Screening for memory disorders, dementia and Alzheimer's disease

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Dementia and its most common cause, Alzheimer's disease, affect memory and occur predominantly in the elderly. Dementia has become increasingly prevalent in the world as health has improved and life expectancy has increased. However, the fields of clinical care have not responded adequately to develop diagnostic tools and treatments for this rapidly increasing group of conditions. While scientists search for cures for the numerous causes of dementia, improvement of diagnostic measures are needed now and should begin with screening elderly populations for memory difficulties and other cognitive problems. This review examines the history of cognitive screening tests, the numerous excellent tests that are currently available and ready for use, and directions and methods that will lead to progressively better evaluations.

Keywords: Alzheimer's disease, cognitive, dementia, item response theory, memory, mental, mini-mental state, modern test theory, neuropsychology, screening

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There has been a growing question of whether to screen for dementia [1]. The proposed answer is that screening for memory dysfunction, dementia and Alzheimer's disease (AD) is important, but there are many practical and ethical considerations that need to be addressed before general screening practices can be widely implemented [2–5].

As of 2008, there are numerous recommendations for screening for a variety of conditions, including breast cancer, cervical cancer, colorectal cancer, skin cancer, diabetes, hypertension, high cholesterol, obesity, osteoporosis and even for depression, provided treatment can be offered [6]. However, the evidence for dementia screening has been complicated by a variety of factors, including the complexities of diagnosis and difficulties in assessing treatment benefits [7]. For example, screening needs to be directed toward dementia (generic inclusion of a group of related conditions that impair memory and other forms of cognition), AD (a specific disease process) or mild cognitive impairment (MCI [8–13], a loosely defined group of conditions considered to include states prodromal to dementia, particularly AD [12,13]). Clinicians should become prepared to evaluate and manage the vast numbers of undiagnosed cases currently estimated as well as the huge increase in numbers of demented patients expected between now and 2050. This preparedness must confront an additional obstacle, the considerable amount of ambivalence related to the prejudices about aging individuals and their optimal care. However, in general, patients have a positive reaction to dementia diagnostic information [14]. As the elderly population has progressively increased over the last 100 years and is expected to become a much greater proportion of the USA and world population in the future, the time has come to address the global medical needs to care for individuals with dementia and AD on a timely basis. Accordingly, there is a present need to develop appropriate screening programs for these conditions, so proper care can be initiated.

The purpose of this discussion is to review the history of testing for the presence of dementia and the problem of screening for dementia and AD. There are published guidelines (**Box 1**) and criteria (**Box 2**) for developing screening programs, which provide specific information about what to consider in the development of screening systems. Finally, an analysis will be presented for making recommendations for useful screening procedures.

The discussion of the secondary steps which must be taken in response to a positive screen to establish any diagnosis is beyond the scope of this presentation. However, it is critical to recognize that a screening test does not produce any diagnosis, anymore than a nonspecific blood test result would be considered a diagnosis. A diagnosis of dementia requires specific criteria (for example, the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [DSM-IV] [15] criteria for Dementia of Alzheimer Type), and the diagnosis of AD has been accepted to require clinical and neuropsychological assessment [16,17] to make a possible or probable diagnosis, with tissue examination required for a certain diagnosis. There are also considerable differential diagnostic issues for memory problems and

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Box 1. User's guides for guidelines and recommendations about screening.

Are the recommendations valid?

- Is there RCT evidence that earlier intervention works?
- Were the data identified, selected and combined in an unbiased fashion?

What are the recommendations and will they help you in caring for your patients?

- What are the benefits?
- What are the harms?
- How do these compare in different people and with different screening strategies?
- What is the impact of people's values and preferences?
- What is the impact of uncertainty?
- What is the cost–effectiveness?

Note: these guidelines are difficult to apply to a large, heterogeneous population such as that at risk for dementia.
Adapted from [119] for the Evidence-Based Medicine Working Group; authors based in the British Commonwealth.

dementia. There are related conditions for which separate screens might be considered, such as vascular dementia, alcohol dependence and depression, which are important for treatment determination. Depression, a treatable condition, may accompany or confuse the dementia diagnosis, in some cases even leading to a wrong diagnosis. Given the difficulties and importance of a correct diagnosis [18], careful attention to full clinical assessment following a positive screen is recommended.

A developing issue which has not yet been addressed in the literature to the point of making a clinical recommendation is screening for MCI. The concept of determining the earliest signs of cognitive impairment that will precede dementia has long been a topic of consideration [19]. The term MCI was introduced in 1991 [9], was defined as a clinically meaningful syndrome in 1999 [8] and has acquired standardized methods for distinguishing its clinical features [20], so that it is now recognized as a formal diagnosis (ICD-9 code 331.83), which Medicare (USA) recognized as a valid reason for neuropsychological testing in 2007. Tests are now being developed for screening for MCI, and these are discussed below.

History & progressive development of cognitive assessment for evidence of dementia

Since the 1930s, clinicians have developed a wide variety of tests for assessing cognitive function and facilitating clinical screening for dementia. In general, such tests have included the assessment of a range of functions, but few tests have been developed using specific theory, either about the mechanisms by which dementing diseases affect the brain, the continua of dementia severity associated with these various diseases, or the methodology of test construction.

Since 1960, many test developers have used classical test theory concepts, recommending unweighted combinations of binary or graded responses (frequently including Likert scaling) to simple tests or questions.

Virtually all cognitive, behavioral and functional tests used in medical research make an *a priori* assumption that the items take on values that are additive. In order for items to be added together to generate a total score, measurement properties of ordinality and concatenability must be demonstrated. If ordinality is satisfied, then nonparametric statistical methods can be used to analyze the test results, but parametric statistics cannot. If the items can be concatenated and ordinality is satisfied, then the items can be added together. Unless appropriate measurement properties are satisfied, the statistical methods that have been applied to the majority of cognitive, behavioral and functional tests in medical research may be invalid. This is a general problem in medical research that has largely been ignored, and is reflected in this review.

Several tests have been studied using the receiver operator characteristic (ROC) curve model (many investigations employing inappropriate subject sampling), though this approach requires a binary diagnostic decision not easily suited for a syndrome such as dementia that is complex and usually has an insidious onset. Modern test theory (item response theory and item characteristic curve analysis [21–26], specifically estimating level of ability/disability on a defined continuum based on performance, provides a considerably more powerful approach for test development. The implementation of this approach will be discussed. A practical example, the brief Alzheimer screen [27], a 3–5 min test (see Appendix), provides more information about the presence of dementia than the Folstein Mini-Mental State Exam (MMSE) [28]. Progressively better tests can be developed with this theory. Ideally, screening tests will become computerized and provide scores that indicate probability of dementia and 'maximum-likelihood estimates' of dementia severity.

Classical Test Theory & early mental status tests

Prior to 1960, there were numerous clinicians and authors studied cognitive function in adults and its deterioration with old age [29,30]. The first test to use an arithmetic summarizing of items to give a score indicative of cognitive function was the Mental Status Questionnaire (MSQ; ten points [31]). A major breakthrough occurred in 1968 with the publication of the Blessed

Box 2. UK National Screening Committee.

Criteria for appraising the viability, effectiveness and appropriateness of a screening program. Ideally all the following criteria should be met before screening for a condition is initiated:

The condition

- The condition should be an important health problem.
- The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
- All the cost-effective primary prevention interventions should have been implemented as far as practicable.
- If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications.

The test: there should be a simple, safe, precise & validated screening test

- The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
- The test should be acceptable to the population.
- There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
- If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening (if all possible mutations are not being tested) should be clearly set out.

The treatment

- There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
- There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
- Clinical management of the condition and patient outcomes should be optimized by all healthcare providers prior to participation in a screening program.

The screening program

- There should be evidence from high quality RCTs that the screening program is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g., Down's syndrome and cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
- There should be evidence that the complete screening program (test, diagnostic procedures and treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
- The benefit from the screening program should outweigh the physical and psychological harm caused by the test, diagnostic procedures and treatment.
- The opportunity cost of the screening program (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e., value for money).
- There should be a plan for managing and monitoring the screening program and an agreed set of quality assurance standards.
- Adequate staffing and facilities for testing, diagnosis, treatment and program management should be available prior to the commencement of the screening program.
- All other options for managing the condition should have been considered (e.g. improving treatment and providing other services), in order to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
- Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
- Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
- If screening is for a mutation, the program should be acceptable to people identified as carriers and to other family members.

Adapted from [305].

Information–Memory–Concentration (BIMC) test; (28 points max), whose values during life were correlated specifically with neurofibrillary tangle counts at autopsy in dementia patients [32]. The BIMC test became the only test that had autopsy validation, and its components are still used in the 21st century. These tests were quickly followed by other assemblies that provided a numerical score for dementia assessment including the Mental Test (34 points max) [33], the Abbreviated Mental Status Test (ten points max) [33], Mattis Dementia Rating Scale (144 points max) [34,35], the Hasegawa Dementia Rating Scale (32.5 points max) [36], the Information-Orientation Section [37], the Short Portable Mental Status Questionnaire (ten points max) [38] and the MMSE (30 points max) [28]; for reviews of early tests, see [19,39,40].

Over time, the MMSE became the most widely studied of these early and relatively similar applications of Classical Test Theory to dementia assessment. The MMSE was a test designed one evening [41] and is a compilation of questions that were generally recommended at that time for assessing patients for specific cognitive problems in medical or neurology settings (**Box 3**). The MMSE was developed as a brief means to administer a standard inventory to screen for mental dysfunction in a medical environment. The sum of correct responses was recommended for estimating normal mental function, the maximum total score is 30 with a score of 24 and above considered normal and scores below considered abnormal. The MMSE was not designed to test for dementia, but the MMSE score later became a popular index of dementia severity. The original MMSE form did not break questions down into individual items, but left them in two groups, the first section: orientation, registration, attention and calculation, recall (21 points); and the second section: language (nine points, including copying a complex figure). Clearly, the MMSE was not developed specifically to be a dementia screening test.

The MMSE and its items were derived from developments in the field of mental status testing that began before 1946. (For specific derivations, see **Box 3**). Clearly, most of the items of the MMSE were taken directly from prior writings and tests. The nature and total number of items, 30, is not substantially different from the tests developed before and at this time (as noted above). Furthermore, there is substantial overlap between the items of these tests and many other older and concurrently published tests and the MMSE (**Table 1**). None of these tests has ever been shown to be unique or significantly superior to any of the others [42], and none of them were developed using modern test theory. Consequently, these tests represent the efforts to develop screening methods for dementia and other types of cognitive impairment during an important early era of scientific advancement in the field of dementia and AD. However, the MMSE stands out more for its widespread use for estimating dementia severity for research studies rather than for any special properties or uniqueness that it has or for its clinical utility [43].

Between 1975 and 1995, the MMSE became the most widely used test for cognitive assessment in academic fields for research studies and among students [44,45]. The reason that the MMSE became the popular test may relate to its successful implementation of Wells' [46] recommendation to use a three-word memory list and orientation in dementia assessment. In addition to date and place orientation, the BIMC uses a memory component, an address of five parts that the subject is to learn and retain, which is not as expedient as the three-item recall. The Hasegawa test uses five objects that have to be shown to the subject, which is somewhat awkward for the subject and examiner. In addition, the MMSE was generally thought to be available for use without a commercial charge, and was accordingly widely reproduced for research, commercial, and clinical use (mostly encouraged by pharmaceutical companies when detailing physicians). Regarding the widespread use of the MMSE, in 1990 Folstein stated, "One possible reason for its popularity is that it is free". When discussing the possibility of copyright, McHugh said, "That would be like copyrighting the Babinski sign" [41]. Although the score of the MMSE has been used in clinical settings for communicating levels of patient severity, it has not found general or routine clinical use because it is too time-consuming, inefficient and incomplete for an adequate cognitive exam.

