Screening Large Populations to Detect Early Stages of Alzheimer's and Related Disorders: Comparison of Available Screening Tests with the MCI Screen

Introduction

Current treatment of mild to moderate Alzheimer's Disease (**AD**) delays its progression for 2.8 or more years(4). Based on costs associated with dementia progression, a 2.8 year delay in AD progression reduces related managed care costs by up to 44%, (from $9092/patient/year to $5067/patient/year)(6,9). The earlier treatment is started, the greater the benefit in quality of life and healthcare cost savings; delaying cholinesterase inhibitor treatment for six weeks or longer leads to irreversible loss of function. These and other reasons are why the Alzheimer's Association supports early detection, accurate diagnosis and treatment. While concern about AD or memory loss may occur among patients in the early stages of mild cognitive impairment to mild dementia, more than 2/3 are not detected, diagnosed and treated by primary care physicians until they become moderately demented, by which time, patients require assistance in all areas of function. Screening to detect Alzheimer's disease and related disorders early must therefore identify patients before they become moderately demented.

Currently Available Screening Tests

Currently used dementia screening tests include the: (1) Mini-Mental Status Exam (**MMSE**), (2) Functional Activities Questionnaire (**FAQ**); (3) Informant Questionnaire for Cognitive Decline in the Elderly (**IQCODE**); (4) Clock Drawing test (**CDT**); (5) Mini-Cog; (6) Cognitive Abilities Screening Instrument (**CASI**); (7) Minnesota Cognitive Acuity Screen (**MCAS**); (8) Telephone Interview for Cognitive Screening; (9) Dementia Questionnaire; (10) Wechsler Logical Memory Scale (**WLMS**); (11) cognitive subtest of the CAMDEX battery (**CAMCOG**); (12) Double Memory test (**DMT**); (13) California Verbal Learning Skills test (**CVLT**); (14) Memory Impairment Screen for Telephone (**MIS-T**); and (15) delayed free recall subtest of the CERAD 10-Word List (**$CWL_{original}$**). While the California Verbal Learning Skills test and Wechsler Logical Memory subtest are sensitive measures of episodic recall, they have been primarily studied in relation to differential diagnosis, require significant training and skill interpreting. They are therefore excluded in our comparison of screening tests for large populations.

10 Criteria for Large Scale Screening Test

For any test to screen large populations and facilitate appropriate follow-up by primary care physicians, at least 10 criteria must be satisfied: 1) low cost; 2) brief time (< 15 minutes); 3) minimal training and easy administration; 4) non-professional test administration; 5) high sensitivity (>80%) for mild cognitive impairment (**MCI**) and mild dementia; 6) high specificity (>80%) for normal aging; 7) ability to educate, motivate and facilitate diagnosis and treatment among abnormal screens; 8) high reliability of scoring and interpretation; 9) automatic tracking of individuals longitudinally; and 10) automated integration with the next step in the healthcare process (differential diagnosis or risk factor assessment).

Comparison of Currently Available Screening Tests

The following **Table 1** below lists which of these criteria are satisfied by each screening test.

Table 1: Criteria Satisfied by Currently Available Screening Tests

Screening Test	Criteria Satisfied By Each Test Are Marked With A "+"									
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
MMSE < 25	+	+	+	+				+		
Mini-Cog	+	+	+	+				+		
Clock Draw	+	+	+	+						
FAQ > 8	+	+	+	+				+		
IQCODE	+	+	+	+				+		
Short CASI	+	+	+	+				+		
MCAS								?		
TICS	+	+	+	+				+		
DQ	+	+	+	+				+		
CamCog								+	+	
DMT	+	+	+	+	?	?		+		
MIS-T	+	+	+	+				+		
$CWL_{original}$		+			+	+		+		
$CWL_{computerized}$	+	+	+	+	+	+	+	+	+	+
? = may possibly be satisfied but could not find published data on the stated criterion.										

