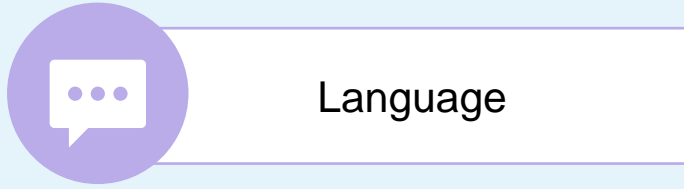
- Available in various languages and appropriate for people with different educational backgrounds

- Available in digital and/or paper-based formats

1. Jutten E, et al. *Alzheimers Dement* (N Y) 2020;6:e12020; 2. Goudsmit M, et al. *Dement Geriatr Cogn Dis Extra* 2018;8:290–305; 3. Matke S, et al. *Alzheimers Dement*. 2023 Apr 19. doi: 10.1002/alz.13051. Epub ahead of print. PMID: 37073874.

Challenges of implementing cognitive assessments

There are a number of key considerations for using cognitive assessments^{1,2}



Cognitive assessments can be specifically chosen for patients based on their primary language and culture and use of education-adjusted norms¹⁻³

The domains of executive function, working memory, episodic memory, attention, and psychomotor processing speed are commonly affected in patients with depression and other psychiatric conditions⁴

1. Franzen S, et al. J Int Neuropsychol Soc 2020;26:331–351; 2. Wang H, et al. J Glob Health 2019;9:020320; 3. Lindgren N, et al. Int J Geriatr Psychiatry 2019;34:1883–1891;
4. McAllister-Williams RH, et al. J Affect Disord 2017;207:346–352

Ruling out other causes of cognitive impairment



Potential reversible causes¹

- Idiopathic depression
- Vitamin B12 and/or folate deficiency
- Medications
- Hypothyroidism / hyperthyroidism
- Normal pressure hydrocephalus



Other neurodegenerative causes of dementia²⁻⁶

- Cerebrovascular disease
- Lewy body disease
- Frontotemporal lobar degeneration
- Mixed pathologies
- Others: Parkinson's disease (similarities with LBD), chronic traumatic encephalopathy, progressive supranuclear palsy, corticobasal degeneration, Huntington's disease

LBD, Lewy body dementia

1. Chari D, et al. J Geriatr Mental Health 2015;2:30-37; 2. Smith EE. Clin Sci (Lond) 2017;131:1059-1068; 3. McKeith IG, et al. Neurology 2017;89:88-100;

4. Young JJ, et al. Ther Adv Psychopharmacol 2018;8:33-48; 5. University of California San Francisco. Available from: <https://memory.ucsf.edu/dementia-overview> (Accessed July 2023); 6. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. Alzheimers Dement 2023;19(4):1598-1695

Example brief cognitive, functional, and behavioral assessments

Example brief cognitive assessments

Note: this is not an exhaustive list of tools; the below tests have all been validated for the early stages of AD

		MCI-Sensitive	Mild Dementia-Sensitive	Test duration			Cognitive domains measured						
				<5 min	5–10 mins	<15 min	Memory	Language	Orientation	Executive function	Praxis	Visuospatial abilities	Attention
Pen and paper	AD8 [†]	●	●	✓			○		○	Judgement			
	Quick Dementia Rating Scale (QDRS) ^{*†}	●	●	✓			○	○	○	Judgement			○
	General Practitioner Assessment of Cognition (GPCOG) [*]		●	✓			○		○	○		○	
	Mini-Kingston Standardized Cognitive Assessment revised (Mini-KSCAR)	●	●		✓		○		○	○		○	
	Mini-Mental State Examination (MMSE)		●		✓		○	○	○		○	○	○
	Quick Mild Cognitive Impairment Screen (Qmci)	●	●	✓					○	○		○	
	Saint Louis University Mental Status Examination	●	●		✓		○		○	○			○
	Rapid Cognitive Screen (RCS)	●	●	✓			○					○	
P&D	Montreal Cognitive Assessment (MoCA)	●	●			✓	○	○	○	○	○	○	○
Digital	Brief Cognitive Assessment Tool (BCAT)	●	●		✓		○	○	○	○		○	○
	CANTAB Mobile	●	●		✓		○						
	Cognigram	●	●			✓	○						○

*performance- and informant-based; †also measures function

P&D, pen and paper and digital

1. Galvin JE. Curr Geriatr Rep 2018;7:19–25; 2. Razavi M, et al. Alzheimer Dis Assoc Disord 2014;28(2):156-161; 3. De Roeck EE, et al. Alzheimers Res Ther. 2019;11:1-14; 4. Iatraki E, et al. Eur J Gen Pract 2017;23:171–178; 5. Glynn K, et al. Int J Geriatr Psychiatry. 2019;1-8; 6. Malmstrom TK, et al. J Nutr Health Aging. 2015;19:741-744; 7. Nasreddine ZS et al. J Am Geriatr Soc. 2005;53(4):695-9 8. MacDougall EE, et al. Int Psychogeriatr. 2015;27:243-250; 9. BCAT Test System Training. 2019; 10. Aslam RW, et al. Int J Geriatr Psychiatry. 2008;33(4):561-575; 11. Maruff P, et al. BMC Pharmacol Toxicol. 2013;1:1-11; 12. Galvin JE, et al. PLoS One 2020;15:e0240422

Cognitive assessment considerations



- No test represents a “gold standard”; evaluations such as the Clinical Dementia Rating (CDR) are used in many research studies but require a trained clinician to administer, interpret and score the CDR and requires an extended period of time with both the care partner and the patient
- The use of brief cognitive assessment tools can aid in the early identification of MCI and mild AD dementia
- **Memory, executive function, visuospatial function, and language** are the most affected cognitive domains in the early stages of AD
- Currently, most cognitive assessment tools focus on a subset of the overall dimensions of cognition; it is important the clinician chooses the correct test to assess impairment in these specific cognitive domains that could be indicative of AD in the early stages

Consider factors that may affect test performance and interpretation: education, skills, pre-morbid functioning/attainment, language, sensory impairment, psychiatric illness, physical or neurologic problems^{2,3}

AD, Alzheimer's disease; CDR, clinical dementia rating; MCI, mild cognitive impairment

1. Galvin JE. Alzheimer's Dement 2015;1:249–259; 2. Porsteinsson AP, et al. J Prev Alzheimers Dis 2021;8:371–386; 3. Kipps CM, Hodges JR. J Neurol Neurosurg Psychiatry 2005;76(Suppl. 1):i22–i30

Example brief functional and behavioral assessments

Note: this is not an exhaustive list of tools; the below tests have all been validated for the early stages of AD

	Test	Test duration			Functional domain		Behavioral domain
		<5 minutes	5–10 mins	>10 minutes	Basic ADL	Instrumental ADL	
Function	Functional Activities Questionnaire (FAQ)		✓			✓	
	DAD-6		✓			✓	
	Amsterdam IADL Questionnaire (A-IADL-Q)			✓		✓	
Behavior	Neuropsychiatry Inventory (NPI-Q)		✓				✓
	Geriatric Depression Scale (GDS)		✓				✓

Functional test considerations: Utilizing functional tests that **measure instrumental ADLs** are preferred as they require a higher cognitive ability compared with basic ADLs and impacted in the earlier stages of AD.

Basic ADLs are relatively preserved until later stages of the disease¹

Behavioral test considerations: Although NPS are observed in the early stages and the later stages, NPS tends to follow a more stable pattern across the continuum²

AD, Alzheimer's disease; ADL, activities of daily living; NPS, neuropsychiatric symptoms

1. Alzheimer's Association. Available from: <https://www.alz.org/careplanning/downloads/functional-activities-questionnaire.pdf> (accessed June 2023); 2. de Rotrou J, et al. Dement Geriatr Cogn Disord 2012;33:210–218; 3. Koster N, et al. Alzheimers Dement 2015;11:1231–1240;; 4. Rosenberg PB, et al. Am J Geriatr Psychiatry 2013;21:685–695; 5. Greenberg S. AJN 2007;107 (10)

Cognitive Assessments

AD8 Dementia Screening Interview

Care partner / patient



OVERVIEW

- Brief screening tool that is completed by a care partner, but can be administered to the patient in the absence of a care partner

Domains tested

- Memory
- Orientation
- Judgement
- Function**

Administration

- Number of items: 8 items**
- Scoring system: > 2 signifies impairment**
- Informants indicate the presence of a change over several years by answering “Yes, a change”, “No, no change”, or “N/A, don’t know”
- To assess cognitive decline, it is best to use the informant version **in addition** to the patient AD8

Domain	Informant/patient questionnaire
Judgement	<ul style="list-style-type: none"> Problems with decision making, financial decisions, thinking Trouble handling complicated financial affairs
Function	<ul style="list-style-type: none"> Less interest in hobbies /activities
Memory	<ul style="list-style-type: none"> Repeats the same things over and over (questions / stories / statements) Trouble learning how to use a tool or appliance (eg microwave) Trouble remembering appointments Daily problems with thinking and/or memory
Orientation	<ul style="list-style-type: none"> Forgets correct month/year

		Languages (beside English)?	Training required?
<3 minutes	License required	Not specified	No
Adapted for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
No	No	No	Not specified