In 1998, Folstein sold the copyright for the MMSE to a private company. Subsequently, attempts to charge for the use of the MMSE have occurred and legal demands made to not use any form of the MMSE or derivations of it in public settings. Consequently, a significant copyright question surfaced as to what extent the MMSE items and their assembly constitutes a unique entity [47]. However, the MMSE really represents a typical test from the period of its publication, not a unique breakthrough, and it

Box 3. Geneology of items from the Folstein MMSE (developments before 1975).

Halstead summarized the literature prior to 1943 to develop his test, "In all, nearly 80 short tests or items were tried before the present scale took shape" [29]:

- Orientation
- Speech
- Memory
- General intellectual evaluation
- Understanding

(MMSE parts in italics, scoring points in parentheses)

***Orientation "what is the (year) (season) (date) (day) (month)"* (5 points)**

- Prior recommendations to assess orientation to time:
  - Day, month, year [29]
  - Date, day of month, month, year [31]
  - Year, month [32]
  - Day of week, date, month, year [162]
  - Day of week, date, year, season [46]
  - Day of week, date, month, year [33]
  - Knows day of week, month, year [163]

***"Where are we: (state) (county) (town) (hospital) (floor)"* (5 points)**

- Prior recommendations to assess orientation to place:
  - Name and location of place [29]
  - Location [164]
  - "Where are we now", "where is this place" [31]
  - Name of this place, address [162]
  - Type of place, name of hospital, ward, town [33]
  - Community, street [163]

***Registration: "name three objects"* (3 points; note: the MMSE does not specify which objects)**

- Prior recommendations to assess ability to repeat and remember items:
  - Two objects, such as pencil, table and a color
  - Tell the patient he will be asked to repeat these in 3 min" [30]
  - "...repeat three unrelated words immediately..." [46]

***Attention & calculation "Serial 7's"* (5 points)**

- Prior descriptions:
  - Studied as early as 1942 [165]
  - Described by Denny-Brown [30]
  - Described [164]
  - Use in prior scales [162]
  - Severe education bias noted [165]

***"Alternatively spell WORLD backwards"* (5 points, alternative to Serial 7's)**

- Reversing items [29]
- Related tests
  - Say the months in reverse order [29,32]
  - Naming of animals in 1 min [29]
  - Trails A,B [93] – count backward from 20 to 1 [32,33]
  - Days of week backwards, in addition to 7's [162]

***Recall: "ask for the three objects repeated above"* (3 points)**

- Prior descriptions of brief memory testing:
  - Retention recommended by Denny-Brown [30]: "two objects, such as a pencil, table and a color"
  - Tell the patient he will be asked to repeat these in 3 min; test after 3 min have elapsed
  - Paragraph retention [29], retention of items [164] and recall of address [32]
  - "...repeat three unrelated words ... after 5 min" [46]

"Mental status evaluation: often the presence of dementia can be established by a simple mental status examination demonstrating loss of memory for recent events, spatial and temporal disorientation, and generally diminished intellectual capacities. A schema for the systematic mental status evaluation is given in Table" (from Wells, 1971 [46]).

Box 3. Geneology of items from the Folstein MMSE (developments before 1975) (cont.).

Language: the MMSE language section follows the outline of the special study of Penfield and Roberts [166]

***"Name a pencil and watch"* (2 points)**

- Prior recommendations to test object naming ability:
  - Described by Denny-Brown [30]: "naming objects. The patient is asked to name a series of common objects shown to him... a suggested list of objects follows: ...pencil, wrist watch"
  - Six items, including point to pencil, name clock [167]

***"Repeat the following "no ifs, and or buts"* (1 point)**

- Prior description:
  This exact phrase was noted to be the most difficult phrase for patients with conduction aphasia to repeat [168]. Repetition of progressively more complex phrases [167]

***"Follow a three-stage command"* (3 points)**

- Prior description:
  - Three-step command [167]
  - Increasing step commands [166]

***"Read and obey the following"* (1 point)**

- Prior similar recommendations:
  - "Reading aloud" described by Denny-Brown [30]
  - Read sentence and respond [167]
  - Follow a written command [166]

***"Write a sentence"* (1 point)**

- Prior similar recommendations:
  - "Write some sentences"
  - Spontaneous writing [167]
  - Write a paragraph [166]
  - Defects in sentence structure [46]

***"Copy design"* (1 point)**

- Prior similar recommendations:
  - Cube imitation [29]
  - Intersecting pentagons [169]
  - The intersecting pentagons is a complex polygon similar to a Bender–Gestalt figure [28]
- Summation schemes applied to similar groups of items [169]
- 10 points – Mental Status Questionnaire – "special ten" [31]
- 28 points – Blessed Orientation–Memory–Concentration Test [32]
- 34 points – Mental Test score [33]
- Mattis Dementia Rating Scale [34]
- Short Portable Mental Status Questionnaire [38]

"Mental status evaluation: often the presence of dementia can be established by a simple mental status examination demonstrating loss of memory for recent events, spatial and temporal disorientation, and generally diminished intellectual capacities. A schema for the systematic mental status evaluation is given in Table" (from Wells, 1971 [46]).

has been reproduced in many variations that are substantively different and more reliable than the original [48–50]. As a result, there is legitimate reason to question a copyright claim for any test that is not identical to the published form of the MMSE. Since the administration of traditional 'bedside' cognitive assessments has now become a legal matter, there is need for judicial clarification of the extent of routine cognitive assessment that can be done without copyright infringements or commercial encumbrance.

The MMSE has been widely used in academic and pharmaceutical studies for estimating dementia severity for entry into clinical trials. However, in the clinical arena of dementia screening and severity assessment, the MMSE is considered a poor test because of its variability, poor sensitivity and specificity for screening purposes, poor precision and high floor effect [45]. A significant part of its problem for screening is the inclusion of items that add noise rather than discrimination between normal and demented individuals [21,51].

Table 1. Cognitive tests published in 1975 or before used for dementia screening.

Part	MSQ [31]	BIMC [32]	AMTS [33]	Mattis [34,35]	HDRS [36]	CAS [37]	SPMSQ [38]	MMSE [28]
Year published	1960	1968	1972	1973	1974	1975	1975	1975
Person								
Name		1		1		1		
Age	1	1	1		2	1	1	
Birthdate	2	1	1			1	1	
Birth place		1			2			
Place								
Name of site	1	1	1	1	1	1	1	1
Type	1	1			1			
Street		1			0.5	1	1	1
Town		1		1		1		1
County								1
State								1
Time								
Hour		2	1					
Date	1	1		1	1		1	1
Month	1	1		1	1	1		1
Year	1	1	1	1	1	1		1
Day of week		1		1		1	1	1
Season		1						1
Register				4				3
Attention								
Serial 7's					4			5
WORLD backwards					4			5
Other task		6	1	15		6	1	
Recall								
Address		5	1					
Objects				16	6			3
Persons		2	1					
Naming				8				2
Reading				4		3		1
Composing				1				1
Fluency				22				1
Visuospatial				25		10		1
Praxis				7		2		
Obeying				10				3
Abstraction				22				
Information								
Pres, etc	1	1	1	1	3	1	1	
Past pres, etc	1	1		1		1	1	
Other		7	1	1	6	1	1	
Total score	**10**	**37**	**10**	**144**	**32.5**	**33**	**10**	**30**

AMTS: Abbreviated Mental Status test; BIMC: Blessed Information–Memory–Concentration test; CAS: Clifton Assessment Schedule, HDRS: Hasegawa Dementia Rating Scale; Mattis: Dementia Rating Scale; MMSE: Mini-Mental State Exam; MSQ: Mental Status Questionnaire; SPMSQ: Short Portable Mental Status Questionnaire.

Furthermore, in many evaluations, the MMSE is not clearly better than any other similar test [52]. The MMSE has questions whose time to ask is considered wasteful and whose variance adds to the imprecision of the dementia severity estimate [53]. For practical clinical purposes, the MMSE is deficient because it leaves out person orientation items. It is also encumbered by its final six items that require props (pieces of paper, a writing implement, a prewritten command and a predrawn figure). Medicare, the major USA insurer for the elderly, specifically singles out the limitation of use of the MMSE in its policy for neuropsychological testing; "Brief screening measures such as the Folstein MMSE or use of other mental status exams in isolation should not be classified separately as psychological or neuropsychological testing, since they are typically part of a more general clinical exam or interview" [301]. It is time to recognize the important advances made by the BIMC and the MMSE in the historical development of dementia screening and severity assessment and move to more advanced test approaches.

Other test development directions

Since 1975, there have been many tests developed for assessing cognition, memory, and dementia, both for estimating impairment severity, for preliminary evaluation of diagnosis and for predicting dementia development some time in the future (**Box 4**). Most of these tests have been assemblies of items by clinicians based on their experience with demented patients. Some tests have been developed based on study samples or after evaluation of a limited number of test items. One direction of dementia severity assessment has been to evaluate the range of moderate to severe dementia severity (severe impairment battery [SIB]) [54,55].

Many studies have developed dementia assessment tools that are strictly cognitive or based on direct evaluation (**Box 4A**). Others have been based on the reports of knowledgeable informants (activites of daily living [ADLs], Functional Activities Questionnaire [FAQ], Alzheimer's Disease Cooperative Study/ADLs [ADCS/ADLs], AD8; **Box 4B**; see [56] for discussion). ADLs can also be assessed by direct observation [57,58]. General tools have been developed to allow clinicians to convey their impression of dementia severity (**Box 4C**). Some efforts have been made to combine direct testing and assessment with informant-derived information (e.g., Global Clinical Scale [GCS]; the Informant Questionnaire on Cognitive Decline [IQ-CODE] and the General Practitioner's Assessment of Cognition [GP-COG]; see **Box 4D**).

Relevant information for estimating whether dementia is present can be obtained over the telephone (**Box 4E**) or through computerized testing (**Box 4F**), even over the World Wide Web. Some tests are useful for assessment but not sufficient for dementia assessment when used alone (**Box 4G**).

A particularly important consideration is the use of a sequence of tests. As a practical approach, currently available tests that are short and sensitive can be used as initial screening tests. Short tests can be followed by more detailed assessment (**Box 4H**), then definitive diagnostic evaluation (e.g., **Box 4I**, [59,60]). Ultimately, breaking testing down into individual items, then allowing a computer to determine each additional item for query based on the performance of prior items, would produce the most efficient testing approach, a method referred to as computerized adaptive testing (CAT) [23]. The near future of such testing will likely be all computer based (**Box 4J**).

Modern test theory & the continuum of memory dysfunction

The problem with the numerous approaches for assessing dementia is the lack of systematic development. None of the past approaches has considered the underlying continuum of dementia severity that needs to be assessed and is essential to address when considering integration of diverse modalities of evaluation [48]. Therefore, the resulting tests are a diverse set of recommendations that have become impossible to reconcile without an extensive, unobtainable and untestable permutation of comparisons.

The first issue in considering the development of modern screening tests is to establish a specific continuum on which ability or disability can be measured [23]. AD is a specific neurodegenerative process that is best understood as a progressive disruption of neuroplastic processes [61–63], which is consequently manifested predominantly as a disruption of memory processing that secondarily affects other cognitive functions [19,52,63–65]. The initial aspect of memory that AD affects is the learning of new, complex information, with later and directly related disruption of recall (hypothetically, the new memory is not stored for later retrieval due to the abnormal metabolism of the amyloid preprotein and inappropriate phosphoryation of tau in the critical neuronal processes), loss of the storage substrate for old information (the tau hyperphosphorylation causes the formation of neuropil threads from tear down the dendrites that form the substrate of old

Box 4. Tests for mild cognitive impairment and dementia screening.

