ORIGINAL ARTICLE

# Neuropsychological Prediction of Conversion to Alzheimer Disease in Patients With Mild Cognitive Impairment

*Matthias H. Tabert, PhD; Jennifer J. Manly, PhD; Xinhua Liu, PhD; Gregory H. Pelton, MD; Sara Rosenblum, BS; Marni Jacobs, BA; Diana Zamora, BA; Madeleine Goodkind, BA; Karen Bell, MD; Yaakov Stern, PhD; D. P. Devanand, MD*

**Context:** The likelihood of conversion to Alzheimer disease (AD) in mild cognitive impairment (MCI) and the "optimal" early markers of conversion need to be established.

**Objectives:** To evaluate conversion rates to AD in subtypes of MCI and to identify neuropsychological measures most predictive of the time to conversion.

**Design:** Patients were followed up semiannually and controls annually. Subtypes of MCI were determined by using demographically adjusted regression norms on neuropsychological tests. Survival analysis was used to identify the most predictive neuropsychological measures.

**Setting:** Memory disorders clinic.

**Participants:** One hundred forty-eight patients reporting memory problems and 63 group-matched controls.

**Main Outcome Measure:** A consensus diagnosis of probable AD.

**Results:** At baseline, 108 patients met criteria for amnestic MCI: 87 had memory plus other cognitive domain deficits and 21 had pure memory deficits. The mean duration of follow-up for the 148 patients was 46.6±24.6 months. In 3 years, 32 (50.0%) of 64 amnestic-"plus" and 2 (10.0%) of 20 "pure" amnestic patients converted to AD ($P=.001$). In 148 patients, of 5 a priori predictors, the percent savings from immediate to delayed recall on the Selective Reminding Test and the Wechsler Adult Intelligence Scale–Revised Digit Symbol Test were the strongest predictors of time to conversion. From the entire neuropsychological test battery, a stepwise selection procedure retained 2 measures in the final model: total immediate recall on the Selective Reminding Test (odds ratio per 1-point decrease, 1.10; 95% confidence interval, 1.05-1.14; $P<.0001$) and Digit Symbol Test coding (odds ratio, 1.06; 95% confidence interval, 1.01-1.11; $P=.01$). The combined predictive accuracy of these 2 measures for conversion by 3 years was 86%.

**Conclusions:** Mild cognitively impaired patients with memory plus other cognitive domain deficits, rather than those with pure amnestic MCI, constituted the high-risk group. Deficits in verbal memory and psychomotor speed/executive function abilities strongly predicted conversion to AD.

*Arch Gen Psychiatry. 2006;63:916-924*

MILD COGNITIVE IMPAIRMENT (MCI) signifies the transitional stage between age-related memory decline and Alzheimer disease (AD).[1] The criteria for MCI[2] require the report of memory problems, cognitive impairment (test score, >1.5 SDs below age-adjusted norms), and intact daily functioning.

Conversion rates from MCI to AD range from 4% to 23% in community-based and 10% to 31% in clinic-based samples.[3,4] This variability may be related to differences in diagnostic criteria and sample selection. Recent studies[1,5,6] suggest that patients with amnestic MCI (ie, patients with scores >1.5 SDs below age-adjusted norms on standard memory tests), with or without deficits in other cognitive domains, constitute subtypes that are most likely to convert to AD. Nonamnestic single- or multiple-domain subtypes are more likely to convert to other dementias.

In MCI, impairment in measures of free recall, particularly verbal recall,[7-10] consistently predict conversion to AD in community-based[7,11-18] and clinic-based[19-29] studies. Executive function deficits also consistently predict AD conversion,[7,16,30,31] with less consistent findings[5,32] for verbal fluency,[11] naming,[15] visuospatial ability,[17] and attention[23] deficits.