Advantages

Assessments relatively unaffected by culture/education as each person serves as their own control. Sensitive to early cognitive changes

Limitations

Depends on a reliable care partner

Validity for MCI

Sensitivity

100%

Specificity

77.3%

1. AD-8 Dementia Screening Interview. Available from: <https://www.alz.org/media/Documents/ad8-dementia-screening.pdf> (Accessed June 2023); 2. Galvin JE. Curr Geriatr Rep 2018;7:19–25; 3. Razavi M, et al. Alzheimer Dis Assoc Disord 2014;28(2):156-161; 4. Washington University School of Medicine. Knight Alzheimers Research Center. AD8 Screening Interview. Available from: <https://knightadrc.wustl.edu/professionals-clinicians/ad8-instrument/> (Accessed June 29 2023)

Quick Dementia Rating Scale (QDRS)

Care partner / patient



OVERVIEW



- QDRS is based on CDR and earlier AD8 informant assessment and was developed to be a quick screening tool for trials
- A patient version is available

Domains tested

- Memory and recall
- Orientation
- Attention and concentration
- Decision-making and problem-solving abilities
- Activities outside the home
- Function at home and hobby activities
- Toileting and personal hygiene
- Behavior and personality changes
- Language and communication abilities
- Mood

Administration and test properties

- **Administered by:** Healthcare providers to a **care partner**
- The QDRS total score is derived by summing up the 10 domains. The first six domains of the QDRS were used to generate a QDRS-derived global CDR and CDR-SB using the published CDR scoring rules
 - Scoring: normal is 0–1; mild cognitive impairment 2–5
- The QDRS rapidly and reliably discriminates individuals with and without cognitive impairment and can provide an accurate staging of disease

		Languages (beside English)?	Training required?
3–5 min	Free to use	Not specified	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Not specified	Yes	No	No

Domain	Informant questionnaire
Memory and recall	Ability to learn new information and impact of memory impairment on daily activities
Orientation	Orientation to person, time, and place
Decision-making and problem solving	Independence in decision-making and problem solving, change in social judgement and behavior
Activities outside the home	Degree of independence and ability to participate in activities
Function at home and hobby activities	Personal interests and ability to complete chores compared with past performance
Toileting and personal hygiene	Level of independence in self-care
Behavior and personality changes	Appropriacy of behavior in public and extent of personality changes
Language and communication abilities	Word finding, speech production, reading and writing
Mood	Sadness, depression, anxiety, nervousness or loss of interest/motivation
Attention and concentration	Interaction with surroundings, and daytime sleeping/drowsiness

Advantages

Excellent known-group validity defined by CDR and performance of global rating scales of cognition, behavior, and function

Limitations

Informant version depends on reliable care partner

Validity for MCI

Sensitivity

88%

Specificity

57%

General Practitioner Assessment of Cognition (GPCOG)



OVERVIEW

- This test was designed as a GP screening tool for dementia
- There are two components: a cognitive assessment conducted with the patient, and an informant questionnaire (only considered necessary if the results of the cognitive section are equivocal, ie score 5-8 inclusive).

Domains tested

- Memory
- Orientation
- Visuospatial
- Executive function

Administration and test properties

- **Administered by:** Healthcare providers
- **6 items:** Name and address for subsequent recall test; Time orientation; Clock drawing; Marking hands on the clock at 10 minutes past 11 o'clock; Information on a recent news event; Recall
- **Total score available:** 9
 - Results >8 or <5 on the GPCOG patient section assumed to be cognitively intact or impaired, respectively
- Scores <5 are considered abnormal; scores of 5–8 are indeterminate and require either further assessment or corroboration from a collateral care partner

		Languages (beside English)?	Training required?
≤5 minutes	Free to use	Yes	Yes
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	No	Not specified	Not specified

Domain	Part 1: Cognitive assessment
Orientation	<ul style="list-style-type: none"> • Know and state the current date
Memory	<ul style="list-style-type: none"> • Delayed recall of an address • Recall a recent news item
Visuospatial	<ul style="list-style-type: none"> • Clock drawing
Domain	Part 2: Informant questionnaire
Memory	<ul style="list-style-type: none"> • Does the patient have more trouble remembering things that have happened recently? • Does the patient have more trouble recalling conversations a few days later? • When speaking, does the patient have difficulty finding the right word or tend to use the wrong word more often?
Executive function	<ul style="list-style-type: none"> • Is the patient able to manage money and financial affairs (eg paying bills)? • Is the patient less able to manage their medication independently? • Does the patient need more assistance with transportation?

Advantages GPCOG is relatively uninfluenced by cultural or linguistic background and is therefore useful in a multicultural patient setting

Limitations Low specificity

Validity for dementia

Sensitivity 85% (if administered to both patient and care partner)

Specificity 86% (if administered to both patient and care partner)

Mini-Kingston Standardized Cognitive Assessment revised (Mini-KSCAr)



OVERVIEW



- Shortened version of the full KSCAr that can be given in far less time
- The mini-KSCAr is made up of 6 tasks from the full KSCAr that are most sensitive to early changes seen in cognitive functioning as seen in the cases of early Alzheimer's disease

Domains tested

- Memory (orientation, immediate and delayed recall, and recognition)
- Executive functioning
- Visuospatial (motor spatial abilities)

Administration and test properties

- **Administered by:** Healthcare providers
- **6 items**
- **Total score available: 55**
 - Scores <37 considered impaired (MCI)

		Languages (beside English)?	Training required?
7–10 minutes	Free to use	Yes (English and French)	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Not specified	No	Yes	No

Subtest	Cognitive assessment
Word recall	Immediate memory for 10 words
Orientation	Orientation to person, place, and time
Delayed recall	Delayed memory for 10 words
Word recognition	Recognition memory with distracters and delay
Abstract thinking	Ability to identify similarities between pairs of words (executive functions)
Clock drawing	Spatial orientation – motor/spatial abilities

Advantages

Maximum clinical information with minimum assessment time.

Limitations

Limited translation to other languages, appropriateness for different levels of education/cultures not known

Validity for MCI

Sensitivity

81%

Specificity

95%

Mini-state Mental Exam (MMSE)

Patient



OVERVIEW

- Most widely used test in clinical practice
- Simple to use

Domains tested

- Orientation to time
- Orientation to place
- Registration
- Visual construction
- Attention and calculation
- Recall
- Language

Administration

- Administered by neurologist or other HCP, although an online version is available that can be administered by a family member or friend
- **Number of items:** 30 items
- **Cutoff for dementia:** 23–24
- **Educational level:** Poor sensitivity for people with very high and low educational levels

Domain	Cognitive assessment
Orientation	<ul style="list-style-type: none"> • Know and state the current date and place • Keep track of time and place in everyday living
Attention and working memory	<ul style="list-style-type: none"> • Follow examiner's instruction with focus • Manipulate information in one's head
Memory	<ul style="list-style-type: none"> • Learn and recall new info during exam
Visuospatial	<ul style="list-style-type: none"> • Copy 2D geometric shapes
Language	<ul style="list-style-type: none"> • Repeat sentences and phrases • Name common objects • Follow written and oral commands

		Languages (beside English)?	Training required?
~5–10 minutes	Fee for test administration	Yes	No
Adapted for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Not specified	Yes	Yes	Yes

Advantages Easy to administer, no special equipment or training needed

Limitations Score influenced by education, ethnicity, and social class
Not ideal to identify mild impairment

Validity for Dementia

Sensitivity 89%

Specificity 89%



1. Galvin JE. Curr Geriatr Rep 2018;7:19–25; 2. Patnode CD, et al. Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force. In: Rockville (MD): Agency for Healthcare Research and Quality (US); Report No: 19-05257-EF-1. US Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews 2020; PAR. Mini-Mental State Examination. Pricing. Available from: <https://www.parinc.com/Products/Pkey/237>; NHS South West London and St George's NHF Foundation Trust. Standardized Mini-Mental State Examination. Available from: chrome-extension://efaidnbmnnnibpcajpgblclefindmkaj/https://www.swlstg.nhs.uk/images/Useful_docs_for_healthcare_professionals/mini-mental_state_examination_form.pdf (Accessed 29 June 2023)

Quick Mild Cognitive Impairment Screen (Qmci)

Patient



OVERVIEW



- A short screening test developed to provide a rapid instrument for early detection of MCI
- A modified version of the AB Cognitive Screen 135, placing greater emphasis on verbal memory and fluency, and delayed recall

Domains tested

- Orientation
- Word registration
- Visuospatial function
- Delayed recall
- Verbal fluency
- Logical memory

Administration and test properties

- **Administered by:** Qualified HCPs, online version available which provides PDF of tabulated results
- **Can be administered remotely:** No (a care partner remote administered screen a possibility)
- **Number of items:** Five orientation items, five registration items, and a clock drawing test. Also includes a recall section, and tests for verbal fluency and logical memory
- **Scoring system:** Scored out of 100 points. Recommended cutoff for MCI or dementia is <62
- **Educational level:** Lower sensitivity in those with ≥12 years in formal education

		Languages (beside English)?	Training required?
~5 mins	Licensing or small fee	Yes (at least 16)	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	No	Yes	No