(A) Relatively brief cognitive & memory tests that have been advocated for dementia screening that are appropriate to administer to at-risk individuals

- Abbreviated Mental Test [33]
- Short Portable Mental Status Questionnaire [38]
- Clifton Assessment Procedures for the Elderly – Cognitive Assessment Scale [170]
- Blessed six-item [171]
- Visual memory, category fluency, temporal orientation [172]
- Short Test of Mental Status [173]
- Delayed Word Recall Test [66]
- Memory Impairment Screen [76]
- Three Word – Three Shapes [174]
- General Practitioner Assessment of Cognition [114]
- Six-item Screener [175]
- Efficient Office-Based Assessment of Cognition [176]
- Mini-Cog [177]
- Rapid Dementia Screening Test [178]
- Brief Alzheimer Screen [27]
- Short Cognitive Evaluation Battery [71]
- AB Cognitive Screen [179]
- Q and E [73]
- Mild Cognitive Impairment Screen [83]
- Blessed Memory Test/Category Fluency [180]
- Ten-item free recall with serial position effect analysis [181]

(B) Brief screening questionnaires for knowledgeable informants & inventories of activities of daily living

- Stockton Geriatric Rating Scale [182]
- Blessed Dementia Scale [32]
- Instrumental Activities of Daily Living (IADLs; note: basic ADLs [BADLs] assess greater impairment) [183]
- Clifton Assessment Procedures for the Elderly – Behavior Rating Scale [170]
- Functional Activities Questionnaire [184]
- Geriatric Evaluation by Relatives Rating Instrument [185]
- Record of Independent Living [186]
- Informant Completed ADLs [186]
- Informant Questionnaire on Cognitive Decline (IQ-CODE) [187]
- Direct Assessment of Functional Status [58]
- Alzheimer's Deficit Scale [188]
- Interview for Deterioration in Daily Life in Dementia [189]
- Nurses' Observation Scale for Geriatric Patients [190]
- Social and Occupational Functioning Assessment Scale [191]
- IADL/BADL [48]
- Cognitive Performance Test [192]
- DECO [193,194]
- Alzheimer's Disease Cooperative Study/ADLs [195]
- MDS Cognitive Performance Scale [196]
- Groningen Activity Restriction Scale [197]
- Cognitive Assessment Screening Test [198]
- Direct Assessment of Cognitive Abilities [57]
- Disability Assessment Scale for Dementia [199]
- Symptoms of Dementia Screener [200]
- Observation List for early signs of Dementia [201]
- General Practitioner's Assessment of Cognition Informant Interview [114]
- Sunnybrook & Women's six-item test (304)
- Financial Capacity Instrument [202]
- Alzheimer's Disease Caregiver Questionnaire [203]
- ADLs Questionnaire [204]
- AD8 [205]
- Patient-reported outcomes in cognitive impairment [206]

Box 4. Tests for mild cognitive impairment and dementia screening (cont.).

(C) Global impression scales

- Clinical Dementia Rating Scale (CDR) [111,112]:
  - CDR-sum of boxes [207]
  - CDR-extended [48]
- Global Deterioration Scale [110]
- Brief Cognitive Rating Scale [113]
- Functional Assessment Test [208]
- Alzheimer's Staging Scale [188]
- Confusion Assessment Method [209]

(D) Global synthesis/combining cognitive testing & informant report

- Global Clinical Scale [48]
- Milan Overall Dementia Assessment [210]
- IQCODE and Mini-Mental State Examination (MMSE) [211]
- IQCODE and 3MS [60]

(E) Telephone screening tests

- Telephone Interview for Cognitive Status [212]
- Telephone-assessed Mental State [213]
- TELE [214,215]
- Minnesota Cognitive Acuity Screen [216]
- Interactive-Voice Recognition Dementia Screen [217]
- Memory Impairment Screen – telephone version [218]
- MMSE – telephone version [219]
- Telephone Brief Screen for Cognitive Impairment [220]
- Indiana University Telephone-Based Assessment of Neuropsychological Status [221]

(F) Other cognitive testing modalities

- Web- and computer-based screening tools:
- Cognitive Stability Index [158]
- Neurotrax (a cognitive battery) [222]
- Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment (a cognitive battery) [160]
- Memtrax (a 2-min memory screen useable on the internet) [161]

(G) Nonspecific brief cognitive tests (useful component tests that are not appropriate for use as stand-alone exams)

- Temporal orientation [29,223]
- Category fluency (e.g., animal naming in 1 min) [29,224]:
  - Variant: the Set Test [225]
  - Category and Letter Fluency [68,74]
- Clock drawing task [226,227]
- Trail making tests A and B [93]
- Mental alternation test [228]
- Time & change test [229,230]
- WORLD test [231]
- Visual association test [86]

(H) Secondary, longer screening tests & cognitive/memory assesments for those positive on preliminary tests, or if there is a concern for detecting or measuring dementia

- Mattis Dementia Rating Scale [34,35,100]
- Cognitive Capacity Screening Exam [232]
- Extended Scale for Dementia – from Mattis [233,234,104]
- Modified MMSE [50,235,236]
- Alzheimer's Disease Assessment Scale – cognitive subscale [237]
- Cognitive section of CAMDEX [238]
- Neurobehavioral Cognitive Status Examination (renamed Cognistat in 1995)[239]
- High Sensitivity Cognitive Screen [240]
- Halifax Mental Status Scale [241,242]
- MMS-extended [48]
- Ottawa Mental Status Exam [243]

Box 4. Tests for mild cognitive impairment and dementia screening (cont.).

- The Repeatable Battery for the Assessment of Neuropsychological Status [244]
- Yokota Memory Test [245]
- Addenbrooke's Cognitive Exam [246]
- 7-min screen [70]
- Short and Sweet Screening Instrument [247]
- Saint Louis University Mental Status Examination [248]
- Rowland Universal Dementia Assessment Scale [249]
- DemTect [250]
- Montreal Cognitive Assessment [251]

(I) Specialty neuropsychological assessments; if questions, consider [252–255]

- Comprehensive neuropsychological batteries:
  - Wechsler Adult Intelligence Scale – Revised [256]
  - Consortium to Establish A Registry for Alzheimer's Disease [257]
  - Neuropsychological Test Battery [258]
- Relevant special tests for further dementia assessment of patients: memory tests (examples of commonly used tests for assessing memory in a patient that may have dementia [259]):
  - California Verbal Learning Test
  - Hopkins Verbal Learning Test
  - Buschke Selective Reminding Test
  - Fuld Object Learning Test
  - Rey Auditory Verbal Learning Test
  - Benton Visual Retention Test
  - Paired Associate Learning
  - Brief Visuospatial Memory Test
  - Rey–Osterreith Complex Figure (delayed recall)
  - Wechsler Memory Scale
  - Visual and Verbal Paired Associates (with delayed test)
  - Paragraph recall
- Tests of other cognitive functions relevant to dementia assessment:
  - General intellectual function: Ravens Progressive Matrices
  - Executive functioning tests (e.g., Wisconsin Card Sort, Stroop Color–Word Test, Digit-Symbol Test and Letter Cancellation)
  - Language Tests (Boston Naming Test)
  - Visuospatial Tests (Trail Making Tests A and B, Hooper Visual Organization Test)
  - Praxis Tests (Consortium to establish a registry for Alzheimer's disease [CERAD] Praxis Test)
- Tests of functions less affected by dementia that provide comparison
  - Vocabulary: National Adult Reading Test
  - Motor function: finger tapping and grooved peg-board

(J) Developments in computerized cognitive screening tests

- CANS-MCI [307]
- Cognosis [308]
- Cognitive Drug Research [309]
- Cognitive Screening Test [310]
- CNS Vital Signs [311]
- Cognometer [312]
- Cogstate [313]
- Cognistat [314]
- Cognisyst [315]
- Cog Screen [316]
- CogTest [317]
- IntegNeuro [159]
- Medical Care Corporation [318]
- Medical Decision Logic, Inc. [319]
- MemTrax [320]
- MicroCog [321]
- NetMet [322]
- Neurotrax [323]

memories), language impairment (aphasia is characterized by lost memory of old words), apraxia (memory of how to do things is lost) and other cognitive dysfunctions. Dementia due to other types of neurodegenerative processes must be understood with respect to how those other processes disrupt cognition (vascular dementia affects white matter cortical connections, B12 deficiency affects hippocampal memory systems, etc.). Thus, the first step in developing a diagnostic test for dementia and AD is to understand exactly what needs to be tested. For AD, the fundamental focus is memory on a unidimensional continuum. However, other causes of dementia (those that result in a posterior-temporal, inferior parietal type of cognitive disruption) may follow a similar pattern, while other causes (e.g., those that cause a fronto-temporal type of dementia) may lead to a different continuum. A dementia syndrome may appear heterogeneous due to disruption of diverse cognitive processes until the underlying vulnerable factor is determined. For screening purposes, the initial focus should be on finding a change in the single underlying factor, while multifactorial or empirical approaches can be considered when the basic mechanism is not understood or there are multiple critical types of pathology that need to be targeted by the screening process.

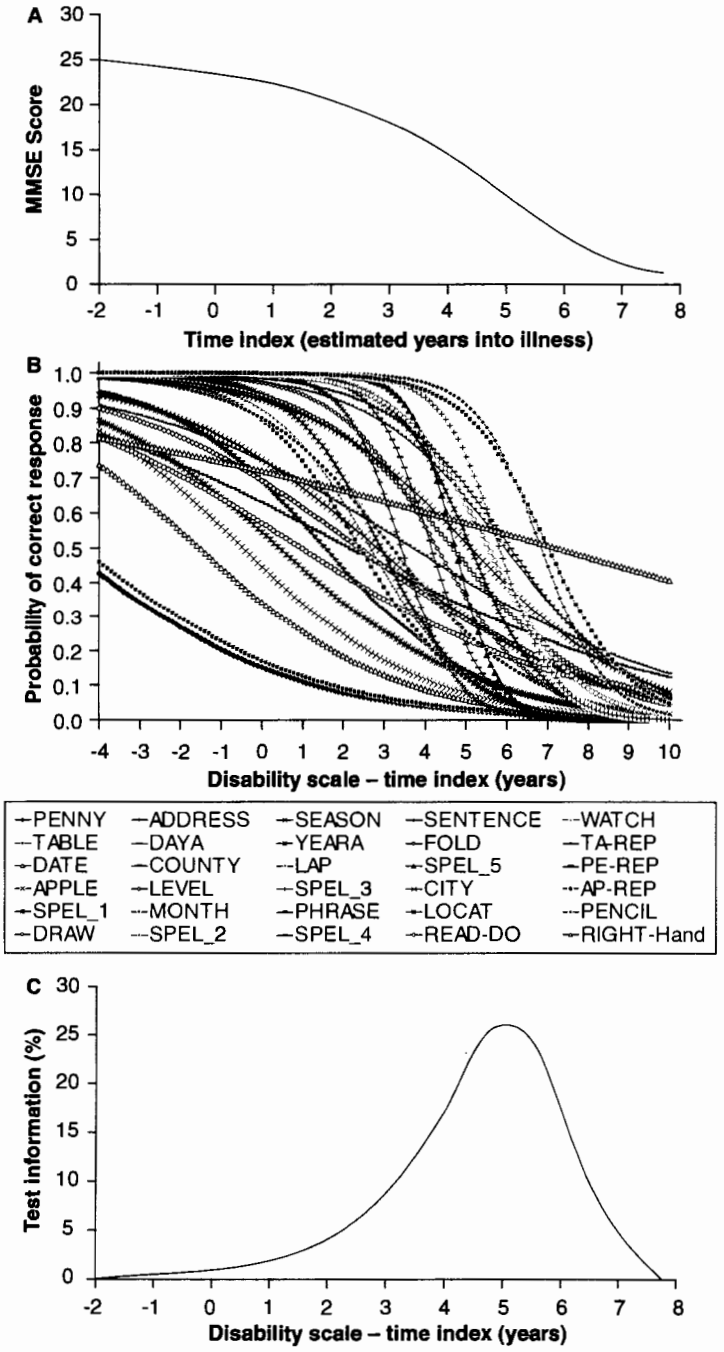
Since the recognition that AD is primarily a disease of memory mechanisms, there have been several efforts to use memory tests for detecting AD. One example is the delayed word recall test (DWR) [66]. For simplicity, many dementia screening tests have extended the three-object memory and temporal orientation using supplemental items that add discrimination power along the continuum from normal through MCI to mild dementia. Useful additional items that indirectly test memory include clock-drawing [67] and animal naming in 1 min [48,68,69–73–75]. An improved memory assessment for dementia, the memory impairment screen [76,77], using theoretical concepts related to the disruption of neuroplastic mechanisms in AD, has shown particular strength as a dementia screening test. A 'double memory test' has also been proposed as an even stronger indicator to evaluate memory dysfunction as a reflection of very early AD [78]. Of relevant interest is the observation that the 1958 Rey Auditory Verbal Learning Test (RAVLT [79]), a classic test of verbal memory function, is still one of the best predictors of MCI indicative of early AD [80–82], and similar tests derived from the basic principle of delayed recall are among the best tests for predicting AD diagnosis in very mildly impaired individuals [75]. Following the development of the focus on learning and memory, a sophisticated mathematical analysis of performance on the ten-word recall of the Consortium to Establish a Registry for AD (CERAD) study discriminates strongly between normal individuals and those with MCI and dementia [83]. Furthermore, a classic test of visual memory, the Benton Visual Retention Test [84] is a good predictor of incipient AD [85], as is a test of visual .associative memory [86]. These clinical research findings support the notion that AD is quintessentially a disease of memory processing and focus on memory dysfunction is the optimal approach to early determination of the presence of AD. However, to apply the study of memory to dementia measurement, it is necessary to define the continuum of memory ability and disability.