In a long-term follow-up study of patients with MCI (hereafter referred to as *MCI patients*) and healthy control subjects, our group examined putative early markers of MCI conversion to AD.[33-36]

**Author Affiliations** are listed at the end of this article.

Based on an earlier study in an independent sample[24] and the literature,[15,23,24] 5 neuropsychological measures were selected as predictors of MCI conversion: percent savings from immediate to delayed recall on the Buscke Selective Reminding Test (SRT)[37] and on the Wechsler Memory Scale (WMS) visual reproduction subtest (WMS-VR),[38] performance on the Wechsler Adult Intelligence Scale–Revised (WAIS-R) Digit Symbol Test,[39] confrontational naming on the Boston Naming Test (BNT),[40] and category fluency on the Animal Naming Test (ANT).[41]

The primary goals were to classify patients according to current MCI criteria and to evaluate conversion rates in MCI subtypes. The secondary goal was to evaluate the predictive utility of our 5 a priori measures for conversion to AD. Finally, we sought to identify which baseline neuropsychological measures from the comprehensive battery were the most predictive of time to AD conversion.

## METHODS

### SUBJECTS

One hundred forty-eight patients who presented with memory problems to a memory disorders center, including a research clinic and affiliated neurologists' private offices, participated in a longitudinal study of putative early markers of AD. All subjects were consecutive newly referred subjects from several sources. Most (52.0%) were physician-referred, 25.0% were self-referred, and 23.0% were referred by family, friends, or other sources. Of the 15 patient deaths during follow-up, we obtained 4 autopsy reports (2 patients had AD, 1 had amyotrophic lateral sclerosis with frontotemporal dementia, and 1 did not have dementia; all clinical diagnoses were consistent with autopsy diagnoses). The clinical diagnosis of the patient with amyotrophic lateral sclerosis was clarified within 6 months, and the subject was therefore excluded from analyses.

Sixty-three healthy control subjects, recruited by advertisement, were examined annually. An additional 20 controls recruited for other studies met the same inclusion/exclusion criteria and completed the same neuropsychological test battery (see "Neuropsychological Evaluation" in the next section). The combined sample of 83 controls was used to establish regression-based norms. The institutional review boards of the New York State Psychiatric Institute and Columbia University Medical Center, New York, reviewed and approved the research protocol, and written informed consent was obtained from each participant.

### PROCEDURES

#### Inclusion/Exclusion Criteria

The current longitudinal study began before the Petersen MCI criteria were established,[2] and the inclusion and exclusion criteria were broadly defined to enroll patients ranging between "normal" and "dementia." For patients, inclusion criteria were age of 40 years or greater, cognitive impairment for at least 6 months but no more than 10 years, and the diagnosis of "not demented" (clinical dementia rating of 0) or "questionably demented" (clinical dementia rating of 0.5). Patients had a minimum Folstein Mini-Mental State Examination (MMSE) score of 22 or higher, except for Spanish-speaking patients with no more than 5 years of education, for whom an MMSE score of 18 or higher was permitted if they met all other neuropsychological and inclusion/exclusion criteria. Study neuropsychological inclusion criteria were the ability to recall 2 or fewer of 3 objects at 5 minutes on the MMSE or a delayed recall score greater than 1 SD below norms on the SRT, or a WAIS-R performance IQ score of 10 or more points below the WAIS-R verbal IQ score. Patients who did not demonstrate an objective cognitive deficit on formal neuropsychological testing were still eligible if they met all of the following criteria: subjective complaint of memory decline (reported by the subject or an informant) and a positive score (endorsed by the subject or an informant) on 1 or more of the first 8 items of the modified Blessed Functional Activity Scale.[42] Detailed medical, neurological, and psychiatric exclusion criteria have been described previously.[34,35] These patients were followed up semiannually.

A study physician (G.H.P., K.B., or D.P.D.) completed a medical history and conducted a general physical, neurological, and psychiatric examination including standard laboratory tests and brain magnetic resonance imaging. A trained neuropsychology technician (M.H.T., S.R., M.J., D.Z., or M.G.) administered a comprehensive diagnostic battery that was evaluated by an experienced neuropsychologist (Y.S.). Two expert clinical raters (Y.S. and D.P.D.) used all available information (baseline cognitive testing, clinical, laboratory, and magnetic resonance imaging) to make a consensus research diagnosis. A similar approach was used for follow-up evaluations, with the raters being blind to data from previous visits. Dementia was diagnosed according to *DSM-IV* criteria and possible or probable AD, according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[43] The consensus diagnosis was the primary outcome. Conversion to AD required meeting clinical diagnostic criteria for possible or probable AD at 2 consecutive assessments.

