Screening for memory disorders, dementia and Alzheimer’s disease

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.

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 non-specific 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
dementia. There are relaxed 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 confound 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 (20,21) as a clinically meaningful syndrome in 1999 (22) and has acquired standardized methods for distinguishing its clinical features (23), so that it is now recognized as a formal diagnosis (ICD-9 code 331.83), which Medicare (USA) recognizes 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 dementia affects the brain, the continua of dementia severity associated with these various diseases, or the methodology of test construction.

Since 1980, many test developers have used classical test theory (16), 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 consistency 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), through 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 (items response theory and item characteristic curve analysis (23–26), 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 studying cognitive function in adults and in dementia with old age (21–50). 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 (49). A major breakthrough occurred in 1968 with the publication of the Blessed

Box 2. UK National Screening Committee.
Criteria for appraising the reliability, 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 causation, pathology 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** should be a simple, safe, precise and 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 optimised 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 actually 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 benefits 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 (50).
Information–Memory–Concentration (BIMC) test (28 points max.), whose values during life were correlated specifically with neuropsychological test scores and autopsy in dementia patients [42]. 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 Mini Mental Test (34 points max) [58], the Abbreviated Mental Status Test (ten points max) [59], Mattis Dementia Rating Scale (144 points max) [24,53], the Hasegawa Dementia Rating Scale (32.5 points max) [59], the Information-Oriented Section [57], the Short Portable Mental Status Questionnaire (ten points max) [58] and the MMSE (30 points max) [50] for reviews of early tests, see [117,20,60].

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 (11) 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 5). 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 5). 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 5). None of these tests has ever been shown to be unique or significantly superior to any of the others [12], 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 [63].

Between 1975 and 1995, the MMSE became the most widely used test for cognitive assessment in academic fields for research studies and among students [54,60]. The reason that the MMSE became the popular test may relate to its successful implementation of Wells’ [40] recommendation to use a three-word memory list and orientation in dementia assessment. In addition to date and place orientation, the BIMC tests 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 Folsen 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” [51]. 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, Folsen 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 [67]. However, the MMSE really represents a typical test from the period of its publication, not a unique breakthrough, and it
Box 3. Genealogy 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
- Name
- Address
- 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 (184)
  - "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" (5 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 7s" (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 7s)
- Reversing items (29)
- Related tests:
  - Say the months in reverse order (29,32)
  - Naming of animals in 1 min (29)
  - Talk A:5-12:10, count backward from 20 to 1 (32,31)
  - Days of week backwards, in addition to 7s (162)

Recall: "ask the three objects repeated above" (3 points)
- Prior descriptions and brief memory testing:
  - 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 mins, last after 3 mins have elapsed
  - Paragraph retention (29), retention of items (164) and recall of address (32)
  - "...repeat three unrelated words...after 5 min" (46)

*Attention 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 Weil, 1977 (162).
**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 (166) |
| - 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 an" [31] |
| • 28 points - Blessed Orientation-Memory-Concentration Test [32] |
| • 34 points – Mental Test score [33] |
| • Matrix 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 scheme for the systematic mental status evaluation is given in Table" from Weeck, 1977 [46]*

has been reproduced in many variations that are substantively different and more reliable than the original (a-e). 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 [41]. A significant part of its problem for screening is the inclusion of items that add noise rather than discrimination between normal and demented individuals [22,51].