The DSM-IV [15] provides a well accepted definition of dementia as an impairment of cognition, including memory, and at least one other function that interferes with social function. The critical issue in screening for dementia, particularly the Alzheimer type, is to assess memory function. Thus, the initial step in discovering dementia is evaluation of memory function. To determine the presence of dementia, a second step is required, involving further assessment of memory, and brief ancillary testing for dysfunction in other areas of cognitive function, including agnosia, anomia, apraxia and executive impairment. Furthermore, to determine dementia criteria, an evaluation should be conducted to determine the impact of cognitive dysfunction on social or occupational function. Screening steps need to be performed and analyzed as quickly as possible. There is a pressing clinical and academic need for the development of shorter, more effective, more efficient, and legally free brief assessment tools.

Modern test theory & dementia screening test development

Modern test theory was first applied to dementia assessment in 1989 when Item Response Analysis was applied to the MMSE [21]. This study demonstrated how the specific items of the MMSE were behaving with respect to the continuum of dementia as indexed by the MMSE score. The most difficult items (those whose function is lost earliest in the progression of the AD-type dementia) are the

Figure 1. Extent of progression of patients with Alzheimer's disease with respect to duration of illness.



(A) Calculation of Mini-Mental State Examination score versus duration of dementia from the Consortium to Establish a Registry for Alzheimer's Disease data. **(B)** Calculation of item characteristic curves with respect to duration of dementia. **(C)** Calculation from 1A, shows square of summed slope.

three memory items and orientation to date (which is also a test of recent memory). The findings of this study were specifically confirmed by an independent group [87].

A problem with the initial item-characteristic curve study was the use of the MMSE as the continuum. Using a mathematical calculation of longitudinal data, a 'time-index' continuum of dementia severity was developed [88]. The time index reflects a specific physical value, time (conveniently in 'year units') related to the AD progression. To expand the applicability of the time index, the analysis was replicated using the CERAD data set, which was drawn from 30 Alzheimer Centers around the USA. This data set was used to recalculate the relationship between the MMSE score and the time-index continuum to reflect the general relationship between the MMSE and the duration of AD-type dementia in the USA, thus providing a reliable estimate of the mean extent of progression of patients with AD with respect to duration of illness (**Figure 1A**) [53].

The cognitive impairment associated with AD forms a continuum from slight memory difficulties (which cannot be distinguished from normal function) through mild impairment, to mild dementia, then to moderate, severe and profound dementia [53,88,89]. Scores on any test of cognitive function can be referenced to a time-index value. Such an index provides a highly useful metric to assess dementia severity and estimate the rate of progression. Early in this continuum, when dementing disease manifestations are just developing, this time index can also be used for developing the first steps of screening, initially focusing on memory function.

Using the time-index scale for gradating the dementia continuum, individual test items can be studied for their levels of difficulty and the extent to which they are able to discriminate lower levels from higher levels of disability. Using this continuum for the analysis, the relation of specific MMSE items to the continuum of progression was assayed [88]. The probability values that a particular item will be performed correctly at each point on the time-index continuum forms an 'item-characteristic curve' (this approach is commonly referred to as item response theory or modern test theory). As further confirmation of the derived values and to provide generally applicable values for difficulty and discriminability, the items of the MMSE administered to patients in the CERAD study (the last major data set collected before wide use of antiacetylcholinesterase medications) were analyzed with this method (**Figure 1B**). These analysis results are similar to prior analyses of these items [21,88], but provide values that

are applicable to the general USA population (Figure 1B; Table 2). Furthermore, item bias related to racial, education and cultural factors can be incorporated into analyses to enhance broad applicability [90].

For the MMSE items, only the three recall items and the date provide relative discrimination at the mild end of the continuum, where discrimination is most critical for dementia screening. Based on these findings, most modern screening tests for dementia have employed the concepts revealed by this item response analysis in their development and have included or focused on memory and related temporal orientation items.

Table 2. Mini-Mental State Examination items numbered and described difficulty (in year units) and discriminability.

Item	Description	Difficulty	Discriminability
1	Date	-0.96	-0.511
2	Month	2.43	-0.785
3	Year	2.94	-0.953
4	Day	1.42	-0.487
5	Season	3.06	-0.705
6	Location	5.11	-1.114
7	Floor	2.43	-0.374
8	City	4.77	-0.672
9	County	2.72	-0.535
10	Address	1.87	-0.684
11	Apple–repeat	6.84	-1.261
12	Table–repeat	5.66	-0.729
13	Penny–repeat	5.62	-0.916
14	Spell-all (WORLD backwards)	1.69	-0.905
15	Spel-4	2.86	-1.271
16	Spel-3	3.43	-1.503
17	Spel-2	4.16	-1.514
18	Spel-1	4.73	-1.896
19	Apple–recall	-0.83	-0.409
20	Table–recall	-5.91	-0.286
21	Penny–recall	-4.35	-0.389
22	Watch–name	5.73	-1.608
23	Pencil–name	7.01	-0.986
24	Repeat 'no-ifs-ands-or-buts'	3.59	-0.576
25	Read and obey 'close-eyes'	5.45	-1.032
26	Take paper in right-hand	5.13	-0.311
27	Fold paper in half	4.54	-0.703
28	Put paper in lap	3.25	-0.827
29	Write a sentence	4.20	-1.069
30	Draw intersecting pentagons	1.83	-0.498

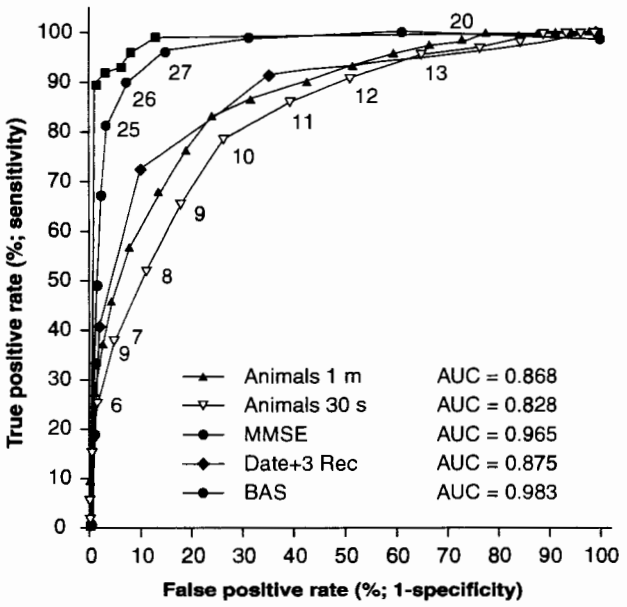
Calculated from the Consortium to Establish a Registry for Alzheimer's Disease data, patients with probable Alzheimer's disease, using Proc Logit (SAS).

The information contributed by each item to understanding a subject's position on the curve can be calculated, and all of the items summed, showing where in the continuum of dementia severity the test provides the most information. The test-information curve for the MMSE (Figure 1C) shows that the MMSE provides a minimal amount of information in the mild impairment range, where screening is at issue.

Using logistic regression analysis of the CERAD data, including the MMSE items, a test with greater power than the MMSE for mild dementia screening was constructed, which includes the three-object recall, temporal orientation, animal naming and spelling WORLD backwards, the final score, constituting the Brief Alzheimer Screen (see Appendix), has more area under the ROC curve than the MMSE (Figure 2) [27,91]. This development shows that attention to test item characteristics (as opposed to classically constructed tests) can improve the power and efficiency of dementia screening. Another study of MMSE items showed that the full set of MMSE items was no better than a reduced set at predicting emergent AD [92]. A prospective study comparing presymptomatic subjects who later developed AD diagnoses with those who did not, examining numerous relevant cognitive tests, showed that delayed word-list memory and trail making tests [93] had the greatest discrimitive power [94], and a logistic combination of these tests provided optimum predictive probability of developing AD within 1.5 years [95]. A 22-year prospective study identified retentive memory and abstract reasoning measures as the strongest predictors of further development of AD [96]. Such studies suggest that the first step in dementia screening is the determination of the presence of significant memory dysfunction, with additional power provided by tests that require manipulation of memory traces.

The screening tests discussed above still do not account adequately for the probabilities of dementia as cognitive function fails in older individuals as part of the continuum from normal aging to mild dementia [97]. Part of the problem is that AD pathology exists in individuals without a diagnosis of dementia [98], and older individuals with these changes may not even show any signs of cognitive impairment [99]. Furthermore, there are ethnic and cultural factors that can influence performance on individual items [100]. ROC conceptualization of the assessment problem leads to the understanding that as there is less and less pathology, performance curves for even the most

Figure 2. Comparison of CERAD data calculated scores for control versus mild Alzheimer's disease.



AUC: Area under the curve; BAS: Brief Alzheimer Screen; CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

discriminating tests will begin to overlap the normal distribution more and more. In the earliest phases of dementia development, less and less distinction can be made between the normal and pathological conditions, thus creating the dilemma of diagnostic uncertainty. An initial focus on memory function appears to be the most effective and least invasive target for screen development, allowing specific determination of a developing problem without a commitment to an uncertain diagnosis.

The important implication of modern test theory is that, with understanding of the characteristics of the performance of items across the temporal continuum of the severity of AD-type dementia, more efficient tests can be tailored to assess the status of an individual. No specific test can provide an appropriate staging system [101]. However, location on the temporal continuum can be estimated by combining the probabilities of where the vector of item responses of a test indicates that a subject should be on the temporal continuum, a point of maximum likelihood, with appropriate error estimation. That calculation provides the optimal estimation of the subject's probability of having significant memory dysfunction or being demented and identifies at what location they lie on the dementia continuum. Modern test theory provides the method to assemble items to form the test that provides the most information in the transition from normal to mild impairment to early AD. Current tests provide numerical scores rather than probabilities of having dementia and are studied with ROC, using binary outcomes related to the presence of a diagnosis rather than a determination of the degree of underlying pathology. Future tests must rely more heavily on modern test theory, provide probabilities of dementia severity or AD pathology, use ROC analysis based on the continuum of progression from normal through MCI to dementia, and be components of systems that are continually improved.