For this prospective study, controls were group matched to patients on baseline age and sex. Inclusion criteria for controls were the absence of memory problems, a score of 34 or higher of 41 on the Telephone Interview for Cognitive Status, a score of 27 or higher (of 30 total) on the MMSE with recall of 2 or more of 3 objects at 5 minutes, and neuropsychological test scores (on the same battery of tests used to evaluate the patient cohort) that were not more than 1 SD below age-adjusted norms. Medical, neurological, and psychiatric exclusion criteria were the same as for patients. The same neuropsychological tests were used during the study for the recruitment of all patients and controls.

#### Neuropsychological Evaluation

The neuropsychological test battery included measures of learning and memory, orientation, abstract reasoning, language, attention, and visuospatial ability.

Verbal list learning and memory were assessed with the 12-item, 6-trial SRT.[37] The total number of words learned in 6 trials (total immediate recall), delayed recall (following a 15-minute delay), and the percent savings from immediate to delayed recall were also examined. Nonverbal learning and memory were assessed with the WMS-VR subtest.[38] Nonverbal recognition memory was also assessed using a multiple-choice version of the Benton Visual Retention Test.[44]

Language tests included a 15-item version of the BNT (total spontaneous responses),[40] the ANT (60-second trial),[41] and the repetition of high-frequency phrases and complex ideational material subtests of the Boston Diagnostic Aphasia Evaluation (BDAE repetition and BDAE comprehension, respectively).[41]

Tests of attention included the digit span subtest from the WMS (forward plus reverse digits) and cancellation tests that featured a diamond-shaped stimulus (cancellation-shape) and a group of letters (cancellation-letter).

Tests of visuospatial ability included the block design and object assembly subtests of the WAIS-R,[39] the 5-item Rosen Drawing Test,[45] and the matching subtest of the Benton Visual Retention Test.[44]

The battery did not include specific tests of executive function (eg, Wisconsin Card-Sorting Test, Stroop Color-Word Interference Test, or Trail Making Test part B). Instead, the following tests were used as indicators of executive function (eg, verbal and nonverbal abstract reasoning, establishing and maintaining set, set shifting, and self-monitoring): the similarities subtest of the WAIS-R,[39] the identities and oddities subtest of the Mattis Dementia Rating Scale (Mattis identities and oddities),[46] the CFL version of the Controlled Oral Word Association Test (COWAT-CFL),[47] and WAIS-R Digit Symbol Test.[39]

## STATISTICAL ANALYSES

### Demographic and Clinical Features and Neuropsychological Performance

Two-sample *t* tests and $\chi^2$ tests were used to compare patients with controls and to compare MCI patients who converted to AD on follow-up evaluation with MCI patients who did not (hereafter referred to as *MCI converters* and *MCI nonconverters,* respectively).

### MCI Subtype Classification

Although data for the current longitudinal study were collected prospectively, the baseline MCI subtype for each patient was determined post hoc on the basis of current Peterson criteria.[1] This retrospective reclassification used the following cognitive domains and measures: (1) memory: SRT total and delayed recall and WMS-VR immediate and delayed recall; (2) executive function: WAIS-R similarities, WAIS-R Digit Symbol Test, and COWAT-CFL; (3) language: BNT, ANT, BDAE repetition, and BDAE comprehension; and (4) visuospatial ability: Rosen Drawing Test, WAIS-R block design, and WAIS-R object assembly.

Regression-based norms adjusted for demographic variables were calculated for the 83 controls.[48,49] Each neuropsychological measure used to classify MCI subtypes was included as a dependent variable. Continuous predictors were age and years of education. The categorical predictor was sex. From the multiple linear regression equations, only demographic variables significant at $P<.05$ were retained. The intercept and unstandardized regression coefficients estimated from the controls were used to calculate predicted scores for each neuropsychological measure. The predicted scores for each patient (based on their demographic characteristics) were then used to calculate residuals that were transformed into demographically corrected T scores (normative mean [SD] of 50 [10]).

