

REVIEW ARTICLE

Advances in screening instruments for Alzheimer's disease

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Email: xzhou@sjnbiomed.com**Abstract**

At its fundamental basis, Alzheimer's disease (AD) is a pathological process that affects neuroplasticity, leading to a specific disruption of episodic memory. This review will provide a rationale for calls to screen for the early detection of AD, appraise the currently available cognitive instruments for AD detection, and focus on the development of the MemTrax test, which provides a new approach to detect the early manifestations and progression of the dementia associated with AD. MemTrax assesses metrics that reflect the effects of neuroplastic processes on learning, memory, and cognition, which are affected by age and AD, particularly episodic memory functions, which cannot presently be measured with enough precision for meaningful use. Further development of MemTrax would be of great value to the early detection of AD and would provide support for the testing of early interventions.

KEYWORDS

Alzheimer's disease, screen, screening instrument

1 | INTRODUCTION

Alzheimer's disease (AD) is an insidious, progressive, and irreversible neurodegenerative disease that is currently considered to start affecting the brain about 50 years before full disease manifestation (Braak stage V).¹ As the leading cause of dementia, accounting for 60-70% of all dementia cases, AD affects about 5.7 Americans² and over 30 million people worldwide.³ According to the "World Alzheimer Report 2018,"³ there is a new case of dementia developed every 3 seconds around the world and 66% of dementia patients live in low- and middle-income countries.

Alzheimer's disease is the only major disease that currently has no effective ways to cure, reverse, arrest, or even slow down disease progression once symptoms start. Despite advances made in understanding the underlying pathophysiology of AD, treatment for this disease has progressed little since AD was first reported by Alois Alzheimer in 1906.⁴ At present only five medications out of hundreds of agents tested have been approved by the US Food and Drug Administration for treatment of AD, including four cholinesterase inhibitors—tetrahydroaminoacridine (Tacrine, which was pulled from the market

due to toxicity issues), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne)—one NMDA receptor modulator (memantine [Namenda]), and a combination of memantine and donepezil (Namzaric). These agents have demonstrated only modest abilities to modify the effects of AD on learning, memory, and cognition for relatively short periods of time, but they have shown no significant effects on disease progression. With an average disease course of 8-12 years and the final years requiring around-the-clock care, the total estimated worldwide cost of dementia in 2018 was US \$1 trillion and this will rise to US \$2 trillion by 2030.³ This estimated cost is believed to be underestimated given the difficulty in the assessment of dementia prevalence and cost. For example, Jia et al⁵ estimated that the cost of AD in China was significantly higher than those figures used in the "World Alzheimer Report 2015"⁶ based on Wang et al.⁷

Developed on a continuum, AD begins with a clinically asymptomatic preclinical phase and continues through an early phase with mild cognitive impairment (MCI; or prodromal AD) affecting the ability to store new information into episodic memory and a progressive loss of old memories before leading eventually to fully manifested dementia.^{8,9}

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2 | THE BENEFIT OF EARLY DETECTION OF AD

Currently, definitive diagnosis of AD still relies on postmortem pathological examination, though even this analysis can be complex.¹⁰ Although significant progress has been made in AD biomarkers, clinical diagnosis of AD remains a process of elimination of other causes of dementia. It is estimated that around 50% of AD patients are not diagnosed during their lifetime in developed countries¹¹ and even more AD patients in low- and middle-income countries are likely undiagnosed.

The emphasis on early detection with subsequent early intervention has increasingly gained traction as the best course of action to combat AD. Significant efforts have been made towards the identification of effective preventative measures that may reduce the incidence of dementia and AD. Long-term follow-up studies have shown, for example, that adherence to the Mediterranean-Dietary Approaches to Stop Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet was associated with a 53% reduction in AD development¹² and that midlife physical and mental activities are associated with a substantial decline in dementia development¹³ with the caveat that these kinds of studies are difficult to control.^{14,15}

Although screening for dementia in populations without symptoms was not recommended by the United States Preventative Services Task Force based on evidence available before the end of 2012,¹⁶ screening in people with symptoms and at high risk for AD is important for early detection and diagnosis of AD, and is particularly critical for preparing patients and family members for the future prognosis of the disease. Furthermore, given the new evidence of potentially effective preventive measures^{12,13} and the benefits of early diagnosis of AD that the Alzheimer's Association outline in a special report entitled "Alzheimer's Disease: Financial and Personal Benefits of Early Diagnosis" in its 2018 "Alzheimer's Disease Figures and Facts"—including medical, financial, social, and emotional benefits² we believe that the United States Preventative Services Task Force may revise their recommendation in the near future in favor of screening people over a certain age without symptoms for AD.