404

Aging Health (2008) 4:41
| Table 1. Cognitive tests published in 1975 or before used for dementia screening. |
|---------------------------------|-----|-----|-------|-------|-------|-------|-------|-------|
| **Part** | MSQ (31) | BMIC (32) | AMTS (33) | Mattis (34,35) | HDRS (36) | CAS (37) | SPMSQ (38) | MMSE (39) |
| **Person** | | | | | | | | |
| Name | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Age | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 |
| Birthdate | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Birth place | 1 | 2 | | | | | | |
| **Place** | | | | | | | | |
| Name of site | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Type | 1 | 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 | 1 | 1 |
| Month | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Year | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Day of week | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Season | | | | | | | | 1 |
| **Registrar** | | | | | | | | 4 |
| **Attention** | | | | | | | | 3 |
| Serial 7’s | | | | | | | | 5 |
| **WORD Backwards** | | | | | | | | 5 |
| **Other tasks** | 6 | 1 | 15 | 6 | 1 | | | |
| **Recall** | | | | | | | | |
| Address | 5 | 1 | | | | | | |
| Objects | 16 | 6 | | 3 | | | | |
| Persons | 2 | 1 | | | | | | |
| Naming | | | | | | | | 2 |
| Reading | 4 | 3 | | 1 | | | | |
| Composing | | | | | | | | 1 |
| Fluency | | | | | | | | 22 |
| **Visuospatial** | | | | | | | | 1 |
| Praxis | 25 | | 10 | 1 | | | | |
| Hapax | 7 | 2 | | | | | | |
| Obeying | 10 | | 3 | | | | | |
| Abstraction | 22 | | | | | | | |
| **Information** | | | | | | | | |
| Pres, etc | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 1 |
| Past pres, etc | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Other** | 3 | 1 | 6 | 1 | 1 | | | |
| **Total score** | 10 | 37 | 10 | 144 | 32.5 | 33 | 10 | 30 |

AMTS: Abbreviated Mental Status Test; BMIC: Blessed Information–Memory–Concentration test; CAS: Clinician Assessment Schedule; HDRS: Hamilton Dementia Rating Scale; Mattis: Dementia Rating Scales; 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 (38). The MMSE has questions whose time to ask is considered wasteful and whose variance adds to the imprecision of the dementia severity estimate (39). For practical clinical purposes, the MMSE is deficient because it leaves out important 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 US insurer for the elderly, specifically singles out the limitation of use of the MMSE in its policy for neuropsychological testing: “Brief screening measure 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” (36). It is time to recognize the important advances made by the BIMC and the MMSE as 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 (38). Most of these tests have been assembled 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]) (34,35).

Many studies have developed dementia assessment tools that are strictly cognitive or based on direct evaluation (44). Others have been based on the reports of knowledgeable informants (activities of daily living [ADLs]; Functional Activity Questionnaire [FAQ]; Alzheimer’s Disease Cooperative Study/ADLs [ADCS/ADLs]; AD8; BS 66, 74) (36-38). AD8 can also be assessed by direct observation (37-38). General tools have been developed to allow clinicians to convey their impression of dementia severity (BS 40). 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 [GQ-COG]; see BS 40).

Relevant information for estimating whether dementia is present can be obtained over the telephone (BS 44) or through computerized testing (BS 48), even over the World Wide Web. Some tests are useful for assessment but not sufficient for dementia assessment when used alone (BS 46). 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 (BS 48), then definitive diagnostic evaluation (e.g., BS 66, 74,39). 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) (32). The near future of such testing will likely be all computer based (BS 47).

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 (41). 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 (28). AD is a specific neurodegenerative process that is best understood at a progressive disruption of neuronal processes (51-53), which is consequently manifested predominantly by a disruption of memory processing that secondarily affects other cognitive functions (53,52,46). 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 precursor protein and inappropriate phosphorylation of tau in the critical neuronal processes), loss of the storage substrate for old information (the tau hyperphosphorylation causes the formation of neurofibril threads from neuron 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)
- CLOT Assessment Procedures for the Elderly – Cognitive Assessment Scale (170)
- Blessed Scale (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 (17)
- AB Cognitive Screen (179)
- Q and E (76)
- 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)
- CLOT Assessment Procedures for the Elderly – Behavior Rating Scale (170)
- Functional Activities Questionnaire (184)
- Genictic 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 (186)
- Alzheimer’s Deficit Scale (186)
- 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)
- DCO (193)
- Alzheimer’s Disease Cooperative Study/ADLs (195)
- MODS Cognitive Performance Scale (196)
- Groningen Activity Restriction Scale (197)
- Cognitive Assessment Screening Test (198)
- Direct Assessment of Cognitive Abilities (192)
- 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 (302)
- Alzheimer’s Disease Caregiver Questionnaire (203)
- ADLs Questionnaire (204)
- ADR (205)
- Patient-reported outcomes in cognitive impairment (206)
Box 4. Tests for mild cognitive impairments and dementia screening (cont.).