Based on these demographically corrected T scores from the baseline evaluation, the "pure" amnestic subtype of MCI [MCI-A] was diagnosed if scores on any 1 of the 4 memory measures were lower than 1.5 SDs below the normative mean and performance on measures from the other cognitive domains was greater than or equal to 1.5 SDs below the demographically corrected mean. The multiple cognitive domain amnestic subtype (md-MCI + a) was defined as impaired memory with impairment (>1.5 SDs below norms) in 1 or more tests from another cognitive domain. Impairment in only a single nonmemory domain led to the following classification: MCI–executive function (MCI-E), MCI-language (MCI-L), and MCI-visuospatial (MCI-V). Finally, impairment on tests from 2 or more of the 3 nonmemory domains with normal scores within the memory domain was classified as MCI–multiple cognitive domain deficits without memory impairment (md-MCI – a). Classification into the 6 subtypes, derived from the baseline evaluation, was mutually exclusive. Conversion rates to AD on follow-up evaluation were calculated for the entire cohort and for specific baseline MCI subtypes.

### Evaluating the Predictive Utility of Neuropsychological Test Measures

With the use of the same linear regression procedures, scores from all neuropsychological measures for all 148 patients were transformed to create demographically adjusted T scores (ie, normative mean [SD] of 50 [10]). The T scores for each patient were then used as continuous predictors of conversion to AD in subsequent analyses. Because the follow-up duration varied across subjects and the hazards of AD conversion varied by baseline age, age-stratified Cox discrete time-regression models were used to examine the effect of the T score–transformed baseline neuropsychological measures on the development of AD. Cox survival analyses were conducted in 2 stages.

**Five A Priori Neuropsychological Measures.** In the first stage, we used separate Cox survival models to assess the individual effect of each of the 5 T score–transformed a priori neuropsychological predictors on AD conversion. We also used a single Cox model that included all 5 predictors to assess their simultaneous effect on AD conversion.

**Identifying a Subset of "Optimal" Neuropsychological Predictors.** In the second stage, we evaluated all neuropsychological measures from the larger battery of tests. In initial screening analyses, separate Cox models were applied to each T score–transformed neuropsychological measure from the comprehensive battery. The *P* values were calculated from 1-sided Wald tests, which tested whether decreased performance on a measure was associated with a concomitant increase in the hazard of conversion to AD. The method of Benjamini and Yekutieli[50] was then used to control the false discovery rate in the multiple tests conducted (false discovery rate, <0.10). Because some measures may be redundant in predicting AD conversion owing to clustering, the individually significant measures were next collectively submitted to a stepwise selection procedure in age-stratified Cox regression analysis with a preset significance level of $P<.10$. Variables were entered into and removed from the model such that 1 or more backward elimination steps could follow each forward selection step. Hence, the variables already in the model did not necessarily remain. The stepwise selection process terminated if no further variable could be added to the model or if the variable just entered into the model was the only variable removed in the subsequent backward elimination.The goal of the initial screening and the stepwise analyses was to identify a subset of measures from the larger battery of tests that in combination contributed the most unique variance among the neuropsychological measures in predicting time to AD conversion. To aid interpretation, we calculated the odds ratios (ORs) of AD conversion in this sample of patients during a 1-year period for each 5-point T score decrease (ie, 0.5 SD of the normative sample) on each predictor retained in the final Cox model.

**Prediction for 3-Year Follow-up Sample.** To evaluate clinically relevant prediction for a fixed follow-up duration, logistic regression analysis was used to test the predictive accuracy of the final predictor model selected by the stepwise selection procedure, restricting the sample to those who had completed 3 years of follow-up (or were diagnosed as having AD by 3 years) and including age as a predictor. For this model, we calcu-