Development of Cost-Effective Screening Tool

Evaluation of CERAD battery

To determine if a cost-effective screening tool can be developed to satisfy all the above criteria, we analyzed 644 community-dwelling subjects, who were evaluated at the UC Irvine Alzheimer's Disease Research Center with MRI, the CERAD battery, physical and neurological exam, and medical history. Their dementia status was classified by ADCSU Clinical Dementia Rating Scale (**CDRS**) criteria. Sample: normal aging (CDRS=0, N=194), MCI (CDRS=0.5, N=224), and mild dementia (CDRS=1, N=226). Dependent Variable: CDRS=0, 0.5, or 1. Independent variables: demographics, CERAD battery test items. Methods: Stepwise logistic regression and Bayesian tree-based classification analysis. Results: 1) Normal Aging vs. MCI: specificity = 87%, sensitivity = 83%; 2) Normal Aging vs. Mild Dementia: specificity = 97%, sensitivity = 97%.

Development of Computerized Version

Based on these analyses, an interactive, computerized version of the CWL (**$CWL_{computerized}$**) was developed to allow an untrained non-professional to test a subject in 8-12 minutes, and be able to immediately generate two reports—one to educate and motivate patients/families to seek further evaluation and treatment when appropriate, and one to facilitate clinicians' use of the NINDS-ADRDA guidelines to accurately diagnose AD when appropriate (3/4 of primary physicians do not use them currently).

Objective: To test the validity of the interactive, computerized CWL.

Sample: 50 normal aging-to-mildly demented subjects followed in a community-based dementia clinic.

Methods: a neuropsychologist used the original CWL, and an office assistant used the online, interactive, computerized CWL to test each subject. Order of test administration to each subject was randomized and tests were given within one month of each other.

Analysis: t-tests for paired comparisons were used to look for significant differences in the CWL subscores (total immediate recall for Trials 1, 2 and 3, delayed free recall, and delayed recognition) between original and computerized CWL.

Results: There were no significant differences between original and computerized CWL for any of the subscores.

Conclusions: Currently, none of the commonly used screening tests satisfy all of the criteria needed to be able to longitudinally monitor, detect early and facilitate differential diagnosis among large at-risk populations for AD and related disorders. The MIS-T appears to be the best among these existing screens for very brief telephone surveys. The $CWL_{computerized}$ was developed and named the MCI Screen (http://www.mccare.com). The MCI Screen satisfies all 10 criteria above, and provides reports for public and professionals to educate, motivate and facilitate proper diagnosis and treatment in compliance with the NINDS-ADRDA diagnostic criteria for AD.

The following **Table 2** summarizes the sensitivities for MCI and/or mild dementia, and the specificities for normal aging for the screening tests we compared.

Table 2: Comparison of Sensitivities for MCI and/or mild dementia and for normal aging.

		MCI vs. NL CDR: 0.5 vs. 0		Mild vs. NL CDR: 1 vs. 0		MCI-Mild vs. NL CDR: {0.5, 1} vs. 0		MCI-Mod vs. NL[1] CDR: {0.5,1,2} vs. 0	
Test	Time (min)	SN (N)	SP (N) (N_{Total})	SN (N)	SP (N) (N_{Total})	SN (N)	SP (N) (N_{Total})	SN (N)	SP (N) (N_{Total})
MMSE<25 (15)	7	30% (227)	88% (198) (425)	66% (237)	84% (210) (447)	83% (514)	84% (210) (724)	I	I
Mini-Cog(13,16)	5	?	?	76% (?)	89% (?) (1119)	?	?	97% (?)	95% (?) (249)
CDT[1](1)	2	?	?	?	?	?	?	82% (170)	92% (125) (295)
FAQ > 8 (14)	5	20% (211)	99% (137) (348)	?	?	?	?	I	I
IQCODE(5)	5	?	?	78% (216)	88% (83) (299)	?	?	I	I
Short CASI(10)[1]	15	?	?	?	?	?	?	89% (918)	90% (1178) (2096)
MCAS(8)[1]	20	?	?	?	?	?	?	97% (99)	98% (129) (228)
TICS(11)[1]	3	44% (324)	? (423) (747)	?	?	?	?	88% (60)	78% (44) (94)
DQ(7)[1]	5	?	?	?	?	?	?	91% (?)	92% (?) (839)
CamCog(12)[1]	20	?	?	?	?	?	?	88% (20)	89% (130) (150)
DMT(3)	10	?	?	93% (30)	99% (90) (120)	?	?	I	I
MIS-T(2)[1,2]	4	?	?	?	?	?	?	<78% (27)	93% (273)
$CWL_{original}$ [1] (< 7)	10	83% (238)	78% (198) (436)	88% (292)	99% (198) (490)	93% (530)	77% (198) (728)	96% (968)	77% (198) (1166)