Attention to the measurement linearity of the continuum from 'normal' through mild cognitive dysfunction to early dementia can improve the assessment of items for selection and combination for screening purposes. The use of z-scores (number of standard deviations) from the normal population mean is not an adequate approach for quantifying this continuum for assessing the likelihood of dementia (as is done with Wechsler Adult Intelligence Scale scoring even in the elderly [102]) because the normal distribution of function is difficult to determine as cognition changes with age and the proportion of individuals with preclinical dementia changes with age (z score = 2 corresponds to 2.3% of the population; z score = 3 corresponds to 0.1% of the population; z score = 4 corresponds to 0.01% of the population – accordingly, to reach a data-set-derived z score of 3, over 1000 normal subjects are needed in a study population and for a z score of 4 over 10,000 are needed; while 0.1% of the population has AD at age 62; 1% at 78; and 10% at age 94 – thus z scores cannot accurately reflect the spectrum of memory dysfunction from normal through MCI to mild dementia and they cannot reflect the spectrum of dementia severity in affected patients). The typical modern test theory approach uses z scores (standard-deviations from mean performance) [103] or eigenvalues [104] (from a principal components analysis that considers the potential multidimensionality of a phenomenon), and therefore does not reflect the continuum of cognitive dysfunction of AD with interval linearity, either from normal to mild cognitive dysfunction or across the duration of dementia. Instead, a scale with equal-interval linearity would best assess the cognitive dysfunction/dementia continuum reflecting the disease process, and in AD, this could be the temporal course of the disease [88] or

an underlying biological factor, as might be determined on a brain scan [105,106]. Such approaches should be used for test development for severity assessment, screening and prediction of cognitive decline. Some recent studies have tried to apply a branch of modern test theory, Rasch modeling, to examine differential item functioning of the MMSE components [107,108]. However, this approach examines the dimensional-order/difficulty of test items without attention to the discriminability of the items along the dementia continuum, and therefore loses the information regarding the relative value of each different item for considering the items' contributions to delineating where along the continuum an individual is most likely to be, for example, for the development of screening tests. Future tests should use computerized-adaptive testing to optimize efficient use of individual test items for determining where a subject is most likely to lie along the continuum [23].

A particularly powerful approach to dementia severity assessment is the combination of information from cognitive testing, a knowledgeable informant, and a clinician's impression [48,109]. This approach improves estimation of dementia severity over the MMSE by a factor of at least 3 [53]. In addition to the cognitive scales that have been developed, there has been considerable attention to ADLs which correspond highly to the degree of cognitive impairment. For screening purposes, there is considerable utility for the higher level instrumental ADLs (including FAQ and AD8, see **Box 4B**). Furthermore, global impressions using structured interviews can give a useful indication of whether dementia is present as well as its severity, for example, the Global Deterioration Scale (GDS) [110], the Clinical Dementia Rating Scale (CDR) [111,112] and the Brief Cognitive Rating Scale [113], although such tests are generally unreliable and imprecise when used alone. Using multiple sources of information and mathematically combining their valuations, considerably increases the reliability of the screening assessment (GP-COG [114] and Global Assessment of Dementia [48]). This approach is successful as each nonredundant item contributes information to predicting where a subject lies on the cognition/dementia continuum and accordingly reduces the standard error of the measurement [23]. By melding these three sources of information using the time-index continuum and modern test theory concepts, substantially better screening tests can be developed (**Box 4D**).

Deciding whether to administer a memory or dementia screen

Now that many good dementia screening tests are available [1,115–118], the time has arrived to consider the implementation of widespread screening for memory problems and dementia in at-risk populations. Task groups from various organizations have made specific recommendations about dementia screening, generally providing negative, ambiguous or ambivalent suggestions [1]. Working groups from the British Commonwealth have developed specific definitions and guidelines for the process of deciding whether screening is appropriate [119] (UK-NSC, 2003) (**Boxes 1 & 2**) [303]. Such guidelines indicate the issues that need to be addressed in developing screening recommendations and tools but do not provide a means to evaluate the data for initiating action. To develop a clear decision process for determining whether a medical test is appropriate to administer, there are specific factors which can be examined mathematically using ROC analysis approaches [120]. In the mathematical approach, the question of whether to screen reduces to: 'Is a screening test costworthy?' There are six factors which must be estimated for this calculation:

- I = incidence of the disease in the population to be screened for the epoch (e.g., number of new cases developing in 1 year);
- Sp = specificity, pertains to the normal, disease-free population and distribution of test scores on the continuum of cognitive ability/disability being measured. The value of this factor relates to where along this continuum the delineation point (cut-point) is selected for study;
- Se = sensitivity, this value relates to the distribution of test scores on the continuum for a group of patients with a specific level of impairment (this must be in the population being studied);
- $B = the benefit (advantage) of a true-positive test for the identified individual;
- $C = the cost (harm) of a false-positive test for a wrongly identified individual;
- $T = the cost of the screening test plus administration and time for all parties.

Sensitivity is the probability of correctly detecting the impaired (target) group of individuals, while specificity is the probability of correctly detecting the normal (control) group. For calculation purposes, the values of

specificity (Sp) and sensitivity (Se) can be estimated from the measured difficulty and discriminability of the test for the normal, unaffected population (dif[sp]) and dis[sp], respectively) and the studied patient population (dif[se]) and dis[se], respectively). These values are determined with respect to a cut-point (cp) for the test being chosen to discriminate between those with and those without the condition. This is an example, using a logistic regression model (other models may be used), of how Sp and Se can be estimated:

$$Sp = \frac{e^{dis(sp)*(cp-dif(sp))}}{1+e^{dis(sp)*cp-dif(sp))}}$$

$$Se = \frac{e^{dis(se)*(cp-dif(se))}}{1+e^{dis(se)*cp-dif(se))}}$$

Plotting Se versus Sp for all possible cut-points gives the traditional ROC curve.

These values are then entered into an equation to determine whether administration of a test can be justified, that is, whether it is costworthy, $W [120]:

$$\$W = (\$B \times I \times Se) - (\$C \times [1-I] \times [1-Sp]) - \$T$$

If $W is positive, then the test is costworthy (this equation is mathematically identical to a cost–benefit ratio, just providing a different and arguably more useful measure).

In this calculation, a false-negative test result is ignored because the cost or harm of this outcome is relative to the true-positive outcome and is not different to the outcome without the screening test being present. The true-negative outcome is similarly ignored because its benefit is similarly relative to the cost or harm of the false-positive result and is trivially different to the condition in which no screening test is available.

With the basic issues of screening established, the value and utility of screening tests can be objectively determined. The value of $W can be calculated for various screening scale delineation points (cut-points) with knowledge of the distribution of scores for the normal and target patient population, and then the optimal delineation point (cut-point) can be estimated. However, each value contributing to $W can be analyzed as a function of factors contributing to that variable. Screening is costworthy if $W is positive.

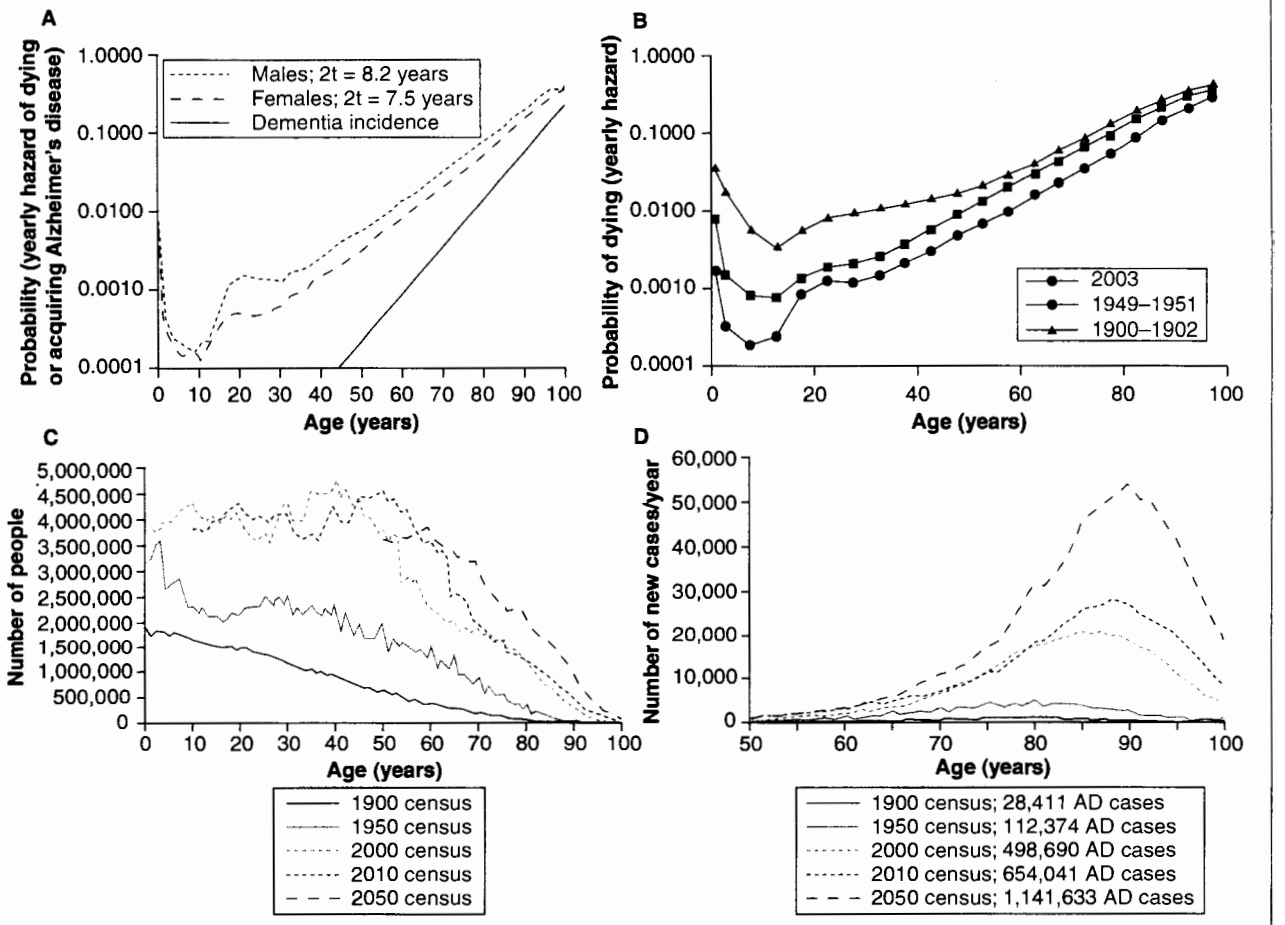
Incidence (annual risk) of dementia & Alzheimer's disease

In the process of deciding whether to screen a person or population for the presence of memory problems or dementia, the primary issue is the incidence of the condition. Incidence is an integral factor in balancing the costs and benefits of testing, affecting the value of the detection of true-positive cases, the price of false-negatives, and, therefore, the total cost of administering the screening system.