**Table 1. Baseline Features of Healthy Control Subjects and MCI Patients (Converters and Nonconverters to AD)**

| Characteristic | Controls vs Patients | | | MCI Patients (n = 148)† | | | MCI Patients (n = 115)‡ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Controls (n = 83) | MCI Patients (n = 148) | *P* Value* | Nonconverters (n = 109) | Converters (n = 39) | *P* Value* | Nonconverters (n = 80) | Converters (n = 35) | *P* Value* |
| Age, mean (SD), y | 66.9 (9.1) | 67.0 (9.9) | .94 | 65.0 (10.0) | 72.6 (7.2) | <.001 | 64.4 (9.8) | 72.7 (7.2) | <.001 |
| Sex, No. (%) F | 49 (59.4) | 81 (55.0) | .58 | 60 (55.0) | 22 (56.4) | .85 | 41 (51.3) | 21 (60.0) | .42 |
| Education completed, mean (SD), y | 16.5 (2.6) | 15.0 (4.3) | .001 | 15.4 (4.2) | 14.1 (4.4) | .11 | 15.7 (3.6) | 13.9 (4.5) | .03 |
| Race/ethnicity, No. (%)§ | | | | | | | | | |
| White non-Hispanic | 70 (84.3) | 108 (73.0) | .04 | 82 (75.2) | 26 (66.7) | .45 | 62 (77.5) | 23 (65.7) | .39 |
| Black non-Hispanic | 7 (8.4) | 8 (5.4) | | 4 (3.7) | 4 (10.3) | | 3 (3.8) | 4 (11.4) | |
| Hispanic | 5 (6.0) | 28 (18.9) | | 20 (18.3) | 8 (20.5) | | 13 (16.3) | 7 (20.0) | |
| Other | 1 (1.2) | 4 (2.7) | | 3 (2.8) | 1 (2.6) | | 2 (2.5) | 1 (2.9) | |
| Apolipoprotein E ε4 status, No. (%) positive | 13 (22.4) (n = 58) | 37 (26.2) (n = 141) | .72 | 25 (23.6) (n = 106) | 12 (33.3) (n = 36) | .18 | 19 (24.4) (n = 78) | 11 (34.4) (n = 32) | .35 |
| Folstein MMSE score, mean (SD) | 29.3 (0.8) | 27.5 (2.2) | <.001 | 28.0 (1.9) | 26.1 (2.2) | <.001 | 28.1 (2.0) | 26.1 (2.1) | <.001 |

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NS, not significant ($P \geq .05$).

*To detect group differences on categorical and continuous variables, $\chi^2$ and independent-samples *t* tests, 2-tailed, were used, as appropriate.

†Includes only those subjects with at least 1 follow-up visit. The baseline features for 6 subjects who lost contact after the baseline evaluation or refused follow-up were similar to those of the rest of the sample (mean [SD] age, 69 [8.6] years; sex, 4 [67%] female; mean [SD] education completed, 15 [3.5] years; ethnicity, 4 [67%] white and 2 [33%] Hispanic; mean [SD] Folstein MMSE score, 28 [3.3]).

‡The patient sample was restricted to 3 years of follow-up (patients who had completed 3 years of follow-up or were diagnosed as having AD by 3 years).

§At baseline, ethnic group was documented by self-report. All subjects were first asked to report their racial group (ie, American Indian–Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, black, or white); in a second question they were asked whether they were of Hispanic origin.

lated sensitivity (percentage of patients with predicted risk of AD conversion ≥0.5 among MCI converters within 3 years), specificity (percentage of patients with predicted risk <0.5 among MCI nonconverters), predictive accuracy (percentage of patients correctly classified), positive predictive value (percentage of MCI converters among patients with a predicted risk ≥0.5), and negative predictive value (percentage of MCI nonconverters among patients with a predicted risk <0.5).

## RESULTS

### DESCRIPTIVE DATA FOR CONTROLS AND PATIENTS

#### Demographic and Clinical Features

At baseline, controls and patients showed no significant demographic and clinical group differences with regard to age, sex distribution, and apolipoprotein E ε4 status (**Table 1**). Patients were less educated and had lower MMSE scores than controls (Table 1). The mean (SD) duration of follow-up was 52.2 (28.4) months in controls and 46.6 (24.6) months in patients. (Follow-up was shorter in patients because MCI converters exited the protocol after 2 consecutive annual diagnoses of AD.) Of the 148 patients enrolled in the longitudinal study, 8 died before the 3-year follow-up. Of the remaining 140 patients, 10 (7.1%) dropped out by the third follow-up visit: 5 (3.6%) refused further follow-up, 2 (1.4%) discontinued owing to serious medical illness, and 3 (2.1%) lost contact. Of the 63 controls enrolled in the longitudinal study, 2 (3%) died before the 3-year follow-up. Of the remaining 61 controls, 5 (8%) dropped out during the same period: 1 (2%) refused further follow-up, 1 (2%) discontinued owing to serious medical illness, and 3 (5%) lost contact.