Episodic memory is the earliest cognitive function that is affected by AD and early detection of AD is hindered by the lack of a convenient, repeatable, reliable, short, and enjoyable tool that provides automatic tracking of progression over time and is easy to administer. There is a major need for episodic memory assessment instruments that are validated and widely available to be used at home and in a doctor's office for the screening and early detection of dementia and AD. Although progress has been made using blood and cerebrospinal fluid biomarkers, genetic testing for risk genes, and brain imaging (including MRI and positron-emission tomography) for predication and early detection of AD, such non-cognitive measures are only distantly related to AD pathology. No strictly biochemical marker presently reflects any brain changes closely related to the fundamental aspect of AD, specifically the change in and loss of synaptic function related to the encoding of new information for episodic memory. Brain imaging reflects

synapse loss, which manifests as either local loss of metabolism or decreased blood flow, or decreases in synaptic markers in living patients, but does not adequately reflect the actual cognitive dysfunctions that characterize the dementia of AD. While the APOE genotype affects age of AD onset, amyloid biomarkers only reflect susceptibility to dementia, and tau has a complex but nonspecific relationship to dementia. All such measures are difficult to obtain, costly, and cannot be easily or frequently repeated. Detailed discussions of these AD-related factors are numerous in the literature and interested readers may examine several reviews and references therein.^{8,9,17,18}

There are three types of cognitive assessment instruments for the screening of AD: (1) instruments that are administered by a health-care provider; (2) instruments that are self-administered; and (3) instruments for informant reporting.¹⁷ This review will briefly summarize the currently available health-provider-administered instruments and status of a self-administered screening instrument that has the potential to (1) detect early AD-related cognitive changes before symptoms start and (2) assess disease progression.^{19,20}

3 | AD SCREENING INSTRUMENTS ADMINISTERED BY A HEALTH PROVIDER

The following should be considered when choosing an AD screening instrument or complementary instruments:

1. The purposes and settings of the screening campaign. For example, for a large-scale nationwide AD screening program, using an easy-to-administer, robust, and valid instrument would be preferred. On the other hand, in a clinical setting, accuracy and ability to differentiate different types of dementia would be more desirable.
2. Cost considerations, including cost of the instrument and health-care-provider training and administration time.
3. Practical considerations, including acceptability of the instrument to regulatory agencies, clinicians, patients; ease of administration, scoring, and score interpretation, including objectivity of the instrument (ie, influence of the technician/clinician administering the test on both the test and the scores); length of time required to complete; and environmental requirements.
4. Instrument property considerations, including: sensitivity to age, sex, education, language, and culture; psychometric properties, including dynamic range; accuracy and precision; validity and reliability, including ruggedness (minimization of changes related to the use of the instrument from, for example, different evaluators on the test results) and robustness (minimization of variability of test results related to different locations and environments); and specificity and sensitivity. Ruggedness and robustness are especially important considerations when choosing the instrument to use for a large-scale national AD screening campaign.

TABLE 1 Recommended screening instruments for Alzheimer's disease (AD) screen recommended by De Roeck et al²²

	Duration (min)	Memory	Language	Orientation	Executive functions	Praxis	Visuospatial abilities	Attention	Suitable for	Specificity for AD	Sensitivity for AD
MIS	4	Y							Population-based screen	97%	86%
									Clinic	97%	NR
MoCA	10-15	Y	Y	Y	Y	Y	Y	Y	Population-based screen	82%	97%
									Clinic	91%	93%
MES	7	Y			Y				Clinic	99%	99%

AD, Alzheimer's disease; MES, Memory and Executive Screening; MIS, Memory Impairment Screen; MoCA, Montreal Cognitive Assessment; NR, not reported; Y, indicated function measured.

An ideal instrument for AD screening would be applicable across sex, age, and sensitive to early changes suggestive of AD before the overt manifestation of clinical symptoms. Furthermore, such an instrument should be language-, education-, and culture-neutral (or at least adaptable) and able to be applied worldwide with minimal cross-validation needs in different cultures. Such an instrument is not currently available though efforts have been started in this direction with the development of the MemTrax memory test system,²¹ which will be discussed in the next section.