The largest causal factor in the incidence of dementia and AD is age. It has been well established that AD accounts for approximately two-thirds of dementia cases. The incidence of AD increases exponentially with age, doubling approximately every 5 years [121,122], with notable rates of one per 1000 individuals at 62 years of age, one per 100 at 78, and one in ten at 94 (**Figure 3A**). One of the reasons that the prevalence of dementia is increasing so dramatically is that the incidence of dementia increases approximately 50% faster with age than mortality rate (which, in the USA, doubles every 7.5 years for women and every 8.2 years for men between 30 and 95 years of age [123]. As numerous causes of mortality have been reduced in the USA in the last century, particularly for younger individuals (**Figure 3B**), and the baby-boom is expected to increase the proportion of older individuals until the year 2050 (**Figure 3C**), a large increase in the incidence of AD is predicted in the near future (**Figure 3D**, **Table 3**). Of further concern, the incidence of MCI, a condition manifesting primarily as memory dysfunction prodromal to AD, is essentially equal to the dementia incidence, making the concern twice as great [12,13].

The next biggest factor affecting incidence of memory problems and dementia is the *APOE* genotype [123–125]. This genotype appears to play a direct role in age-related incidence [126,127] and can easily be incorporated into the age-related estimation of incidence (**Figure 4**) [128]. The reported autosomal dominant genetic factors (e.g., presenilin and amyloid-preprotein mutations) cause AD at a much younger age, but contribute very little (generally considered to be less than 5%) to the total incidence of the disease [129,130]. However, the *APOE* genotype plays such a major role that genotyping, at a cost of US$200 per subject, for the purpose of determining at what age screening would be recommended, would be worth the cost of the test (**Figure 5A**) [4].

Figure 3. US population: census data and population mortality, and dementia incidence estimations and projections.



(A) Taken from [306] and [324] and estimation of dementia incidence as described. **(B)** Taken from [324] (mortality is risk of dying in 1 year; dementia hazard calculated from an estimation of 4 million getting dementia in 2000, risk doubling in 5 years).
(C) Data from [324], according to age to 2000, projected up to 2050. **(D)** Alzheimer incidence calculated from hazard rate (in **B** and **C**).

There are numerous other factors that have been shown to affect dementia risk or that may affect risk, including education, gender, history of head injury, history of headache, etc. Each one of these factors has been shown to have an odds-ratio for its effect on risk. If these odds-ratios are applied to the incidence factor for age and possibly genotype, then there would be a substantial improvement in the calculation of the costworthiness for a memory or dementia screening test (this approach is often referred to as Bayesian).

Memory & dementia screening tests: evaluating accuracy

There are numerous tests that have been studied for their efficacy in assessing individuals for the presence of cognitive impairment, dementia and AD. At this time, there is no one test that is clearly better than all of the others.

There are two test-related criteria that must be considered when evaluating the accuracy of a test, sensitivity and specificity [120]. Many screening exams have been subjected to an analysis of these factors and reported on a ROC curve, frequently showing the AUC. However, except for head-to-head comparisons, such curves are meaningless independently unless the data have been collected from a population prospectively, with the diagnosis determined with blinding to the administration of the screening test (usually needed to be done before the diagnostic evaluation). For a common example, administering a test to a group of patients being brought for dementia evaluation and the individuals bringing them for visit, then calling the proportion of failed tests in the diagnosed patients sensitivity and the proportion of incorrect tests in their companions specificity, are not data that can be

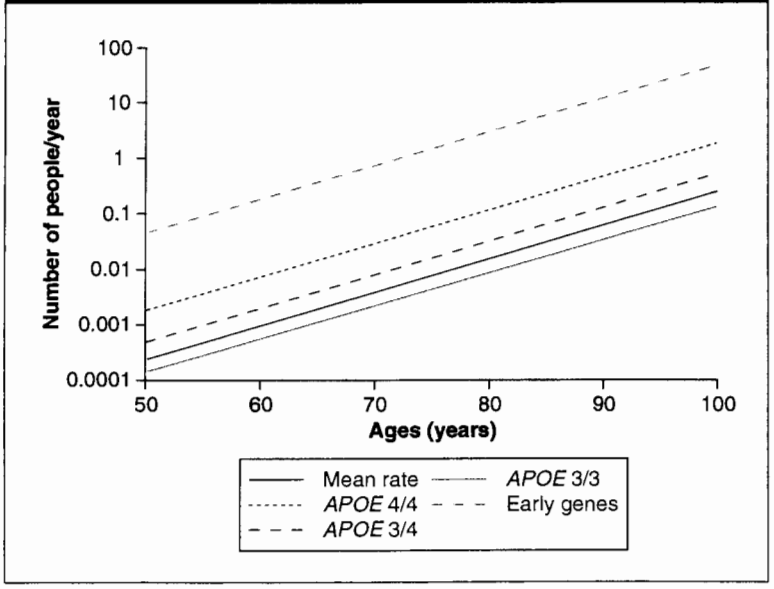
Table 3. Estimated incidence of Alzheimer's disease in the population over 50 years of age and based on age-specific incidence estimations for a single year.

Year	Number of people over 50 years of age	Number of people over 50 years of age developing AD/year (%)
1900	10,025,861	28,411 (0.28)
1950	33,604,790	112,374 (0.33)
2000	76,818,531	498,690 (0.65)
2010	96,130,417	654,041 (0.68)
2050	116,203,744	1,141,633 (0.98)

Estimates for future years based on 2000 census and increase of longevity with the same age-specific Alzheimer rate for all years (e.g., one per 1000 at age 62 and doubling every 5 years).
Adapted from [306].

used to assess the utility of the test (such information is of preliminary interest in comparing different tests only). Even if the study was just applied to all presenting patients, the result could only be applied to the population of patients sampled. For an extreme example, if all nursing home patients fail a test and all college students pass a test, it is not permissible to infer that the test has 100% sensitivity and 100% specificity. Clearly, for a test to be fairly evaluated, a representative community sample must be chosen and studied prospectively, first using the screening test, then applying the diagnostic criteria, including precise assessment of disease severity, to determine the sensitivity and specificity of the test. This analysis approach still does not account for the ultimate diagnostic uncertainty, the controversies and complexities of pathological analysis at autopsy [131,132].

Figure 4. Incidence rate of Alzheimer's disease according to *APOE* genotype.



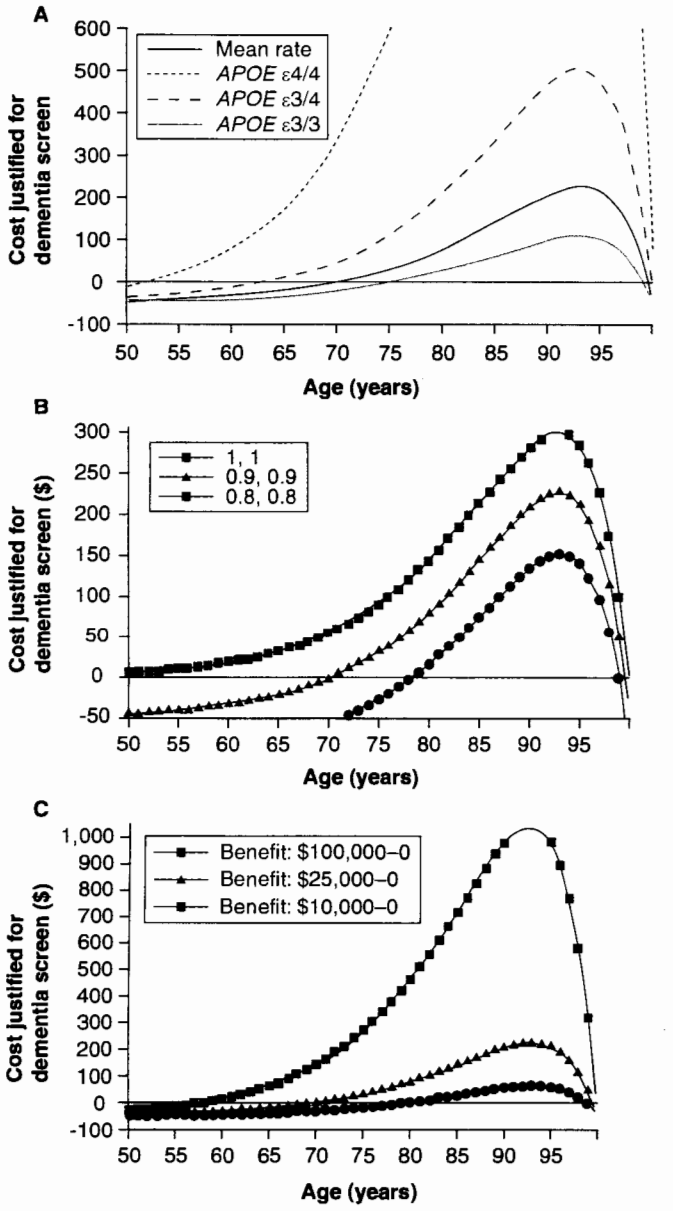
Part of the difficulty in using the ROC curve approach is that the ROC is really designed to distinguish two discrete signals, where each creates a normal but overlapping distribution in perception (this methodology was originally developed for radar signal detection during World War II). Accordingly, the ROC approach is most useful for distinguishing a normal population (with no dementia or AD) from a sample population with a specific amount of memory problems, dementia and/or AD. Hence, it is fundamentally important to determine disease severity in patients, beyond the question of the manifest dementia. When populations are mixed, then the analyses only apply to the population being studied.

Variations in the specificity and sensitivity of a test can have a substantial impact on $W, the cost justified for a screening test (Figure 4B). Furthermore, using the age-specific incidence curves, $W can be positive for a range of cut-points, as well as other measurable or cost factors.

Cognitive memory, dementia-screening tests: evaluating efficiency

An additional factor that must be considered in evaluating a screening test is efficiency, which relates to how long the test takes and how many resources must be available for test administration. Presumably a longer test could provide more information than a short test, but the question is whether there is sufficient improvement of sensitivity and specificity to warrant the increase of resource use. Furthermore, a test could involve numerous props or computers to improve sensitivity and specificity, but there must be sufficient improvement in the accuracy of the test to warrant the added costs. In the current analysis, the aspect of costs are reflected in the value of $T.

Figure 5. Calculations of costworthiness of dementia screening.



(A) Calculations of costworthiness of a hypothetical test according to *APOE* genotype. **(B)** Calculations of costworthiness of a hypothetical test according to the sensitivity and specificity of the test (assuming equal values of 1, 0.9 and 0.8). **(C)** Calculations of costworthiness of a hypothetical test according to benefit.

Additional issues in evaluating the utility of a test are the costs and benefits of the various possible outcomes. These factors interact with the sensitivity and specificity and must be included in the determination of whether a test is costworthy. For example, whether an illness is very rare or common makes a considerable difference in how much benefit the screening provides, as does the potential seriousness of the condition. Specific analyses must be performed to determine the costworthiness of the screening test for its efficiency in distinguishing various levels of memory dysfunction, predementia or mild dementia from normal. Of interest, is the long-term benefit of identifying a particular level of cognitive impairment (particularly as opposed to the current situation where early recognition is near random) [1,3].

An important factor in determining the utility of a test is its cost-per-unit-time efficiency. The precise amount of time that a test requires is relevant to the cost of the test. Long tests often do not have significantly greater diagnostic accuracy than shorter tests, and it may not be possible to use them cost effectively in a setting where the highly valuable time of a clinician is required for the test. Various subjects will have different constraints on the availability of their time for testing. These time factors can be precisely measured and valued.

The cost efficiency (total energy used in administration) of a test may be calculated from the power that it provides for discriminating dementia patients from unaffected individuals per unit time (these parameters can be related to basic physics quantities: power across time, which yields energy). The power of a test can be calculated from information theory and item response theory. The spectrum of cognitive function from the normal range to mild dementia then through the phases of dementia to profound impairment can be conceived as a continuum [53]. When a test estimates the position of a patient's impairment on the dementia ability–disability continuum, the more precisely it is estimated on the continuum, the more information that is provided by either that test or that item of the test (for example, see **Figure 1c**). The power of the test can be calculated from the performance curve of the test on a population of individuals that has been drawn from across the continuum of severity. In turn, the efficiency (energy) of the test is derived by multiplying the power (P) by the time (T) required for the test ($P \times T$, like relating the wattage of a lightbulb to the amount of electricity charged by the power company, it corresponds to how long the bulb was lit). Extending the ROC approach, the application of the test to a clinical population requires judicious direction of the energy in a population with relevant incidence and defined costs and benefits of the testing.