Patients with MCI who did and did not convert to AD on follow-up did not differ in the distribution of sex, years of education, and apolipoprotein E ε4 status (Table 1). The MCI converters were older and scored lower on the MMSE at baseline. During the 3-year follow-up, compared with MCI nonconverters, converters had greater decline on MMSE scores (mean [SD] difference in scores [year 3 visit minus baseline visit]: MCI converters, –1.5 [2.8] vs nonconverters, –0.07 [1.8], $P = .05$; WAIS-R full-scale IQ: MCI converters, –3.2 [7.5] vs nonconverters, 3.2 [7.2], $P = .005$; and WMS memory quotient: MCI converters, –12.8 [10.5] vs nonconverters, 2.7 [11.6], $P < .001$).

#### Neuropsychological Test Performance

The WAIS–Third Edition (WAIS-III) was administered to 16 patients. For these patients, WAIS-R equivalent scores were assigned by converting raw WAIS-III scores that were uncorrected for demographic factors to scaled scores for the WAIS-R standardization sample.[51]

On baseline testing, patients had mean scores that were significantly lower than controls ($P < .05$) on all neuropsychological measures except for the WMS digit span test, the Mattis identities and oddities subtest, and the Rosen Drawing Test (**Table 2**). Moreover, within the patient group, after restricting the sample to patients with 3 years of follow-up (or those diagnosed as having AD by 3 years), MCI converters scored lower than nonconverters on all measures of verbal and nonverbal memory and executive function abilities. Differences between MCI converters and nonconverters were also observed on some tests of language (BNT and ANT) and visuospatial ability (WAIS-R block design), but not on tests of attention (WMS digit span total, cancellation-shape, and cancellation-letter).

**Table 2. Baseline Neuropsychological Performance of Healthy Control Subjects and MCI Patients (Converters and Nonconverters to AD)***