Domain	Cognitive assessment
Orientation	Know and state the current date and place
Word registration	Recall five words
Visuospatial function	Draw a clock showing a specified time
Delayed recall	Delayed memory for five words
Verbal fluency	Generate words of a specific category
Logical memory	Recall details of a story

Advantages

Rapid, reliable, and valid, and easy to administer

Limitations

Cost

Validity for MCI

Sensitivity

82%

Specificity

82%

1. O'Caioimh R, et al. Age Ageing. 2012;41:624-629; 2. O'Caioimh R, et al. J Alzheimers Dis. 2016;51:619-629; 3. Glynn K, et al. Int J Geriatr Psychiatry. 2019;1-8

Montreal Cognitive Assessment (MoCA)

Patient



OVERVIEW

- Brief screening tool that is completed by the individual with the cognitive complaint
- Easy to administer, with shortened versions available to reduce clinician burden
- Most recommended for detection of early AD

Domains tested

- Short term memory
- Visuospatial abilities
- Executive function
- Attention
- Concentration and working memory
- Language
- Orientation

Administration and test properties

- **Administered by:** Healthcare providers
- **Can be administered remotely:** abbreviated telephone version and full MoCA via audio-visual conference
- **Number of items:** 12 items
- **Scoring system:** < 26/30 signifies impairment
 - Introducing two separate cutoff scores increases diagnostic accuracies. A cutoff of 23/24 (high specificity) should be used in combination with a cutoff of 25/26 (high sensitivity), with an indecisive area in between
- **Educational level:** Add one point for individuals with less than a 12th grade education

		Languages (beside English)?	Training required?
~10 minutes	Fee for training	Yes (>100)	Yes
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	No	Yes	Yes

Domain	Cognitive assessment
Orientation	Know and state the current date and place
Attention and working memory	<ul style="list-style-type: none"> • Sustain attention • Repeat a series of digits • Manipulate information in one's head
Memory	Learn and recall new info during exam
Visuospatial	<ul style="list-style-type: none"> • Copy 3D geometric shapes • Draw a clock without copying • Copy a drawing of a cube
Language	<ul style="list-style-type: none"> • Repeat sentences and phrases • Name common objects • Generate words from a specific category
Executive function	<ul style="list-style-type: none"> • Generate alternating numbers and letters • Generate words starting with a specific letter • Think abstractly • Plan clock drawing

Advantages Minimal training and sensitive to early stages of AD

Limitations Floor effects at moderate AD dementia

Validity for MCI

Sensitivity 90%

Specificity 87%



St. Louis University Mental Status Exam (SLUMS)

OVERVIEW

- The Saint Louis University Mental Status exam is an assessment tool for mild cognitive impairment and dementia and was developed in partnership with the Geriatrics Research, Education and Clinical Center at the St. Louis Veterans Administration Medical Center

Domains tested

- Attention
- Orientation
- Immediate and delayed recall
- Numeric calculation
- Registration
- Digit span
- Visuospatial
- Executive function
- Extrapolation

Administration and test properties

- Administered by:** Healthcare providers
 - Before administering, it is recommended that the SLUMS the training video should be viewed and then annually reviewed.
- Total score available: 30**
- Cutoff for dementia or mild cognitive impairment are based on educational level (high school and above or below high school)**
 - 27 to 30: Normal in a person with a high school education
 - 21 to 26: Suggest a mild neurocognitive disorder
 - 0 to 20: Indicate dementia

		Languages (beside English)?	Training required?
~7 minutes	Free to use	Yes (15 languages)	Yes
Adapted for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Not specified	No	Yes	Not specified

Domain	Cognitive assessment
Orientation	<ul style="list-style-type: none"> Know and state the current date and place
Immediate recall	<ul style="list-style-type: none"> Name items in a specific category
Delayed recall	<ul style="list-style-type: none"> Delayed recall of five words
Numeric calculation	<ul style="list-style-type: none"> Perform a calculation during the exam
Digit span	<ul style="list-style-type: none"> Recall sequence of numbers in reverse order
Visuospatial	<ul style="list-style-type: none"> Drawing a clockface Identifying shapes and size
Executive function	<ul style="list-style-type: none"> Recall information provided in a short story

Advantages	Sensitive to milder stages of disease
Limitations	Lack of research regarding psychometric properties and use with different populations.
Validity for MCI	
Sensitivity	84.5%
Specificity	75.3%

Rapid Cognitive Screen (RCS)

Patient



OVERVIEW

- RCS is an abbreviated form of SLUMS; it includes three items from The St Louis University Mental Status (SLUMS) exam



Domains tested

- Recall
- Visuospatial function
- Insight / executive function

Administration and test properties

- Administered by:** Qualified healthcare providers
- Can be administered remotely:** No
- Number of items:** Three items
- Scoring system:** Scored out of 10, recommended cutoff for cognitive impairment is 7

Domain	Cognitive assessment
Recall	Repeat a series of words and recall immediately and with delay
Visuospatial function	Layout a clock face
Insight	Recall information provided in a short story

		Languages (beside English)?	Training required?
<3 mins	Free	No	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Not specified	No	Not specified	No

Advantages	Easy to administer and free of charge
Limitations	Utility as a first-line screening tool needs further validation

Validity for MCI

Sensitivity	87%
Specificity	70%

Malmstrom TK, et al. J Nutr Health Aging. 2015;19:741-744

Brief Cognitive Assessment Tool (BCAT)

Patient



OVERVIEW



- Items were chosen to emphasize contextual memory, executive functioning and attention
- Predicts: ADL, IADL, “falls,” residential placement, “person-centered” ability to participate in care decisions

Domains tested

- Multi-level memory components
- Complex executive functions features

Administration and test properties

- **Administered by:** Technician or healthcare provider
- **Can be administered remotely:** Yes, interactive website scoring program with test report
- **Number of items:** 21 items
- **Scoring system:** Ranges from 0 to 50, scores <45 suggest cognitive impairment

		Languages (beside English)?	Training required?
10–15 mins	Yes (License fee)	No	Yes
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Not specified	No	Yes	Yes

Domain	Cognitive assessment
Orientation	Know and state the current date and place
Recall	Immediate verbal recall of word list
Visual recognition and delayed visual recognition	Name items pictured
Attention	Eg read letter list, backward countdown from 20
Abstraction	Finding similarities between words
Language	Repeat and generate words
Executive function	Cognitive reasoning, arithmetic reasoning, judgement
Immediate and delayed story recall	Repeat elements of a story
Story recognition	Answer questions based on a brief story

Advantages

Can track cognitive changes over time

Limitations

Requires specific training and annual fee

Validity for MCI

Sensitivity

81%

Specificity

80%

1. MacDougall EE, et al. Int Psychogeriatr. 2015;27:243-250; 2. BCAT Test System Training. 2019



OVERVIEW



- CANTAB Mobile delivered via an iPad
- Sensitive touchscreen memory test with a depression screen to differentiate symptoms

Domains tested

- Memory (using CANTAB Paired Associates Learning (PAL) test)
- Optional questionnaires: Geriatric Depression Scale (GDS-15), activities of daily living assessment

Administration and test properties

- **Administered by:** Provider on provider-owned touch-screen device
- **Can be administered remotely:** No
- **Number of items:** Not specified
- **Scoring system:** Not specified

		Languages (beside English)?	Training required?
~10 mins	Usage fee	Yes (~20)	Not specified
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	No	Not specified	Not specified

Advantages

Accounts for age, gender and educational level

Limitations

Cost

Validity for MCI / early dementia

Sensitivity

96.9%

Specificity

80.8%

1. AlzheimersWeekly.com Cantab Mobile Dementia Test Approved By FDA. 2017. Available from: <https://alzheimersweekly.com/2017/02/cantab-mobile-dementia-test-approved-by/> (Accessed 8 June 2023); 2. Aslam RW, et al. Int J Geriatr Psychiatry. 2018;33(4):561-575

Cognigram (Cogstate Brief Battery)

Patient & care partner



OVERVIEW



- Cogstate Brief Battery is a brief, computer-administered cognitive test battery
- Four cognitive tasks constructed using playing cards as stimuli, with the test taker required to answer 'yes' or 'no' on each trial according to a simple rule

Domains tested

- Psychomotor function
- Visual learning
- Visual attention
- Working memory

Administration and test properties

- **Administered by:** Completed by patients, in clinic or at home, requires internet connected computer or tablet
- **Can be administered remotely:** Yes
- **Number of items:** four
- **Scoring system:** Not specified

		Languages (beside English)?	Training required?
~10 mins	Not specified	Language neutral	Not specified
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	Not specified	Yes	Yes

Cognitive test

- Four different test sections
- Each section uses playing cards as stimuli, eg:
 - Psychomotor function – 'Has the card turned over'?
 - Attention – 'Is the card red'?
 - Learning – 'Have you seen this card before'?
 - Working memory – 'Is this card the same card as the previous card'?