Benefits for an individual with a correct positive screen

As outlined in Box 5, there are numerous benefits and harms potentially associated with dementia screening. There are extensive subjective and cultural considerations in balancing many of these issues [2]. A recent study shows that AD diagnostic information actually decreases anxiety in most groups, regardless of diagnostic outcome or dementia severity, and actually provides some relief [14]. However, for considering objective analysis of whether to screen for memory dysfunction or dementia, factors must be selected that can be summarized as specific monetary values. The specific values to estimate are the costs associated with a false-positive test and those of a true-positive test.

The value of an accurate dementia diagnosis has been the source of considerable debate. Clearly, in the occasional case of a treatable condition, the value is very large. For routine cases that turn out to have AD, there is benefit that is difficult to quantify related to providing the patient and family clear information to plan for the extensive issues that can be expected to arise in the future. Medications have also been shown to have benefit [133], which has been recognized by the US FDA. However, there is the continued question of what value interventions have. One point that can provide a benchmark for estimation purposes is the nursing home placement delay of nearly 2 years that has been observed for cholinesterase-inhibitor medications [134,135]. Using an average delay in nursing home placement for an early diagnosis, and valuing that delay at either $10,000, $25,000 or $100,000 for a 50-year old individual, with a linear decline to zero for a 100-year old individual, the value of the true-positive early diagnosis, $B, can be entered into the calculation (Figure 5C). As can be seen, the value of benefit, $B, also has a substantial impact on $W, the cost justified for dementia screening.

The costs & harms of a false-positive screen

For the sake of estimation, the cost of a false-positive result on a primary screening test should include the cost for performing a secondary, more complete assessment, whose result can be considered to be highly reliable. It is essential to recognize that receiving a failing result on a screening test is not a diagnosis. False-positive results are a statistical probability in a normal population for such tests. There is a range of low performances that should lead to a more complete and reliable assessment. In the dementia screening process sequence, that resulting assessment should involve a preliminary examination by a trained professional and include a more extensive cognitive evaluation, interview of an informant knowledgeable about the patient's daily function, appropriate neuropsychological assessment, and a summary rating, followed by a discussion of the implications of the conclusions with the subject and a caregiver. One consideration to reduce this misconception that a failed screen diagnoses dementia (by both subjects and clinicians) is to call the initial step in this disease discovery process memory screening. A failure at the initial screening stage would then carry less stigma and be more likely to lead to proper dementia assessment. A current problem in medical systems is that there are inadequate resources to properly assess individuals that have failed a screening test. There is then the added risk of inappropriate management of the false-positive tests in clinical systems that are not prepared to accommodate screening testing. This state of lack of preparation adds to the cost of a false-positive diagnosis. However, over time, with progressive improvement in the education of clinicians concerning dementia diagnosis and management, this cost of the false-positive screening tests will diminish and the value of the true-positive screens will increase.

The cost of a secondary memory assessment will depend on a variety of local economic conditions. For the purposes of this analysis, that cost is estimated to be $250 (in 2008 dollars). If the evaluation is negative, the subject has confidence that there is not a problem. If the assessment is positive, it is based on a high-quality analysis, and the next step is a complete dementia evaluation [89,136,137], incurring costs that are probably tenfold beyond the preliminary assessment. However, a decision to initiate the complete evaluation should be based on appropriate clinical information and concern. At this point, there should be an insignificant number of inaccurate decisions to advance subjects to further study. If the false-positive rate at this point were as high as 10%, then an additional cost of $250 should be added to the above estimate, yielding a value of $500 for the false-positive cost, $C (used in Figure 5).

Calculation of costworthiness of screening

The value of $W can be calculated for various values for the ages 50 to 100 years, when the incidence of AD is estimated to approximately double every 5 years (Figure 3A). Costworthiness graphs

Box 5. Benefits of dementia screening; costs and harms of not screening.

Psychological & social benefits from early dementia recognition

- Early education of caregivers on how to handle the patient.
- Advance planning while patient is competent, establishing a will, proxy, power of attorney and advance directives.
- Reduced patient and family anxiety, uncertainty and stress, and improved family understanding of demented patient, reduced caregiver burden, blame and denial.
- Promote safety in driving, medication compliance, cooking, etc.
- Patient's and family's right to know, especially regarding genetic risks.
- Promote advocacy for research and treatment development.

Medical benefits from early dementia recognition

- Early diagnosis and treatment and appropriate intervention might improve overall disease course substantially, including lessening the disease burden on caregivers and society.
- Specific treatments are now available for Alzheimer's disease (e.g., anticholinesterases and memantine). These medications have been shown to:
  - Temporarily improve cognitive dysfunction
  - Temporarily improve function (activities of daily living)
  - Delay conversion from mild cognitive impairment to Alzheimer's disease
  - Decrease development of behavior problems
  - Delay nursing-home placement

Harms from failure to recognize early dementia

- Dangerous behaviors (e.g., cooking and operating machinery).
- Driving problems.

Listing & accounting for the harms of not screening for dementia:

- Missed opportunities for:
  - The application of available treatments
  - Participation in research
  - Advance care planning
  - Support of caregivers

Harms that might occur to those with a negative screening test result

- False reassurance: a false-negative might wrongly diminish concern and motivation to participate in future evaluation. The consequences of incorrect results are factors that can be accounted for in the decision to screen.

Costs/harms of dementia screening

- Listing and accounting for the harms of dementia screening.
- Harms that might occur to those with positive screening test result:
  - Clinical error of equating positive screen with diagnosis (education about screening and proper dementia diagnostic implementation can address this issue).
  - Complications arising from further testing (only additional clinical questions necessary to inquire about the patient's history should be considered at this point, as is recommended for evaluation of suspicion of dementia by the American Academy of Neurology).
  - Adverse effects of treatment must be considered with respect to the benefits, on their own merits, based on the opinion of the clinician that makes the decision for treatment.
  - Anxiety generated by investigation and treatment; such anxiety must be balanced against the already considerable and appropriate anxiety regarding Alzheimer's disease in our society.
  - Screening in the context of proper diagnosis and medical management can help manage that anxiety.
  - Costs and inconvenience incurred during evaluation; the cost of dementia evaluation needs to be entered in the calculation of whether screening is costworthy.

Adapted from [1].

can be constructed for numerous factors. Interestingly, *APOE* genotype greatly affects incidence, and the *APOE* ε4/4 genotype (2% of the US population but 20% of the AD population) will be associated with a cost justification at a much younger age, the *APOE* ε3/4 at a slightly younger age than average, and the *APOE* ε3/3 at an older age than average, depending on the accepted relationship of the AD probability with respect to age for this gene (**Figure 4 & Figure 5A**) [123,128].

Analyses according to test specificity and sensitivity suggest that for a benefit of $25,000, that a perfect (sensitivity and specificity equal to 1.0) $25 test is justified by 65 years of age (**Figure 5B**). A $25 test with specificity and sensitivity at 0.9 and 0.9, respectively, is not justified until after 70 years of age, but with 0.8 and 0.8, no test is justified until after 80 years of age.

Curves are shown for various levels of benefit, not including $T (**Figure 5C**). The points on the graph where the values exceed those of a screening test indicate those ages at which screening tests of that value, $T, would be worth doing. For $100,000 of benefit, a $10 test is justified yearly at 60 years of age and a $50 test is justified at 65 years. For a benefit of $25,000, the justifications are at 75 and 80 years, respectively. If the benefit is only $10,000, then the justification for testing is weak across the age range.

More specific justification of the application of screening tests to a population can be made using the ROC method and analyzing costworthiness for each term, for disease incidence, test accuracy, costs of false-positive results, benefits of true-positive results and test cost. In applying this method to the continuum of early dementia, the value must be determined with respect to at what point in the continuum the assessment is being made, and that point will be associated with a specific test sensitivity and population incidence. The benefit ($B) will also be affected by the exact point of early dementia being targeted. If the value fluctuations as a function of this continuum can be established, then this analysis will provide a clear recommendation for when to implement screening at both clinic and community levels. The difficulty then is to determine how these functions vary with normal aging and the early phases of dementia. Once the values of the factors are estimated, the costworthiness calculations show at what ages a screening test is justified.

Considering the numerous possible assumptions for the values pertinent to the modeling, the general impression is that annual dementia screening with a short cognitive test for memory problems is clearly supported between 75 and 95 years of age. Given various risk factors, annual screening might begin as early as 60 years of age.

Recent developments in memory & dementia screening testing

As clinicians specialize in dementia, they begin to develop a clear concept of what problems their patients are having and strive to recognize these problems more efficiently. Accordingly, clinicians have developed a large number of screening tests. Several review articles discuss various tests and their advantages and disadvantages, as well as their applicability in clinical practice (**Box 4**) [74,75,95,115–117,138–143] for many examples according to categories). Currently recommended tests include the Min-Cog, Memory Impairment Screen, GP-COG and the Brief Alzheimer Screen (see Appendix). Many screening tests currently available are short and have relatively good specificity and sensitivity (close to 0.9 and 0.9, respectively), and are easily integrated into clinical practice [144]. The abundance of such tests is an indication of the extensive efforts being made in this field without a clear unifying principle to identify the optimum screening process. There have also been concerns that screening tests have so many shortcomings that they cannot provide adequate power to be of overall value [145,146] (see response in [147]). However, the analyses in this review demonstrate that the power of the tests is actually quite strong, and improvements in the power of the screening tests would contribute little screening efficiency relative to augmentation possible for other factors. Item response analysis offers an approach to coordinate this field to increase the power of screening tests, and costworthiness analysis provides a solid approach to assure the value of screening.

In the future, it is important to continue to develop progressively better tests. It is clear from the costworthiness analysis that optimizing the sensitivity and specificity, as well as the cost/time-efficiency, of a screening test does improve the value of screening for the whole population. Accordingly, there needs to be a refinement of screening tests to the most efficient level. Tests that are multistep, beginning with very sensitive questions, then leading to more specific questions, can improve test efficiency [59,60,148]. In the near future, computerized testing is likely to prove much more cost-effective than paper-and-pencil testing. Screening for memory and other cognitive difficulties could become a monthly activity (just as breast-self examination), that would lead to a clinician visit for further assessment if particular criteria were failed. The ease of providing screening tests leads to the question about whether to support in-home testing, a notion that has been criticized [149]. However, methods to provide tests that individuals themselves can control leads to empowerment of the consumer, especially as tech-savvy baby-boomers age. Better

test systems should soon be able to guide individuals through a highly efficient and costworthy memory disorder, dementia and AD screening process.

It is beyond the scope of this article to discuss biomarkers of AD and their role in screening. Such measures include blood tests, cerebrospinal fluid analyses and brain scans. Biomarkers are an important area, and tests may soon be available that can indicate who is going to develop dementia or AD in the near future. For example, a recent report of a proteomics blood test claimed a specificity and sensitivity of approximately 0.9 and 0.9, respectively, similar values to the better available cognitive screening tests [260]. Event-related potentials, particularly the P300, may play a role in early detection of memory dysfunction [150–152]. New brain scan techniques appear to show actual AD pathology at the MCI level of impairment [106]. However, biomarker tests are likely to be more expensive and closely associated with specific conditions. Accordingly, such tests are more likely to play an integral role, with cognitive tests serving as secondary assessments for those with problems on a cognitive screen or with very high risk factors.