$CWL_{computerized}$	10	87% (224)	83% (194) (418)	97% (226)	97% (194) (420)	92% (450)	90% (194) (644)	I	I

[1]I=Inappropriate: Including moderately demented patients in screening analyses artificially elevates sensitivity and specificity. Moderately demented patients do not need screening because their dementia is obvious. To show the effect of including moderately demented subjects, see the last two columns of the CERAD row.
[2]When the cognitively impaired or demented sample only includes AD, this artificially elevates the sensitivity for screening tests that primary measure episodic (delayed) recall (short-term memory). Valid measures of screening should include all types of disorders causing cognitive impairment or dementia because a screening test can not restrict itself to examining just normal aging vs. AD patients.
? = no published data could be found.

Reference List

1. Borson S, Brush M, Gil E, Scanlan J, Vitaliano P, Chen J, Cashman J, Sta Maria MM, Barnhart R, Roques J. The Clock Drawing Test: utility for dementia detection in multiethnic elders. J Gerontol A Biol Sci Med Sci 54: M534-M540, 1999.

2. Buschke H, Kuslansky G, Katz M, Stewart WF, Sliwinski MJ, Eckholdt HM, Lipton RB. Screening for dementia with the memory impairment screen. Neurology 52: 231-8, 1999.

3. Buschke H, Sliwinski MJ, Kuslansky G, Lipton RB. Diagnosis of early dementia by the Double Memory Test: encoding specificity improves diagnostic sensitivity and specificity. Neurology 48: 989-97, 1997.

4. Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 58: 427-33, 2001.

5. Flicker L, Logiudice D, Carlin JB, Ames D. The predictive value of dementia screening instruments in clinical populations. Int J Geriatr Psychiatry 12: 203-9, 1997.

6. Gutterman EM MJL. Cost of Alzheimer's disease and related dementia in managed-medicare. J Am Geriatr Soc Year > 1999 47: 1065-71.

7. Khachaturian AS, Gallo JJ, Breitner JC. Performance characteristics of a two-stage dementia screen in a population sample. J Clin Epidemiol 53: 531-40, 2000.

8. Knopman DS, Knudson D, Yoes ME, Weiss DJ. Development and standardization of a new telephonic cognitive screening test: the Minnesota Cognitive Acuity Screen (MCAS). Neuropsychiatry Neuropsychol Behav Neurol 13: 286-96, 2000.

9. Leon J. Alzheimer's disease care: costs and potential savings. Health Aff (Millwood) 17: 206-16, 1998.

10. Lin KN, Wang PN, Liu CY, Chen WT, Lee YC, Liu HC. Cutoff scores of the cognitive abilities screening instrument, Chinese version in screening of dementia. Dement Geriatr Cogn Disord 14: 176-82, 2002.

11. Lines CR, McCarroll KA, Lipton RB, Block GA. Telephone screening for amnestic mild cognitive impairment. Neurology 60: 261-6, 2003.

12. Lolk A, Nielsen H, Andersen K, Andersen J, Kragh-Sorensen P. CAMCOG as a screening instrument for dementia: the Odense study. Cambridge Cognitive Examination. Acta Psychiatr Scand 102: 331-5, 2000.

13. Scanlan J, Borson S. The Mini-Cog: receiver operating characteristics with expert and naive raters. Int J Geriatr Psychiatry 16: 216-22, 2001.

14. Shankle WR, Datta P, Pazzani M. Machine Learning Methods and Dementia Diagnosis. Alzheimer's Research 2: 95-9, 1996.

15. Shankle WR, Mani S, Pazzani MJ, Smyth P. Use of a Computerized Patient Record Database of Normal Aging and Very Mildly Demented Subjects to Compare Classification Accuracies Obtained with Machine Learning Methods and Logistic Regression. Computing Science and Statistics 29: 201-9, 1997.

16. Tariska P, Paksy A. [Mini-Cog: a simple method for very brief screening of mental decline]. Orv Hetil 144: 803-9, 2003.