Advantages

Composite cognitive scores may be useful in settings where issues such as educational level or mood affect assessment

Limitations

Results may vary depending on whether the test is taken at home or in clinic, and practice effects may occur with repeated sessions

Validity for MCI

Sensitivity

Learning/working memory: 80.4%
Psychomotor/attention: 41.1%

Specificity

Learning/working memory: 84.7%
Psychomotor/attention: 85.7%

Functional Assessments

Functional Assessment Questionnaire (FAQ)

Care partner



OVERVIEW



- The test measures instrumental activities of daily living (IADLs), such as preparing balanced meals and managing personal finances
- This tool is useful to monitor these functional changes over time

Domains tested

- Instrumental ADLs

Administration and test properties

- **Administered by:** Healthcare providers
- **10 items**
- **Total score available:** sum scores range 0–30
 - Cut-point of 9 (dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment
 - A total score of 0, 1, or 2 indicates higher likelihood of clinically important cognitive impairment
- Tests of validity have been performed on the FAQ, establishing it as an instrument for the bedside and research setting because it can discriminate among different functional levels of individuals

		Languages (beside English)?	Training required?
~7 minutes	Free to use	Not specified	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	Yes – can discriminate between different stages	Yes	No

1. Writing checks, paying bills, keeping financial records
2. Assembling tax or business records
3. Shopping alone
4. Playing a game of skill
5. Making coffee or tea
6. Preparing a balanced meal
7. Keeping track of current events
8. Attending to and understanding a television program, book, or magazine
9. Remembering appointments, family occasions, medications
10. Traveling out of the neighbourhood

SCORE: 0 = Normal; 1 = Has difficulty but does without assistance; 2 = Requires assistance; 3 = Dependent

Advantages

Efficient and consistent results across a broad range of professions and settings

Limitations

May be over or under estimation of abilities because of the lack of direct observations

Validity for dementia

Sensitivity

85%

Specificity

Not specified

Disability Assessment in Dementia Scale (DAD-6)

Care partner



OVERVIEW

- Developed to detect early changes in instrumental activities of daily life, focusing on executive components of 6 instrumental items

Domains tested

- Instrumental ADLs

Administration and test properties

Administered by: Healthcare providers

- 6 items: each item has 3 executive subscores ranging from 0 to 3**
- The care partner can answer “yes” or “no”; each ‘yes’ or ‘no’ is scored one point
- The response “no” is grouped into three categories based on the cause of difficulty:
 - ✓ sensorimotor deficit
 - ✓ depression
 - ✓ cognitive reasons
- The maximum global score is 18 corresponding to 18 answers ‘yes’; higher the score, the more autonomous
 - Optimal cut-off score 14 for MCI
- The higher the global score, the more autonomous the patient. The lower the executive subscores, the more impaired in executive components the patient.

		Languages (beside English)?	Training required?
~5 minutes	Free to use	Yes	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	Differentiates MCI	Not specified	Yes

- Meal preparation
 - Telephoning
 - Going on outings
 - Finances and correspondence
 - Medication
 - Leisure and housework
- Each IADL activity includes three questions pertaining to:
- ✓ initiation
 - ✓ planning and organization
 - ✓ effective performance

TOTAL GLOBAL SCORE: 18

Executive scores: initiation score = 6; planning and organization = 6; effective performance = 6.

Advantages

May be able to distinguish between MCI from those with mild AD dementia

Limitations

Relies on a reliable care partner

Validity for MCI

Sensitivity

83% - distinguish between MCI and mild AD dementia

Specificity

84% - distinguish between MCI and mild AD dementia

Amsterdam IADL Questionnaire (A-IADL-Q)

Care partner



OVERVIEW

- The A-IADL-Q, developed at the Alzheimercentrum Amsterdam, is a computerized questionnaire **aimed at measuring difficulties with complex daily activities**

Domains tested

- Instrumental ADLs

Administration and test properties

Administered by: Healthcare providers

- It consists of 70 items; for each item, difficulty is rated on a five-point scale (**shorter versions available**)
- The care partner always starts with the main question, which assesses whether the activity was performed by the patient in the past 4 weeks
- To optimize individual differences in premorbid IADLs, items are tailored to individual responses
- The total score is calculated using an item response theory (IRT) method of scoring (20–80)
- Optimal cutoff score for dementia diagnosis = 51.4**
- The following score categories have been proposed: no problems (score ≥ 60), mild problems (score 50–59), moderate problems (score 40–49), and severe problems in daily functioning (score < 40)

Example: Did he / she carry out household duties in the past 4 weeks?

Yes



Did he / she find it more difficult to perform household duties than he / she had in the past?

- No
- Yes, slightly more difficult
- Yes, more difficult
- Yes, he / she is no longer able to perform this task

No



He / she did not carry out any household duties for the following reason:

- He / she was unable to do so because of his / her cognitive problems
- He / she was unable to do so because of his / her physical problems
- He / she has never done that before
- Other, please state...

Don't know

Advantages

A-IADL-Q is less influenced by education, gender, and age

Limitations

Requires a reliable care partner and clinician required to tailor questionnaire to responses

Validity for Dementia

Sensitivity

74%

Specificity

65%

		Languages (beside English)?	Training required?
10–15 minutes (short-form)	Application-based – fee unknown	Yes	Yes
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	Not specified	Yes	Yes

Behavioral Assessments

Neuropsychiatric Inventory Questionnaire (NPI-Q)

Patient and care partner



OVERVIEW

- NPI-Q is a simplified clinical version of the NPI, which measures neuropsychiatric symptoms without the sub-questions, their severity (not frequency) and the distress on the care partner



Domains tested

- 12 neuropsychiatric symptoms (NPS) domains

Administration and test properties

Administered by: Healthcare providers

- Higher scores indicate greater levels of NPS severity and higher caregiver distress**
- Three scores reported for each domain
 - presence of symptoms
 - severity on a 0–3 scale

		Languages (beside English)?	Training required?
~5 minutes	Free to use	Yes	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	No	Not specified	No

Symptom	No / Yes	Severity	Caregiver distress
Delusions	0 1	1 2 3	0 1 2 3 4 5
Hallucinations	0 1	1 2 3	0 1 2 3 4 5
Agitation/aggression	0 1	1 2 3	0 1 2 3 4 5
Depression/dysphoria	0 1	1 2 3	0 1 2 3 4 5
Anxiety	0 1	1 2 3	0 1 2 3 4 5
Elation/euphoria	0 1	1 2 3	0 1 2 3 4 5
Apathy/indifference	0 1	1 2 3	0 1 2 3 4 5
Disinhibition	0 1	1 2 3	0 1 2 3 4 5
Irritability/liability	0 1	1 2 3	0 1 2 3 4 5
Motor disturbance	0 1	1 2 3	0 1 2 3 4 5
Night-time behaviors	0 1	1 2 3	0 1 2 3 4 5
Appetite/eating	0 1	1 2 3	0 1 2 3 4 5
Total	/12	/36	/60

Advantages

Short and reliable across different languages and cultures

Limitations

Requires a reliable care partner

Validity for Dementia (NPI)

Sensitivity	86%
Specificity	76%

Geriatric Depression Scale (GDS)

Patient



OVERVIEW

- The GDS short form (15 questions) has been derived from the 30-question version. It has been designed for the assessment of depressive symptomatology in elderly people and excludes any questions relating to the physical symptoms of depression common in old age
- The Short Form is more easily used by physically ill patients and those with mild to moderate dementia who have short attention spans and/or feel easily fatigued

Domains tested

- Two domains; depression and positive effect

Administration and test properties

Administered by: Healthcare providers

- 15-item, self-report scale with a “yes” or “no”. The GDS score represents the sum of the total number of depressed responses (values range from 0 to 15)
- Of the 15 items, 10 indicated the presence of depression when answered positively, while the rest (question numbers 1, 5, 7, 11, 13) indicated depression when answered negatively
- Scores of 0–4 are considered normal, depending on age, education, and complaints; 5–8 indicate mild depression; 9–11 indicate moderate depression; and 12–15 indicate severe depression

		Languages (beside English)?	Training required?
5–7 minutes	Free to use	Yes	No
Appropriate for different cultures/education?	Can stage dementia?	Can measure over time?	Telemedicine accessible?
Yes	No	Not specified	Yes

1	Are you basically satisfied with your life?	No	Yes
2	Have you dropped many of your activities or interests?	Yes	No
3	Do you feel that your life is empty?	Yes	No
4	Do you often feel bored?	Yes	No
5	Are you in good spirits most of the time?	No	Yes
6	Are you afraid that something bad is going to happen to you?	Yes	No
7	Do you feel happy most of the time? No Yes 8 Do you often feel helpless?	No	Yes
8	Do you often feel helpless?	Yes	
9	Do you prefer to stay at home, rather than going out and doing new things?	Yes	No
10	Do you feel you have more problems with your memory than most?	Yes	No
11	Do you think it is wonderful to be alive?	No	Yes
12	Do you feel pretty worthless the way you are now?	Yes	No
13	Do you feel full of energy?	No	Yes
14	Do you feel your situation is hopeless?	Yes	No
15	Do you think that most people are better off than you are?	Yes	No
> 5 problems (answers in BOLD) indicates probable depression TOTAL:			

Advantages	Reliable
Limitations	GDS does not distinguish between the NPS of AD dementia and idiopathic depression syndrome
Validity for MCI	
Sensitivity	Not available for MCI – high sensitivity and specificity for depression
Specificity	

Additional measures: Quality of Life

The importance of QOL in Alzheimer's disease (AD)

AD places a **significant burden** on both caregivers and individuals with AD, and impacts significantly on public health¹