Clinicians started developing cognitive assessment instruments in the 1930s and a large number of instruments have been developed over the years.¹⁷ Excellent reviews have been published on a number of instruments—including the Mini-Mental State Examination, the Montreal Cognitive Assessment (MoCA), the Mini-Cog, the Memory Impairment Screen (MIS), and the Brief Alzheimer Screen (BAS)—that can be used in the screening and early detection of AD administered by a health provider.^{17,22,23} One of the most carefully developed screening tests is the BAS,²⁴ which takes about 3 minutes. Each of these instruments measures unique but often overlapping sets of cognitive functions. It is well recognized that each test has its own unique features and utility and a combination of instruments is often used to make a complete assessment in a clinical setting. Of note, most of these instruments were first developed in the English language in a Western cultural context and therefore require familiarity with both. Notable exceptions include the Memory and Executive Screening (MES),²⁵ which was developed in Chinese, and the Memory Alteration Test, which was developed in Spanish.²⁶

Table 1 lists validated instruments suitable for AD screening under different settings and recommended by De Roeck et al²² based on a systematic review of cohort studies. For a population-wide screen, MIS is recommended as a short screening instrument (<5 minutes) and MoCA as a longer screening instrument (>10 minutes). Both of these tests were originally developed in English, and the MoCA has many versions and translations so the variation between the versions needs to be considered. In a memory clinic setting, MES is recommended in addition to MIS and MoCA to better differentiate between AD-type dementia and frontotemporal type dementia. It is important to note that the results of screening tests are not a diagnosis but an important first step toward proper detection and treatment of AD by clinicians.

With the realization that AD develops on a continuum over a long period of time potentially stretching back over five decades before the manifestation of full-onset dementia, an instrument that could repeatedly measure episodic memory and other cognitive functions, such as attention, execution, and response speed, longitudinally and in different contexts (home versus health-care center) worldwide, is in great demand.

4 | CURRENT STATUS OF AD SCREENING INSTRUMENTS THAT CAN BE SELF-ADMINISTERED

Accurate measurement of AD from its preclinical phase through its progression to mild dementia is necessary for identifying AD early,

but a robust tool has not yet been identified for this purpose. As AD is predominantly a disorder of neuroplasticity, the central issue becomes identifying an instrument or instruments that can accurately probe AD-specific changes across all stages of AD. It is also critical to be able to measure these changes using metrics universal to the population yet unique to the individual over time, to detect the interaction between AD and sequelae of normal aging, and to assess where a subject lies on the continuum of early cognitive decline associated with AD relative to normal aging. Such an instrument or instruments would more properly ensure adequate enrollment, protocol adherence, and retention of subjects likely to benefit from therapeutic interventions and enable design of treatments and assessments of their effectiveness.

Scrutiny of several cognitive theories and approaches to memory assessment identified the continuous recognition task (CRT) as a paradigm²⁷ having a suitable theoretic basis to develop an early AD measurement instrument. CRTs have been applied extensively in academic settings to study episodic memory.²⁸⁻³⁰ Using a computerized CRT online, episodic memory can be measured at any interval, as often as several times per day. Such a CRT can be adequately precise to measure the subtle changes associated with early AD and distinguish these alterations from other neurological impairments and common age-related changes. The MemTrax memory test developed for this purpose is one such online CRT²¹ and has been available on the World Wide Web since 2005 (www.memtrax.com). MemTrax has strong face- and construct-validity. Pictures were selected as stimuli so that the influences of language, education, and culture could be minimized for easy adaptation in different countries around the world, which has proven to be the case with the implementation of a Chinese version in China (www.memtrax.com.cn and the development of a WeChat mini program version to accommodate user habits in China).

The MemTrax memory test²¹ presents 50 stimuli (pictures) to subjects instructed to attend to each stimulus and detect repetition of each of stimulus by a single response generated as quickly as the subject is able. A MemTrax test lasts less than 2.5-minutes and measures accuracy of memory of learned items (represented as percent correct [PCT]) and recognition time (average reaction time of correct responses [RGT]). MemTrax PCT measures reflect neurophysiological events that occur during the encoding, storage, and retrieval phases supporting episodic memory. MemTrax RGT measures reflect efficiency of the brain's visual system and visual recognition networks for identifying the complex repeated stimuli, as well as executive and other cognitive functions and motor speed. The brain has several steps for processing visual information and storing it in a distributed network of neurons. Recognition speed reflects how much time brain networks require to match a stimulus that has been recently presented and execute a response. The fundamental deficit of early AD is failure of the establishment of network encoding, so that information is progressively less adequately stored for it to be accurately or efficiently recognized.