Conclusion

There are extensive studies throughout the medical literature dating back to the 1930's addressing the evaluation of cognitive function in adults. A progressive increase in attention to screening for memory dysfunction, MCI, dementia and AD has occurred since the 1970s as these conditions have become better understood. It is now recognized that these conditions have a clear association with age, and as the population is aging, these conditions are becoming the most important health problem in the World, creating an imperative to develop methods for early detection. The difficulty in recognizing the onset of these problems in clinical practice has created an immediate need for implementing widespread screening programs. The technology for developing cost-effective screening tests is now well understood, and adequate tests for implementation of memory and dementia screening systems are available. The calculation of costworthiness indicates support for annual screening beginning at 75 years of age and as early as 60 years of age depending on risk factors and other considerations. However, progressively better tests need to be developed to improve the value of screening.

Future perspective

In the development of broad-based population screening, it is necessary to determine what venue is feasible. While it may be useful to test an individual's cognitive function, it is much better to also involve a reliable informant, who will not only provide additional useful information but can assure that appropriate secondary recommendations are followed.

One example of a screening venue is a Senior Health Fair. In such a setting, most of the participating individuals are worried about their memories, but they frequently have no significant problems. A fair is also an anonymous environment, which provides a high margin of confidentiality. When blood sugar or cholesterol levels are reported to a participant in such an environment, an individual can act on an abnormal result. If an individual is found with poor memory in such a location, they may not remember to follow through with recommendations. Accordingly, appropriate follow-up mechanisms and systems need to be developed [153].

The Alzheimer's Foundation of America instituted 'National Memory Screening Day' in 2003, the second Tuesday in November; this event has increased progressively to reach 2000 venues in 2007. The interest in this event signifies the US population demand for indicators of whether memory problems or dementia are present.

Computerized testing and the Internet are extremely fertile opportunities for accurately testing memory and other cognitive functions (**Box 4J**) [154–160]. Moving into the field of computer games, a subject can enjoy a test and develop skills, while the test is probing for strengths and weaknesses of function. For an individual with memory problems, a computer can use an interactive approach to rapidly determine the presence of memory difficulties and other cognitive dysfunctions then make specific recommendations for subsequent assessments. Computer tests can store extensive information in the electronic medical/health record, which can be used for determining longitudinal change in the normal range, progression of disease and the effects of therapy, both for research studies and for outcomes in community and clinical settings. A computerized slide presentation (MemTrax) testing the individual for recognition of repeated pictures has been shown to be a well-tolerated method and highly specific and sensitive to memory difficulties [161].

It is now time to consider community-based screening testing for memory problems. Developing such programs should be similar to other screening and warning sign recommendations (moles that bleed, breast self-exam, persistent cough, blood in the stool, etc). Clinicians should be able to have their patients participate in brief cognitive screens in their offices, such as measuring temperature, weight, heart-rate, respiration-rate and blood pressure. However, specific recommendations need to be developed for community clinicians and other venues [153].

Executive summary

Introduction

- The evidence for a need to screen for dementia is growing, including inadequate clinical recognition, improved care with early recognition, increasing prevalence of dementia and Alzheimer's disease (AD), and powerful yet inexpensive screening tests.

History of cognitive assessment for evidence of dementia

- The critical dysfunction in dementia and AD is loss of memory.
- Clinicians have been developing tests to assess patients for cognitive dysfunction since the 1930s.

Classical test theory & early mental status tests

- In the past, many test developers have used Classical Test Theory for developing cognitive screening tools. This approach requires the selection of a set of items, then the answers are coded numerically, with the sum of the values representing the score of the test.
- The pivotal application of this method was the Blessed Dementia Scale (1968), which changed the field by relating cognitive and social function to AD.
- The culmination of this method was the Mini-Mental State Exam (1975), which found widespread usage among researchers for estimating the severity of dementia patients for clinical studies.

Modern test theory & new dementia tests

- Modern test theory provides an approach to assess where an individual is along an ability/disability continuum, analyzing item characteristic curves.
- This approach was first used in 1989 to analyze the individual items of the Mini-Mental State Exam.
- Subsequently, there has been a continually growing focus on determining the best items to use in a dementia screening test.
- As computer analysis of patient performance has been growing, there is an emerging effort to calculate a patient's probability of having cognitive impairment based on a computation of their performance measures using Modern Test Theory.

Other test development directions

- The approach of combining information from patient performance, informant report and clinician observation can provide a particularly robust assessment of a patient's likelihood of having cognitive impairment and the severity of a dementia.

Deciding whether to administer a memory/dementia screen

- Using a comprehensive medical test assessment approach, a calculation can be made to estimate whether a memory or dementia screening test is worth the cost of administration.
- Costworthy calculations can be made for a population, for a clinic office or for a particular individual, with inclusion of specific predetermined risk factors.
- The calculation requires specific parameters, as follows:
  - I = incidence of the disease in the population to be screened for the epoch.
  - Sp (specificity), pertains to the normal population and the distribution of test scores on the continuum of cognitive ability/disability being measured. The value of this factor relates to where along this continuum the delineation point (cut-point) is selected for study.
  - Se (sensitivity), this value relates to the distribution of test scores on the continuum for a group of patients with a specific level of impairment (this must be in the population being studied).
  - $B = the benefit (advantage) of a true-positive test for the identified individual.
  - $C = the cost (harm) of a false-positive test for a wrongly identified individual.
  - $T = the cost of the screening test plus administration and time for all parties.
- The calculation of costworthiness, $W, is a combination of these factors:
  - $\$W = (\$B \times I \times Se) - (\$C \times (1 - I) \times (1 - Sp)) - \$T$

Incidence of dementia & Alzheimer's disease

- The incidence of dementia, and particularly AD, increases with age, doubling every 5 years.

Executive summary (cont.).

Dementia screening tests

- Evaluating accuracy
  - The specificity and sensitivity of a test must be measured in the specific population to be assessed. The Receiver Operator Characteristic (ROC) curve demonstrates how the values of these two measures fluctuate with respect to each other.
- Evaluating efficiency
  - The efficiency of a screening test requires knowledge not just of the specificity and sensitivity, but what the outcomes are for the test as well as the costs of test administration. These values must be known to determine what point along the reciprocal relationship of specificity and sensitivity the optimum value is to recommend that a patient with a particular score be considered to have a positive test.

Benefits for an individual with a correct positive screen test

- There is an extensive list of beneficial measures that can be instituted for a patient with a correct diagnosis of dementia, which include both medical interventions and social supports.

Costs & harms of a false-positive screening test

- The principle cost of a false-positive dementia screening test is the additional time and expense of secondary dementia assessment.
- The ideal secondary dementia assessment can be quite limited. However, the application of the second step may not be performed appropriately if clinicians are not adequately trained. Hence, without further education, the potential for harm from dementia screening is currently considered high.
- Many of the concerns regarding harms from screening tests have been related inappropriately to the outcomes of actually having a dementing condition, particularly AD. The presence of the dementia may be uncovered by the screening test, but cannot be attributed to the screening test.

Calculation of costworthiness of screening

- Calculation of costworthiness is a derivation of cost–benefit ratio. Rather than providing a percentage result, it yields a specific value (positive or negative) of benefit, either for a specific individual or a population. This value can be plotted to determine what factors affect the result. With relatively conservative assumptions, memory and dementia screening clearly has a positive value for elderly individuals and populations.

Recent developments in memory & dementia screening testing

- As greater attention has been paid to dementia screening test development, a variety of tools have been developed and reviewed in many recent articles. There are now several tests that are shorter than 5 min with reasonably good accuracy. There are also better combinations of patient performance and informant information. Several telephone screens have been published, and there are several computerized testing directions being followed, including marketed software and internet websites that can provide relevant information for dementia screening. There are also blood and cerebrospinal fluid tests that have clear utility. The integration of genetic information, particularly apolipoprotein-E, is advancing. There are progressively better brain scan approaches for defining brain changes associated with dementia as well as markers for specific aspects of AD that are being studied.

Conclusion

- There is a long history of evaluating cognitive function in adults for evidence of impairment.
- The need for screening has reached a point where implementation of memory and dementia screening programs needs to occur.
- Annual screening beginning at 75 years of age is supported by costworthiness calculations, but earlier screening may be indicated depending on risk factors and other considerations.
- The technology for cost-effective screening is adequate now for the implementation of memory and dementia screening systems and large-scale programs need to be developed.

Future perspective

- Dementia screening should no longer be limited to clinician offices as 'case-finding'.
- There are now screening methods for application at 'senior-fairs'.
- The Alzheimer's Foundation of America has instituted 'National Memory Screening Day', which will increase the interest and acceptance of screening.
- There is a need for greater education of individuals about the need to monitor dementia risk and cognitive function, as well as a complementary requirement to educate clinicians on proper dementia diagnosis and management.
- Widespread screening should be an ultimate goal, but this goal should be reached through gradual stages of implementation, with simultaneous study of outcomes to assure that full benefit to the population is being achieved.

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•• **Dementia screening tool described in the appendix.**

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314. Neurobehavioral Cognitive Status Examination – Cognistat www.cognistat.com
315. Cognisyst; Research@cognisyst.com www.cognisyst.com
316. Cog Screen; gkay@tidalwave.net www.cogscreen.com
317. CogTest; info@cogtest.com www.cogtest.com
318. Medical Care Corporation; rshankle@mccare.com www.mccare.com/content/mcis/mcis_overview.html
319. Medical Decision Logic, Inc.; allen@mdlogix.com www.mdlogix.com
320. Memtrax; washford@medafile.com www.memtrax.net
321. MicroCog http://harcourtassessment.com (Also see reference [157] and the commercial reference in the original manuscript)
322. NetMet, Crooks T, info@netneuromet.com www.netneuromet.com
323. Neurotrax, Simon E, info@neurotrax.com www.neurotrax.com
324. US Centers for Disease Control and Prevention www.cdc.gov

Appendix

Brief Alzheimer Screen (BAS)

I would like to ask you some questions to check your memory.

1. "I am going to say three words. After I have said them, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. They are: 'PEN', 'TABLE', 'ORANGE'. Could you please repeat these for me?"

The items should be read at a rate of one per second, speaking clearly and audibly.

You are allowed to read the words only once before scoring.

Score on first trial: 'PEN', 'TABLE', 'ORANGE'

Repeat the words until:

1) The subject correctly repeats all three or;

2) Three total trials have been presented (including initial presentation).

After the subject has said them once correctly, ask: "Please repeat them once more so you will remember them."

2. "What is the date today?" (score for day of the month, ±2 days is acceptable)

D = #1 if correct (else D = 0)

3. "In 30 s, name as many animals as you can, GO": (stop after 30 s)

A = Number of animals named

4. Spelling/reverse spelling:

"Now, I am going to give you a word and ask you to spell it forwards and then backwards. The word is 'WORLD'. spell 'WORLD' forwards."

If the subject is unable to spell the word, spell it out loud, and ask the subject to repeat the spelling. Continue until it has been spelled successfully or until you have spelled it to the subject three times.

"Now spell the word 'WORLD' backwards":

D, L, R, O, W

Score 5 points for a correct sequence. Count one error for each omission, letter transposition (switching adjacent letters), insertion (inserting a new letter) or misplacemeent (moving W, O, R, L, D by more than one space).

S = Number of points (backward spelling)

5. Delayed verbal recall:

"Now, what were the three words I asked you to remember?"

(This should be administered as soon as the reverse-spelling item is completed.)

Cueing is allowed if the subject is not able to recall words, but credit is not given for any word recalled after a cue.): 'PEN', 'TABLE' and 'ORANGE'.

R = Number of words spelled correctly.

$BAS = 9 \times R + 2 \times A + 15 \times D + 6 \times S$

(BAS, maximum score = 100)

Results

80–100: normal, depending on age, education and complaints

70–79: possible impairment

60–69: probable impairment

<60: definite impairment

Note: Addition of the Clock Drawing Task at the end of the BAS will provide additional screening for visuospatial function.

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