Maintaining QOL for both caregivers and individuals with AD is an important goal of AD management; therefore, measuring QOL in clinical practice is key^{2,3}



Measuring QOL is an integral part of AD management and research;³ it enables patient-reported outcomes to be evaluated, alongside efficacy and cost-effectiveness variables⁴



Caregiver QOL important given the burden of caring and the direct effect it can have on the patient across the AD continuum^{6,7}



- **Measuring QOL in AD is challenging:**
- Individuals with AD can lack insight due to progressive cognitive dysfunction.^{4,5}
- AD QOL assessments almost always require caregiver opinion in addition to patient self-assessment; however, changes may be too subtle to be reliably observed by others in the early stages and there may be less impact on QOL and burden^{6,8}
- Behavioral, emotional, and functional symptoms can affect a patient's ability to understand and rate their own QOL^{3,4,6}



Currently there is **no optimal assessment for QOL in AD**; QOL assessments involve subjective perceptions and any negative correlation observed between patient and caregiver reports likely reflects a real difference in the way they perceive the patient's QOL, rather than a lack of reliability of the measure itself^{3,6}

AD, Alzheimer's disease; QOL, quality of life

1. Alzheimer's Association Report. Alzheimer's Dement 2021;17:327-406; 2. Alzheimer's Association. Management of Alzheimer's Disease. Available from: <https://www.alz.org/professionals/health-systems-clinicians/management> (Accessed July 2023); 3. Landeiro F, et al. Alzheimers Res Ther 2020;12:154; 4. Michalowsky B, et al. Value Health 2020;23:760-767; 5. Mlinac ME, Feng MC. Arch Clin Neuropsychol 2016;31:506-516; 6. Burks HB, et al. Dement Geriatr Cogn Disord 2021;50:103-110; 7. Farina N, et al. Alzheimers Dement 2017;13:572-581; 8. Cohen S, et al. J Prev Alzheimers Dis. 2022;9(3):507-522.

Quality of Life–AD (QOL-AD)



Free for non-commercial use¹

Number of items	Scoring system	Validity	Limitations
13 items ²	<ul style="list-style-type: none"> The measure consists of 13 items, rated on a four-point scale (with 1 being poor and 4 being excellent)^{2,3} Total scores range from 13 to 52 Patient and caregiver reports can be evaluated separately and/or combined into a single score A high score indicates a good QOL 	Good internal reliability, test-retest reliability and validity ²	<ul style="list-style-type: none"> Inter-rater agreement can differ considerably³

- Individuals with MMSE scores ≥ 10 should be able to complete the questionnaire without any problem; caregivers can complete it as a proxy for individuals with MMSE scores < 10 ²
- The QOL-AD can be used in individuals with mild-to-moderate AD dementia to reliably rate their own QOL³
- The QOL domains measured by QOL-AD include perceived QOL, behavioral competence, psychological status, interpersonal environment, and physical functioning²
- The QOL-AD is available in multiple languages¹

13 items of the QOL-AD ²	
Physical health	Marriage
Energy	Friends
Mood	Self as a whole
Living situation	Ability to do chores around the house
Memory	Ability to do things for fun
Family	Money
Life as a whole	

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; QOL, quality of life; QOL-AD, Quality of Life–Alzheimer's Disease

1. ePROVIDE. Quality of Life in Alzheimer's Disease. Available from: <https://eprovide.mapi-trust.org/instruments/quality-of-life-in-alzheimer-s-disease> (Accessed June 2023); 2. Logsdon R, et al. Psychosom Med 2002;64:510–519; 3. Römhild J, et al. Health Qual Life Outcomes 2018;16:131

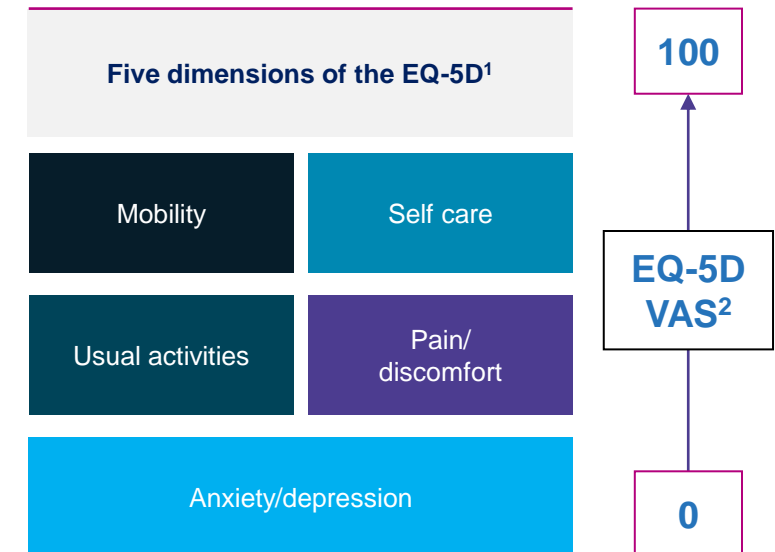
EuroQol 5 Dimensions (EQ-5D)



Free for non-commercial use¹

Number of items	Scoring system	Validity	Limitations
Five health state items and one VAS score ²	<ul style="list-style-type: none"> The descriptive element produces a five-digit health state profile (11111 indicating no problems in any dimension, and 33333 indicating extreme problems in all dimensions)² Each health state can be converted into a single summary number (index value)² Scores of the EQ-5D visual analog scale (VAS) are a measure of overall self-rated health status (from 0–100)² 	Satisfactory convergent validity (with QOL-AD) ³	<ul style="list-style-type: none"> Prone to ceiling effects in AD^{3,4} The VAS has poor reliability, even in individuals with mild and moderate AD dementia⁴ Lack of association between patient and proxy ratings³

- The EQ-5D is a standardized measure of health status developed to provide a simple, generic measure of health for clinical and economic appraisal²
- The first part of the EQ-5D assesses health in **five dimensions**, each of which has three or five levels of response²
 - The second part consists of a VAS on which the patient rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health)
- The EQ-5D is designed for self-completion by respondents and available in both paper and digital versions²
 - Proxy (caregiver) versions are also available for populations in which self-completion is not possible
- The EQ-5D test is available in multiple languages²



AD, Alzheimer's disease; EQ-5D, EuroQol 5 Dimensions; QOL-AD, Quality of Life–Alzheimer's Disease; VAS, visual analog scale

1. EuroQol. EQ-5D. Available from: <https://euroqol.org/euroqol-extends-free-use-of-eq-5d-for-non-commercial-users/> (Accessed June 23, 2023);
 2. EQ-5D-3L User guide. Available from: <https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-3LUserguide-14-0421.pdf> (Accessed June 23, 2023);
 3. Michalowsky B, et al. Value Health 2020;23:760–767; 4. Hounsborne N, et al. Value Health 2011;14:390–399

Zarit Burden Interview (ZBI)



Free for non-commercial use¹

Number of items	Scoring system	Validity	Limitations
22 items or 12 items (shortened version)	<ul style="list-style-type: none"> All items are scored on a five-point scale ranging from 0 to 4² Higher scores indicate that caregiving has a greater impact on the caregiver's life² <ul style="list-style-type: none"> ≥40/88 (full version) and ≥17/48 (shortened version) indicates a high level of burden³ 	Excellent internal consistency ($\alpha=0.83$ and 0.89) ⁴	<ul style="list-style-type: none"> The time taken to administer the 22-item version may deter HCPs;⁴ the shortened 12-item version has reported high correlation to the full version⁴

- The ZBI was developed specifically for caregivers of people with dementia and provides a comprehensive assessment of subjective burden²
- It focuses on different aspects of caregiving such as burden, emotional well-being, social and family life, finances, and feelings of control over their life²
- The ZBI is seen to be a valid, reliable, and widely recognized assessment for measuring subjective caregiver burden in AD⁵
- There are short versions of the ZBI available, such as the ZBI-7⁶

AD, Alzheimer's disease; HCP, healthcare practitioners; ZBI, Zarit Burden Interview; ZBI-7, 7-item Zarit Burden Interview

1. ePROVIDE. Zarit Burden Interview. Available from: <https://eprovide.mapi-trust.org/instruments/zarit-burden-interview> (Accessed June 2023);

2. Zarit Burden Interview. Available from: <https://nursekey.com/zarit-burden-interview-zbi/> (Accessed June 2023); 3. Stagg B, Lerner AJ. Prog Neurol Psychiatry 2015;19:23–27; 4. Bédard M, et al. Gerontologist 2001;41:652–657; 5. Reed C, et al. Health Qual Life Outcomes 2017;15:16;