Furthermore, MemTrax also examines inhibition. The subject is instructed to respond during the test only when a repeated stimulus/

signal is present. A correct rejection is when a subject does not respond to a picture shown for the first time. Consequently, a subject has to inhibit the impulse to respond to a new picture, which can be particularly challenging after two or three consecutive repeated pictures are shown. Therefore, false-positive responses are an indication of a deficit in the inhibitory systems of the frontal lobes, and such a pattern of deficits appears in patients with frontotemporal dementia (Ashford, clinical observation).

MemTrax now has been used by over 200,000 individuals in four countries: France (HAPPYneuron, Inc.); the United States (Brain Health Registry, a leader in recruiting for AD and MCI studies, www.brainhealthregistry.org), the Netherlands (University of Wageningen); and China (SJN Biomed LTD). Data comparing MemTrax to MoCA in elderly patients from the Netherlands³¹ show that MemTrax can assess cognitive function distinguishing normal elderly from individuals with mild cognitive dysfunction. Furthermore, MemTrax appears to distinguish Parkinsonian/Lewy body dementia³² (slowed recognition time) from AD-type dementia based on recognition time, which may potentially contribute to more diagnostic accuracy. A published case study also indicated that MemTrax could be used to track efficacy for effective therapeutic interventions in early AD patients.³³

Further studies are needed to determine:

1. MemTrax's precision, particularly in distinguishing common age-related effects on cognition, including learning and memory, from the longitudinal changes associated with early AD.
2. The specific relationship of MemTrax metrics to the continuum of AD progression from very early slight cognitive impairment to moderate dementia. As MemTrax can be repeated frequently, this approach can potentially provide a cognitive baseline and could indicate clinically relevant changes over time.
3. Whether MemTrax could measure subject cognitive decline (SCD). Currently, there are no objective assessment instruments that could detect SCD. MemTrax's unique properties demand an in-depth study of its utility for detecting SCD and one study is currently ongoing in China in this regard.
4. The extent to which the MemTrax test can predict future changes in AD patients on its own and in conjunction with other tests and biomarkers.
5. The utility of MemTrax and metrics derived from MemTrax measures alone or in conjunction with other tests and biomarkers as AD diagnostics in the clinic.

5 | FUTURE DIRECTIONS

For clinical and societal acceptance, there should be a "cost-worthiness" analysis for determining test benefit for early AD detection and early detection instruments. When screening for AD should start is an important issue that requires future consideration. This determination largely depends on how early before onset of symptoms a clinically relevant deficit can be

detected. There are studies indicating that the first detectable cognitive changes associated with the development of dementia occur 10 years before onset of clinically diagnosable symptoms.^{34,35} Neurofibrillary studies at autopsy trace AD back to about 50 years and may even extend into adolescence.¹ It has yet to be determined whether these early changes can be translated into detectable markers of cognitive dysfunction. Certainly, current instruments lack this level of sensitivity. The question then is whether future, substantially more sensitive, tests can identify much earlier changes in cognitive function related to AD and with adequate specificity. With the precision of MemTrax, particularly with multiple testing frequently repeated over an extended period, it could be possible for the first time to track the memory and cognitive changes in individuals at risk over a decade before clinically apparent cognitive impairment develops. Data on a variety of epidemiological factors (eg, obesity, hypertension, post-traumatic stress disorder, traumatic brain injury) suggest that some individuals are already predisposed to memory impairment and/or to developing dementia and AD in their forties or earlier.^{36,37} These widespread populations at risk demonstrate a clear need to identify and determine the earliest cognitive markers of early neurodegeneration and AD with suitable screening instruments.³¹

ACKNOWLEDGEMENTS

The authors thank Melissa Zhou for her critical reading of the article.

AUTHOR CONTRIBUTIONS

X.Z. participated in conceiving the review and drafted the manuscript; J.W.A. participated in providing contents relating to MemTrax and revising the manuscript.

CONFLICTS OF INTEREST

Xianbo Zhou: I serve as the General Manager and Legal Representative for SJN Biomed LTD, which brought the MemTrax memory test to China. J. Wesson Ashford: Patents/Royalties: I serve as an unpaid scientific advisor to MemTrax, LLC (a company managed by my adult son, Curtis Ashford).

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How to cite this article: Zhou X, Ashford JW. Advances in screening instruments for Alzheimer's disease. *Aging Med*. 2019;2:88-93. <https://doi.org/10.1002/agm2.12069>