(C) Global impression scales
- Clinical Dementia Rating Scale (CDR) [111,112]
  - CDR: sum of items [207]
  - CDR: extended [44]
- Global Deterioration Scale [110]
- Brief Cognitive Rating Scale [113]
- Functional Assessment Test [298]
- Alzheimer’s Staging Scale [118]
- Confusion Assessment Method [296]

(D) Global synthesis/combining cognitive testing & informant report
- Global Clinical Scale [48]
- Mini-Mental Dementia Assessment [210]
- GT/B/C and Mini-Mental State Examination (MMSE) [211]
- ICD-10 and 3MS [60]

(E) Telephone screening tests
- Telephone Interview for Cognitive Status (TICS) [212]
- Telephone-assessed Mental State [117]
- TICS [13,215]
- Minnesota Cognitive Acuity Scale [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-Assessed Status on Neuropsychological Functioning [221]

(F) Other cognitive testing modalities
- Web- and computer-based screening tools:
  - Cognitive Stability Index (CSI) [158]
  - Neurotra (a cognitive battery) [222]
  - Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment (a cognitive battery) [160]
- Mentra (a 2-min memory screen usable on the internet) [161]

(G) Non specific 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 (CDT) [226,227]
- Trail making tests A and B [228]
- Mental alternation test [229]
- Time & change test [229,230]
- WORLD Test [231]
- Visual association test [86]

(H) Secondary, longer screening tests & cognitive/memory assessments 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 (CSE) [232]
- Extended Scale for Dementia—four parts (CSE, MMS, 233,234,235,236)
- Modified MMSE [50,235,236]
- Alzheimer’s Disease Assessment Scale—cognitive subscale [237]
- Cognitive section of CAMDEX [235]
- Neuropsychological Cognitive Status Examination (renamed Cognistat in 1995) [238]
- High Sensitivity Cognitive Screen [240]
- Halstead Mental Status Scale [241,242]
- MMSE-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)
- Yorkston Memory Test (245)
- Addenbrooke’s Cognitive Exhbit (246)
- 7 min screen (246)
- Short and Sweet Screening Instrument (249)
- St. Louis University Mental Status Examination (248)
- Rowland Universal Dementia Assessment Scale (244)
- DemTest (250)
- Montreal Cognitive Assessment (251)

(1) 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 (251)
- 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: Raven’s 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 likely affected by dementia that provide comparison
  - Vocabulary: National Adult Reading Test
  - Motor function: finger tapping and grooved peg-board

(1) Developments in computerized cognitive screening tests

- CAiNS-MC (307)
- CogniDx (308)
- Cognitive Drug Research (309)
- Cognitive Screening Test (310)
- CNS Vital Signs (311)
- Cognitive (312)
- Cognitivis (313)
- Cognitiva (314)
- CogniTest (315)
- CogScreen (316)
- CogTest (317)
- InteLinesc (318)
- Medical Care Corporation (318)
- Medical Decision Logic, Inc. (319)
- MemTest (320)
- MicroCog (321)
- NetMet (322)
- Neurotrax (323)
memories), language impairment (aphasia is characterized by loss of 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, BI2 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 multidimensional 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 simple underlying factor, while multifaceted 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.