6. Kühnel MB, et al. Support Care Cancer 2020;28:5185–5193

Clinical Endpoints

Design of clinical studies largely depends on the clinical stage

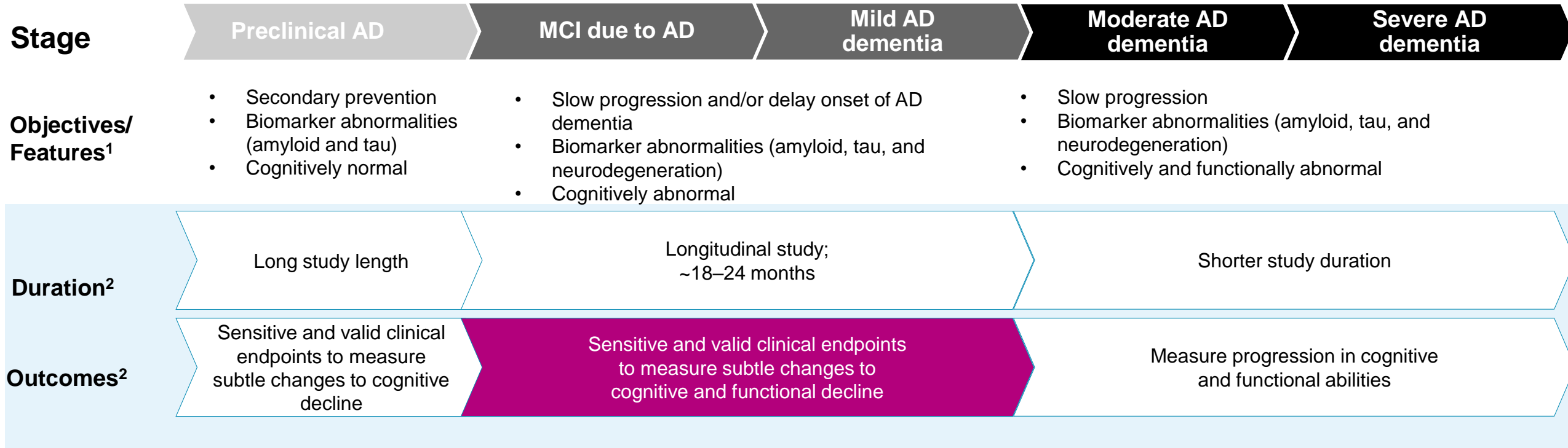


Image from Cohen S, et al. J Prev Alzheimers Dis. 2022;9(3):507-522. (License: CC BY 4.0 <https://creativecommons.org/licenses/by/4.0/>)

AD, Alzheimer's disease; MCI, mild cognitive impairment

1. Cummings J, et al. Alzheimers Res Ther 2019;76:11; 2. Cohen S, et al. J Prev Alzheimers Dis. 2022;9(3):507-522

History of clinical endpoint development for AD studies

- Historically, studies measuring efficacy of symptomatic treatments for the treatment of AD dementia were validated for overt dementia, not the early stages of AD¹
- In the early stages of AD, measurement may be more challenging; the FDA and EMA both called for novel approaches to assess efficacy of treatments in these early stages, recognizing the limitations of those validated for overt dementia¹
- The FDA guidance stated that a treatment should demonstrate efficacy on both a cognitive measure and a functional measure i.e., determine “that a clinically meaningful effect was established by a demonstration of benefit on the functional measure and that the observed functional benefit was accompanied by an effect on the core symptoms of the disease as measured by the cognitive assessment”^{1,2}
- It was suggested that integrated cognitive and functional endpoints, such as the **Clinical Dementia Rating — Sum of Boxes (CDR-SB)** score, could fulfil the requirement¹

CDR-SB, clinical dementia rating – sum of boxes; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration

1. McDougall F, et al. J Prev Alzheimers Dis 2020; 8:151–160; 2. FDA. Early Alzheimer’s Disease: Developing Drugs for Treatment Guidance for Industry, Draft Guidance. 2018

What are key considerations for choosing sensitive measures for clinical trials

Do they have acceptable levels of reliability and validity, as well as sensitivity to change over time?¹

Do the functional skill assessments feature instrumental activities of daily living, which are prone to early cognitive decline, or items indexing contemporary everyday activities, e.g., electronic banking, smartphone use?²

To what extent does any change in cognitive or functional scores reflect clinically meaningful changes?^{1,2}

For any test to be useful, its psychometric properties must be explored and shown to be adequate^{1,2}

1. Posner H, et al. *Innov Clin Neurosci* 2017;14:22–29; 2. Jutten E, et al. *Alzheimers Dement (N Y)* 2020;6:e12020

Clinical endpoints



Commonly used validated measures of cognitive, functional, and behavioral impairment in clinical trials include the following:¹

	Prevention trials	MCI due to AD trials	AD dementia trials
Cognition	<ul style="list-style-type: none"> • APCC • PACC 	<ul style="list-style-type: none"> • NTB • ADAS-Cog 	<ul style="list-style-type: none"> • ADAS-Cog (in mild to moderate AD dementia) • SIB (in moderate to severe AD dementia)
Function	–	<ul style="list-style-type: none"> • ADCS-ADL-MCI scale • A-IADL scale 	<ul style="list-style-type: none"> • ADCS-ADL scale
Behavior	<ul style="list-style-type: none"> • NPI-Q 	<ul style="list-style-type: none"> • NPI-Q 	<ul style="list-style-type: none"> • NPI-Q
Global/composite	–	<ul style="list-style-type: none"> • CDR-SB • ADCOMS • iADRS 	<ul style="list-style-type: none"> • CIBIC-Plus (in shorter trials) • CDR-SB (in longer trials)
Quality of life²	–	<ul style="list-style-type: none"> • EQ-5D • QOL-AD • Zarit Burden Interview 	

- Current clinical outcome measures for neurodegenerative disorders are limited because they are: **(1) rater dependent, (2) highly variable, and (3) episodic³**
- For any test to be clinically useful, its psychometric properties must be explored and shown to be adequate⁴
 - Indeed, while commonly employed cognitive and functional measures have acceptable levels of reliability, they often fare less well with regard to their validity and sensitivity to change over time⁵

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Scale; ADCOMS, Alzheimer's Disease Composite Scale, Alzheimer's Disease Cooperative Study Activities of Daily Living scale; ADCS-ADL, Alzheimer's Disease Cooperative Study—Activities of Daily Living; A-IADL, Amsterdam Instrumental Activities of Daily Living; APCC, Alzheimer's Prevention Initiative (API) Composite Cognitive; CDR-BS, Clinical Dementia Rating Dementia – Sum of boxes; CIBIC-Plus Clinical Interview-Based Impression of Change with Caregiver Input; EQ-5D, EuroQol 5-Dimension Questionnaire; iADRS, integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; NPI-Q Neuropsychiatric Inventory Questionnaire; NTB, neuropsychological test battery; PACC, Preclinical Alzheimer Cognitive Composite; QOL-AD, Quality of Life in Alzheimer's Disease Scale; SIB severe impairment battery

1. Cummings J, et al. Alzheimers Res Ther 2019;76:11; 2. Cohen S, et al. J Prev Alzheimers Dis. 2022;9(3):507-522; 3. Dorsey ER, et al. Digit Biomark 2017;1:6–13; 4. Posner H, et al. Innov Clin Neurosci 2017;14:22–29; 5. Jutten E, et al. Alzheimers Dement (N Y) 2020;6:e12020

Alzheimer's Disease Assessment Scale—Cognitive (ADAS-Cog)

- ADAS-Cog is utilized for assessing the efficacy of AD therapies and remains the most widely used measure of general cognition in AD clinical trials^{1,2}
 - The lack of reliability, sensitivity, and validity makes it generally **unsuitable for clinical settings**³
- Searches of electronic databases have identified **31 versions of the ADAS-Cog**²
- ADAS-Cog11 (11-item scale) can discriminate between the diagnostic categories of MCI, AD dementia, and cognitively normal²
- Responsiveness of ADAS-Cog11 to treatment effects appears low compared with other global endpoint measures²
- Simple modifications of ADAS-Cog11 have led to the development of ADAS-Cog12 (12 items), ADAS-Cog13 (13 items), and ADAS-Cog14 (14 items)²

AD, Alzheimer's disease, ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive; eADAS-Cog, electronic Alzheimer's Disease Assessment Scale—Cognitive; MCI, mild cognitive impairment

1. Evans S, et al. Eur J Epidemiol 2018;33:635–644; 2. Kueper JK, et al. J Alzheimers Dis 2018;63:423–444; 3. Cogo-Moreira H, et al. Assessment 2021;28:1708–1722

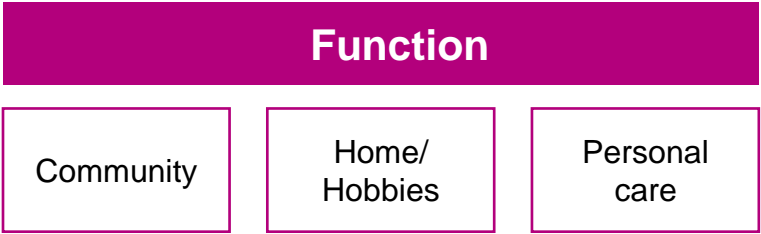
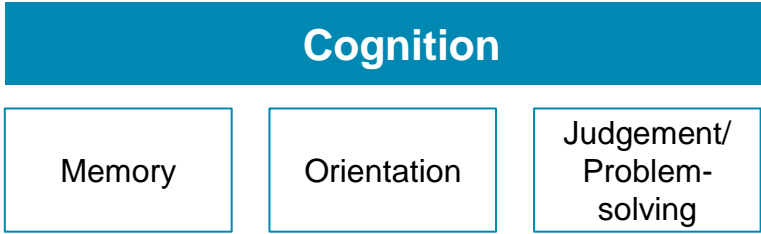
What is the CDR-SB?

- CDR is a global measure of cognition and function obtained by interviewing both patient and care partner difficulty¹⁻³
- It is a commonly used staging tool for AD in research settings, requires training, and takes ~25 minutes to administer, and conducted sequentially with the care partner^{1,4}
- The CDR is intended to measure “the influence of cognitive loss on the ability to conduct everyday activities”¹
- It covers six domains covering cognition and function; there are up to 10 questions per domain¹
- The sum of boxes of the CDR (CDR-SB) is the sum score of the six domains – it has been emphasized and applied to interventional clinical trials to track progression in the early stages²

1. Tzeng, RC, et al. Front. Aging Neurosci. 2022;14:1021792; 2. O'Bryant S, et al. Arch Neurol. 2008; 65(8): 1091–1095; 3. McDougall F, et al. J Prev Alzheimers Dis 2020; 8:151–160; 4. Cohen S, et al. J Prev Alzheimers Dis. 2022;9(3):507-522

What does the CDR-SB cover?

Domains¹



Scoring¹

- Each domain is graded as follows: 0, 0.5, 1, 2, 3
- Total scores range from 0 to 18
- Higher scores indicate greater disease severity

In the very early stages of AD (CDR 0.5)², the annual rate of change in CDR-SB scores is around 1–2

Scores by AD Severity¹

CDR-SB Total Score	Disease Severity	Global CDR score
0	Normal	0 (normal)
0.5–4.0 ➤ 0.5–2.5 ➤ 3.0–4.0	Suggests questionable cognitive impairment to very mild dementia	0.5 (very mild)
	Suggests questionable cognitive impairment	
	Suggests very mild dementia	
4.5–9.0	Suggests mild dementia	1 (mild)
9.5–15.5	Suggests moderate dementia	2 (moderate)
16.0–18.0	Suggests severe dementia	3 (severe)

1. O'Bryant S, et al. Arch Neurol. 2008; 65(8): 1091–1095; 2. Williams M, et al. Alzheimers Dement. 2013; 9(1 0): S39–S44

Domains measured in cognition



	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss, or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; “benign” forgetfulness.	Moderate memory loss, more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationship; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgement and problem solving	Solves everyday problems, handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in these activities	Moderate difficulty in handling problems, similarities and differences; social judgment usually maintained	Severely impaired in handling problems, similarities and differences; social judgment usually impaired	Unable to make judgments or solve problems

Table used with permission from Hughes CP, et al. Br J Psychiatry. 1982;140:566–572




Domains measured in function



	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Community affairs	Independent function at usual level in job, shopping, volunteer and social groups.	Life at home, hobbies and intellectual interests slightly impaired.	Unable to function independently at these activities, although may still be engaged in some; appears normal to casual inspection.	No pretense of independent function outside the home; appears well enough to be taken to functions outside the family home.	No pretense of independent function outside the home; appears too ill to be taken to functions outside the family home.
Home & Hobbies	Life at home, hobbies and intellectual interests well maintained.	Life at home, hobbies, and intellectual interests slightly impaired.	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned.	Only simple chores preserved; very restricted interests; poorly maintained.	No significant function in the home.
Personal care	Full capable of self-care		Needs prompting.	Requires assistance in dressing, hygiene, keeping of personal effects.	Requires much help with personal care; frequent incontinence.

Table used with permission from Hughes CP, et al. Br J Psychiatry. 1982;140:566–572

What does a change in score from 0.5 to 1 mean?

	Memory	Community Affairs	Home/Hobbies
CDR Domain Score 0.5 (Very mild impairment)	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Slight impairment in these activities	Life at home, hobbies, and intellectual interests slightly impaired
			
CDR Domain Score 1 (Mild impairment)	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned

Such losses of cognition and function (from 0.5 to 1 point), at these early stages of mild illness, are likely to be meaningfully felt by most patients, families, and care partners; delaying such losses for several months may therefore be of meaningful value

Scoring and interpretation of CDR-SB

- CDR yields two scores: Global CDR score and CDR-SB scores¹⁻³
- The global CDR score ranges from 0 to 3 and requires computation into an algorithm to stage dementia severity^{1,2}
- CDR-SB scores, with total scores ranging from 0 to 18, can track changes within and between stages of dementia severity over time. It also provides more information than the global CDR score in patients with both very mild and mild AD dementia¹

1. O'Bryant S, et al. Arch Neurol. 2008; 65(8): 1091-1095; 2. Tzeng, RC, et al. Front. Aging Neurosci. 2022;14:1021792; 3. Petersen RC, et al. Alzheimers Dement. 2023;19(6):2730-27

Alzheimer's Disease Composite Score (ADCOMS)

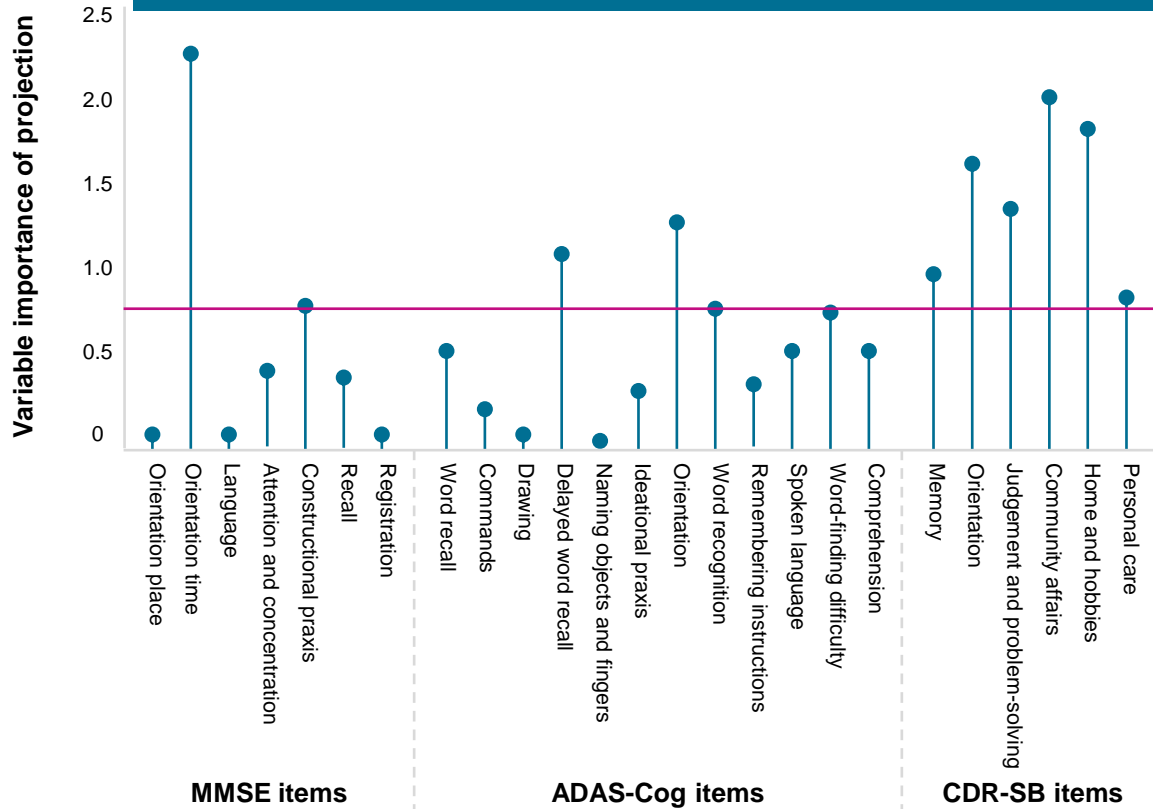
- ADCOMS combines items from existing scales and is used as a clinical outcome for preclinical AD and mild AD dementia trials
 - It consists of two MMSE items (**drawing** and **orientation**), four ADAS-Cog items (**delayed word recall**, **orientation**, **word-finding difficulty**, and **word recognition**), and all six CDR-SB items
- ✓ It has been shown to optimize sensitivity to clinical disease progression and specificity to the clinical decline in characteristics of early-stage AD dementia
- ✓ It shows superior sensitivity to change and treatment effects than individual trial instruments
- ✓ It may enable smaller sample sizes to show a drug-placebo difference

AD, Alzheimer's disease; ADCOMS, Alzheimer's Disease Composite Score; ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive; CDR-SB, Clinical Dementia Rating Dementia – Sum of boxes; MMSE, Mini-Mental State Examination