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 (68-69,73-75). An improved memory assessment for dementia, the memory impairment screen (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 (76). Of relevant interest is the observation that the 1958 Rey Auditory Verbal Learning Test (RAVLT) (78), a classic test of verbal memory function, is still one of the best predictors of MCI indicative of early AD (60-62), 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 (79). Following the development of the focus on learning and memory, a sophisticated mathematical analysis of performance on the ten-word recall of the California to Establish a Registry for AD (CERAD) study discriminates strongly between normal individuals and those with MCI and dementia (80). Furthermore, a classic test of visual memory, the Benton Visual Retention Test (81), is a good predictor of incident AD (82), as is a test of visual associative memory (83). These clinical research findings support the notion that AD is quasioptically 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 (18) 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 tests for dysfunction in other areas of cognitive function, including apraxia, anoma, 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 (31). 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
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 (46). 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 onset of progression of patients with AD with respect to duration of illness (Figure 1A) (56).

The cognitive impairment associated with AD forms a continuum from slight memory difficulties (which cannot be distinguished from normal function) through mild impairments, mild dementia, to moderate, severe and profound dementia (57,58,59). 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 demeniting 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 grading 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 difficulty. Using this continuum for the analysis, the relation of specific MMSE items to the continuum of progression was assayed (46). 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 discrimimability, the items of the MMSE administered to patients in the CERAD study (the last major data set collected before wide use of anticholinesterase medications) were analyzed with this method (Figure 1B). These analysis results are similar to prior analyses of these items (52,56), but provide values that
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 backwords, the final score, constituting the Brief Alzheimer Screen (see Appendix), has a score area under the ROC curve than the MMSE (Figure 2) (73). 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 emerging AD (70). 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 (70) had the greatest discriminative power (70), and a logistic combination of these tests provided optimum predictive probability of developing AD within 1.5 years (70). A 12-year prospective study identified recentive memory and abstract reasoning measures as the strongest predictors of further development of AD (71). 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 (17). Part of the problem is that AD pathology exists in individuals without a diagnosis of dementia (91), and older individuals with these changes may not even show any signs of cognitive impairment (91). Furthermore, there are ethnic and cultural factors that can influence performance on individual items (83). ROC conceptualization of the assessment problem leads to the understanding that as there is less and less pathology, performance curves for even the most
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 [29,30]. However, location on the temporal continuum can be estimated by combining the probabilities of which 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. This 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 test 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 [23]) 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 the mean performance) of eigenvalues [28] 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 or

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.

413
an underlying biological factor, as might be determined on a brain scan [109,116]. 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 [117,118]. However, this approach examines the dimensional-order/difficulty of test items without attention to the dis- crimina bility 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 different 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 [21].

A particularly powerful approach to dementia severity assessment is the combination of infor- mation from cognitive testing, a knowledgeable informant, and a clinician’s impression [110]. This approach improves estimation of dementia severity over the MMSE by a factor of at least 3 [112]. 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 8(b)). 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 Deteriora- tion Scale (GDS) [114], the Clinical Dementia Rating Scale (CDR) [111,113] and the Brief Cog- nitive Rating Scale [115], 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 [46]). This approach is successful as each nonredundant item contributes information to predicting where a subject lies on the cognition/dementia contin-uum and accordingly reduces the standard error of the measurement [22]. 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 4(b)).

Deciding whether to administer a memory or dementia screen.

Now that many good dementia screening tests are available [115,116], 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 [21]. Working groups from the British Commonwealth have developed specific definitions and guidelines for the process of deciding whether screening is appropriate [119] (UK-CNS, 2003. Br J Clin Psychol 42, 3). 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 techniques [120]. In the mathematical approach, the question of whether to screen reduces to: "Is a screening test cost-effective?" There are six factors which must be estimated for this calculation:

1. p = incidence of the disease in the population to be screened for the epoch (e.g., number of new cases developing in 1 year);
2. 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;
3. 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);
4. B = the benefit (advantage) of a true-positive test for the identified individual;
5. C = the cost (harm) of a false-positive test for a wrongly identified individual;
6. ST = 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 discriminating ability of the test for the normal, unaffected population (d(isp)) and d(isn), respectively, and the studied patient population (d(isp)) and d(isn), 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:

\[ Sp = \frac{e^{\beta_0+\beta_1 x}}{1 + e^{\beta_0+\beta_1 x}} \]

\[ Se = \frac{e^{\beta_0+\beta_2 y}}{1 + e^{\beta_0+\beta_2 y}} \]