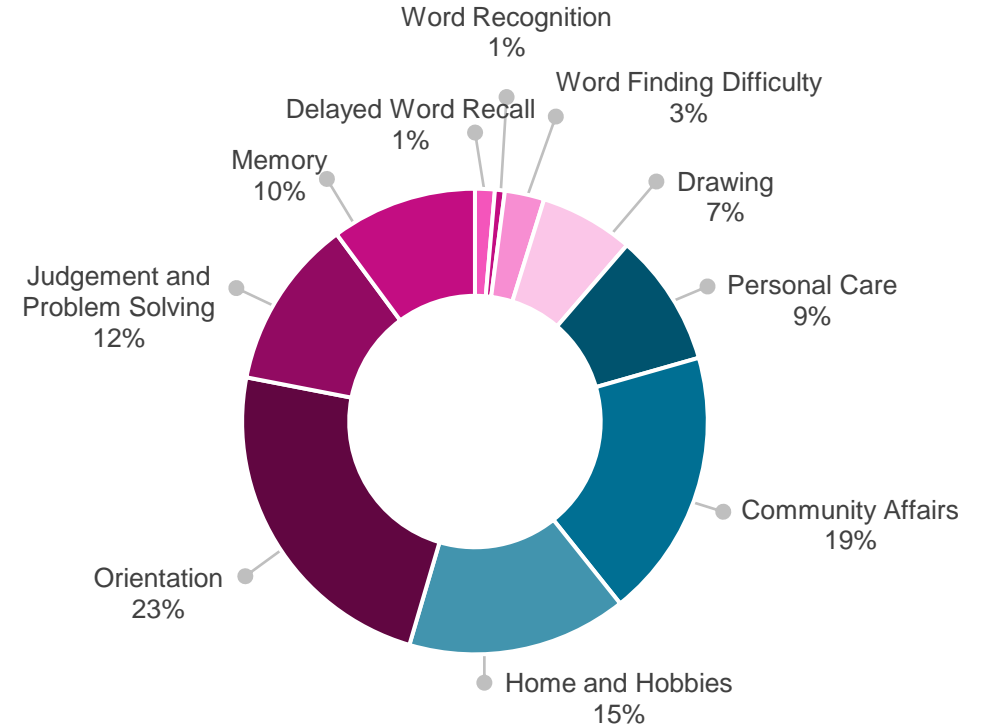
Wang J, et al. J Neurol Neurosurg Psychiatry 2016;87:993–999

ADCOMS was developed from commonly used scales

Variable importance of projection plot of PLS model fitted using the pooled-MCI dataset*



ADCOMS component selected to provide the most sensitive weight combination



Original weights for all items obtained from PLS analysis where total PLS weights alone is 1.97 - The PLS regression coefficients were scaled to form weighted composite score up to 101 for convenience

Left hand figure adapted from: Wang J, et al. J Neurol Neurosurg Psychiatry. 2016;87(9):993-999 (CC-BY 4.0: <http://creativecommons.org/licenses/by-nc/4.0/>).

*Items were selected if their variable importance of projection (VIP) scores were >0.8. The VIP summarizes the contribution each variable makes to the model. -ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADCOMS, Alzheimer's Disease Composite Score; CDR-SB, Clinical Dementia Rating-sum of boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PLS, partial least squares
 1. Wang J, et al. J Neurol Neurosurg Psychiatry. 2016;87(9):993-999. 2. Hendrix S et al. Presented at Alzheimer's Association International Conference, Vancouver, Canada, July 14-19, 2012.

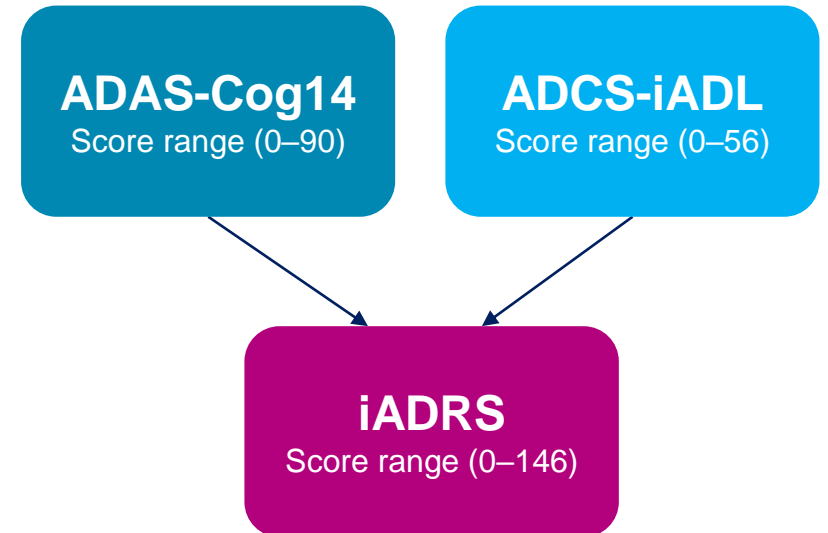
Integrated Alzheimer's Disease Rating Scale (iADRS)

A composite scale developed to measure the **cognitive** and **functional** domains of AD over time in observational studies and effects of treatments in clinical trials¹

- The iADRS is a composite scale that is calculated as a linear combination of total scores of the two individual components, the ADAS-Cog14 (score range 0–90) and the instrumental items of the ADCS-ADL (ADCS-iADL; score range 0–56)¹
- The iADRS score ranges from 0–146 with lower scores indicating worse performance¹
- Analyses using different data sets have shown that the iADRS is sensitive to disease progression, and has acceptable psychometric properties¹



Composite scales are potentially desirable for assessing treatment effects in clinical trials as they, in theory, provide a single primary outcome comprising cognitive and/or functional domains. However, they have been subject to criticism due to various limitations such as redundant tests, confounding practice effects, and lack of validation prior to use in trials²

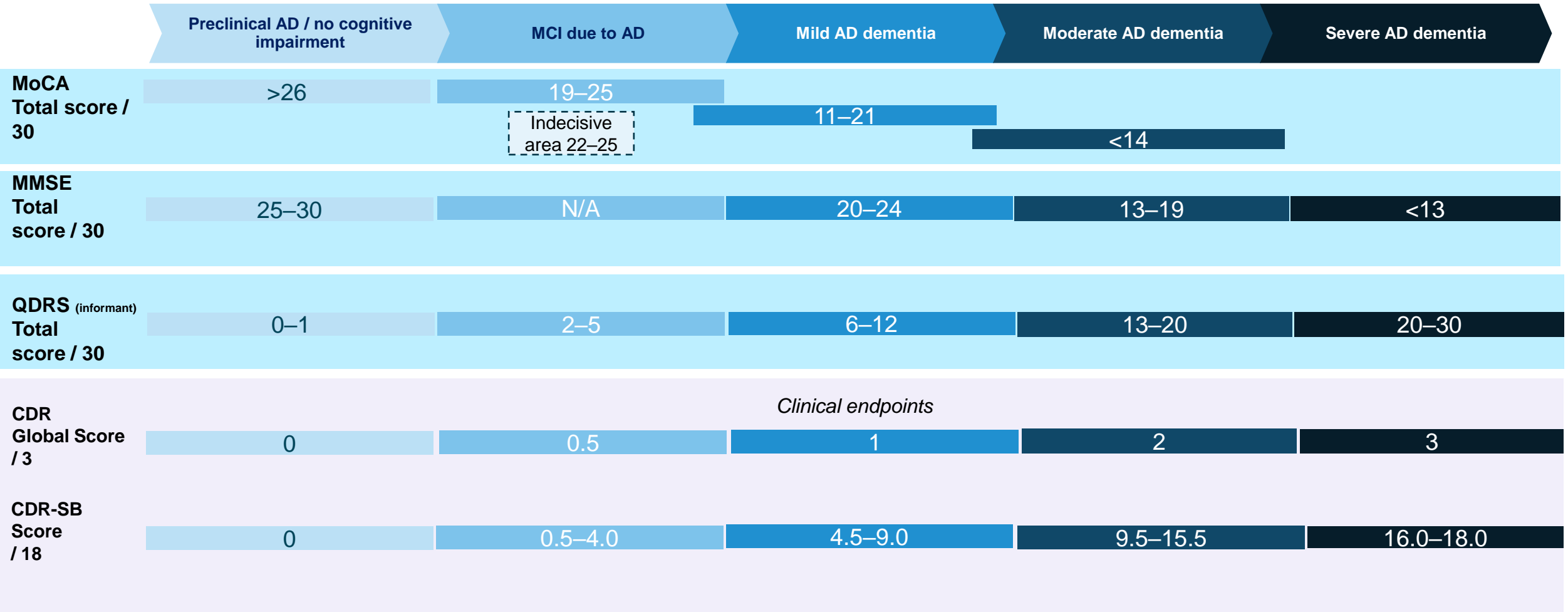


AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-(i)ADL, Alzheimer's Disease Cooperative Study-(instrumental) Activities of Daily Living; iADRS, integrated Alzheimer's Disease Rating Scale

1. Wessels AM, et al. J Prev Alzheimers Dis 2015;2:227–241; 2. Schneider LS, Goldberg TE. Alzheimers Dement 2020;12:e12017

Interpreting test scores

Interpreting test scores: where on the AD continuum?



1. Thomann AE, et al. *Alzheimers Res Ther* 2020;12:39; 2. Personal communication by Dr Nasreddine. 3. Alzheimer's Association. Medical Tests. Available from: https://www.alz.org/alzheimers-dementia/diagnosis/medical_tests; 4. Galvin JE, New York University of Langone Medical Center. The Quick Dementia Rating System (QDRS) 2013. Available from: <http://med.fau.edu/research/The%20Quick%20Dementia%20Rating%20System%20Instructions%20and%20Form.pdf>; 5. Galvin JE. *Curr Geriatr Rep* 2018;7:19–2; 6. Tzeng, RC, et al. *Front. Aging Neurosci.* 2022;14:1021792

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