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. ($SW$)

$SW = (SB \times IS - Se) - (SC \times [1 - L] \times [1 - Sp]) - ST$

If $SW$ 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 similar relative to the cost or harm of the false-positive result and is trivially different to the condition in which a 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 $SW$ can be calculated for various screening scale delineation points (cut-points) with knowledge of the distributions 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 $SW$ can be analyzed as a function of factors contributing to that variable. Screening is costworthy if $SW$ 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-positives, 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 (127, 128), with a notable rate of one per 1000 individuals at 62 years of age, one per 100 at 78, and one in ten at 94 (Figure 5A). 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 (129). As numerous causes of mortality have been reduced in the USA in the last century, particularly for younger individuals (Figure 5B), and the baby-boom is expected to increase the proportion of older individuals until the year 2050 (Figure 5C), a large increase in the incidence of AD is predicted in the near future (Figure 5D).

Current efforts to prevent dementia, as Alzheimer’s disease, are centered on disease-modifying agents that target specific molecules, such as cholinesterase inhibitors, which reduce the production of amyloid-beta, which can cross the blood-brain barrier. The next biggest factor affecting incidence of memory problems and dementia is the APOE genotype (130-133). This genotype appears to play a direct role in age-related incidence (120, 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-protein 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) (1).
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 test that have been studied for their efficacy in assessing individuals for the presence of cognitive impairments, 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
used to assess the utility of the test (such information is of preliminary interest in computing 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 [31,32].

Part of the difficulty in using the ROC curve approach is that the ROC is easily 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 SW, the cost justified for a screening test (Figure 4B). Furthermore, using the age-specific incidence curves, SW can be positive for a range of cut-points, as well as other measurable or cost factors.

Cognitive memory, dementia-screening tests: evaluating efficiency

As 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 $T$.

### 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 simple year

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of people over 50 years of age</th>
<th>Number of people over 50 years of age developing AD/year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>10,025,861</td>
<td>28,411 (0.28)</td>
</tr>
<tr>
<td>1950</td>
<td>33,604,790</td>
<td>112,374 (0.33)</td>
</tr>
<tr>
<td>2000</td>
<td>76,818,531</td>
<td>498,690 (0.65)</td>
</tr>
<tr>
<td>2010</td>
<td>96,130,417</td>
<td>654,041 (0.69)</td>
</tr>
<tr>
<td>2050</td>
<td>116,223,744</td>
<td>1,141,633 (0.98)</td>
</tr>
</tbody>
</table>

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 [106].

![Figure 4. Incidence rate of Alzheimer’s disease according to APOE genotype.](www.futuremedicine.com)

417
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 cost-worthy. 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) [3].

An important factor in determining the utility of a test is its cost-per-unit-time efficiency. The per-time 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 phase of dementia to profound impairment can be conceived as a continuum [13]. When one 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 * T). Like relating the wattage of a light bulb to the amount of electricity charged by the power company, it corresponds to how long the bulb was ‘on’.

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 [20]. A recent study showed 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 remarkable 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 [17], 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 [18,19,17]. 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 50-year-old individual, with a linear decline to zero for a 100-year-old individual, the value of the true-positive early diagnosis, SB, can be entered into the calculation (Equation 5). As can be seen, the value of benefit, SB, also has a substantial impact on SW, 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 neurophysiological assessment, and a summary rating. Stabilized by a discussion of the implications of the conclusions with the subject and a caregiver. One consideration to reduce this misinterpretation 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 weight 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 costs 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 screen 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 [6,12,13,17], 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, BC (used in Figure 5).

Calculation of costworthiness of screening

The value of SW 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 5). 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

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 equalizing 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 patient and 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. Interest-
ingly, the APOE ε4/ε4 genotype greatly affects incidence, and the APOE ε4/ε4 genotype (2% of the US pop-
ulation 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/ε4 at an older age than average, depending on the accepted rela-
tionship of the AD probability with respect to age for this gene (Figure 6 & Figure 5A) [125, 123].
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 5A). 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 $7 (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, $7, 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 cost/benefit for each test, 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 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 ($8) 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 provides 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 value of the test factors are estimated, the cost/benefit calculations show at what ages a screening test is justified.

Considering the numerous possible assumptions for the values pertinent to the modelling, 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 begin 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: 17,55,18,19,17,7,55,58,39 for many examples according to categories). Currently recommended tests include the Mini-Cog, Memory Impairment Screen, G3-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 [134]. 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 (143.149) (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 cost/benefit 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 cost/benefit 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 (139,141). 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 (115). 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 cost-effective 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 protein biomarker blood test claimed a specificity and sensitivity of approximately 0.9 and 0.9, respectively, similar values to the better available cognitive screening tests [196]. Event-related potentials, particularly the P300, may play a role in early detection of memory dysfunction [196-198]. New brain scan techniques appear to show actual AD pathology at the MCI level of impairment [199]. 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 in 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 1930s 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 cost-effectiveness 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 participants 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 [198].

The Alzheimer's Foundation of America institutionalized 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 4) [199-198]. 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 (MemTran) 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 [191].
It is now time to consider community-based screening tools for memory problems. Developing such programs should be similar to other screening and warning sign recommendations (motes that bleed, breath 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 physicians and other venues (e.g.,

### 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.
- Cost/benefit 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:
  - \( I = \text{incidence of the disease in the population to be screened for the epoch} \)
  - \( Sp = \text{specificity,} \) pertains to the normal population and the distribution of test scores on the continuum of cognitive ability/disability being measured.
  - \( P \) = the value of this factor relates to where along this continuum the delineation point (cut-point) is selected for study.
  - \( Se = \text{specificity,} \) 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).
  - \( B = \text{the benefit (advantage) of a true positive test for the identified individual.} \)
  - \( FA = \text{the cost of the screening test plus administration time for all patients.} \)
  - \( FT = \text{the cost of the screening test plus administration time for all patients.} \)
  - \( S \) = the calculation of costeffectiveness, \( S \) = the combination of these factors.

\[ S = \frac{(B - FA - Sp)}{(P - B)} \]

**Incidence of dementia & Alzheimer's disease**

- The incidence of dementia, and particularly AD, increases with age, doubling every 5 years.
Benefits for an individual with a correct positive screen test

- Screening may reduce the risk of Alzheimer’s disease.
- Early detection of disease helps in planning for future care needs.
- Early treatment of the condition can improve quality of life.

Costs & harms of a false-positive screen test

- The cost of an incorrect positive test can lead to unnecessary stress and anxiety.
- Further tests and treatments may be required, incurring additional costs.
- False positives may cause worry and distress for those affected.

Future perspective

- Continued research is needed to improve the accuracy of Alzheimer’s disease screening tests.
- Development of more specific and sensitive biomarkers is essential for early detection.

Recent development in memory & dementia screening testing

- Newer technologies, such as fluid biomarkers and genetic testing, show promise.
- The role of non-invasive imaging techniques is increasingly being explored.

Calculation of cost-effectiveness of screening

- Cost-benefit analysis of screening programs is important for resource allocation.
- Evaluating the long-term benefits and costs is crucial for making informed decisions.

Conclusion

- Early detection of Alzheimer’s disease is critical for improving patient outcomes.
- Future research should focus on improving screening strategies and methodologies.

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Screening for memory disorders, dementia & Alzheimer’s disease – REVIEW


Websites


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 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, x2 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 misplacements (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.
   \[
   \text{BAS} = 9 \times R + 2 \times A + 15 \times D + 6 \times S \\
   \text{BAS (maximum score} = 100) \\
   \]

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. Developed by Maria Mendiondo, PhD, Wes Ashford, MD, PhD, Richard Kryscio, PhD and Frederick A Schmitt, PhD. First published in [27].