| Domain, Cognitive Measure | Controls (n = 83) | MCI Patients (n = 148) | *P* Value† | MCI Nonconverters (n = 80)‡ | MCI Converters (n = 35) | *P* Value† |
|---|---|---|---|---|---|---|
| Verbal memory | | | | | | |
| SRT immediate recall | 53.0 (6.8) | 42.6 (9.3) (n = 147) | <.001 | 46.5 (7.8) | 34.3 (7.4) (n = 34) | <.001 |
| SRT delayed recall | 8.7 (2.3) | 5.5 (3.0) (n = 147) | <.001 | 6.5 (2.8) | 2.3 (2.9) (n = 34) | <.001 |
| SRT percent savings | 85.3 (18.8) | 60.7 (28.7) (n = 147) | <.001 | 69.2 (24.2) | 38.2 (27.1) (n = 34) | <.001 |
| Nonverbal memory | | | | | | |
| WMS-VR immediate recall | 8.8 (3.1) (n = 65) | 7.6 (3.4) (n = 147) | .02 | 8.1 (3.4) (n = 79) | 6.2 (3.1) | .005 |
| WMS-VR delayed recall | 7.8 (3.4) (n = 65) | 5.6 (3.8) (n = 147) | <.001 | 6.9 (3.8) (n = 79) | 3.0 (2.7) | <.001 |
| WMS-VR percent savings | 87.1 (25.5) (n = 65) | 68.8 (35.9) (n = 147) | <.001 | 80.1 (27.7) (n = 79) | 51.1 (45.0) | .001 |
| BVRT recognition | 9.3 (0.9) | 8.4 (1.5) | <.001 | 8.7 (1.3) | 7.9 (1.6) | .004 |
| Language | | | | | | |
| 15-Item BNT | 14.8 (0.5) | 14.4 (1.1) | .001 | 14.6 (0.9) | 13.9 (1.3) | .01 |
| ANT | 22.2 (5.6) | 18.0 (5.9) (n = 147) | <.001 | 19.4 (5.6) (n = 79) | 16.0 (6.0) | .004 |
| BDAE repetition | 7.9 (0.3) | 7.8 (0.5) | .04 | 7.8 (0.6) | 7.8 (0.4) | .92 |
| BDAE comprehension | 5.9 (0.2) | 5.8 (0.6) (n = 145) | .02 | 5.9 (0.4) (n = 79) | 5.7 (0.7) (n = 38) | .12 |
| Attention | | | | | | |
| WMS digit span total | 11.8 (2.3) | 11.4 (2.4) | .28 | 11.7 (2.5) | 11.1 (2.3) | .26 |
| Cancellation-shape (omission errors) | 3.41 (3.0) | 4.47 (3.61) | .02 | 4.2 (3.7) | 5.3 (3.6) | .18 |
| Cancellation-letter (omission errors) | 0.43 (0.9) | 0.74 (1.4) | .04 | 0.5 (0.9) | 1.0 (1.7) | .18 |
| Visuospatial ability | | | | | | |
| WAIS-R block design | 26.9 (8.1) (n = 65) | 22.5 (10.6) | .001 | 24.2 (11.4) | 18.7 (10.3) | .02 |
| WAIS-R object assembly | 26.5 (6.7) (n = 65) | 24.3 (7.2) (n = 139) | .04 | 25.4 (7.7) (n = 77) | 22.1 (6.1) (n = 34) | .03 |
| 5-Item RDT | 3.7 (1.0) | 3.5 (0.9) | .08 | 3.5 (0.9) | 3.2 (1.1) | .20 |
| BVRT matching | 9.8 (0.5) | 9.5 (0.9) | .005 | 9.6 (0.8) | 9.4 (1.0) | .29 |
| Executive function | | | | | | |
| WAIS-R similarities | 21.7 (3.8) | 19.7 (5.3) | .001 | 20.6 (4.1) | 17.9 (6.7) | .03 |
| Mattis identities and oddities | 15.5 (0.9) | 15.5 (1.1) | .49 | 15.6 (1.0) | 15.0 (1.4) | .02 |
| COWAT-CFL | 48.0 (12.9) | 42.2 (13.9) | .002 | 46.5 (13.6) | 36.5 (14.0) | <.001 |
| WAIS-R Digit Symbol Test | 50.2 (11.2) (n = 65) | 40.8 (12.7) | <.001 | 45.2 (12.2) | 32.5 (10.7) | <.001 |

Abbreviations: AD, Alzheimer disease; ANT, Animal Naming Test; BDAE, Boston Diagnostic Aphasia Examination; BNT, Boston Naming Test; BVRT, Benton Visual Reproduction Test; COWAT-CFL, Controlled Oral Word Association Test (CFL letters used); MCI, mild cognitive impairment; RDT, Rosen Drawing Test; SRT, Selective Reminding Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised; WMS, Wechsler Memory Scale; WMS-VR, WMS visual reproduction.

*Data are expressed as the mean (SD) score unless otherwise indicated.

†Two-tailed *t* tests (for continuous variables) were conducted as appropriate.

‡For comparisons between MCI nonconverters (n = 80) and converters (n = 35), the sample was restricted to patients who had completed 3 years of follow-up (or were diagnosed as having AD by 3 years).

## CLASSIFICATION OF MCI SUBTYPES AND CONVERSION RATES ON FOLLOW-UP

### The MCI Subtype Distribution at Baseline

For the entire sample of patients, the MCI subtype distribution was as follows: MCI-A (amnestic single domain), n = 21; md-MCI + a (multiple-domain deficits plus memory), n = 87; MCI-E (executive function), n = 3; MCI-L (language), n = 12; MCI-V (visuospatial), n = 2; md-MCI – a (multiple-domain deficits without memory), n = 3; and non-MCI (cognitively impaired but not meeting the 1.5-SD cutoff threshold), n = 20.

### Conversion Rates to AD on Follow-up Evaluation

Thirty-nine of 148 MCI patients converted to AD on follow-up. The mean (SD) time to AD diagnosis was 21 (15) months. Thirty-eight of the 39 MCI converters were classified at baseline as having amnestic MCI (MCI-A plus md-MCI + a) and 1 as having multiple-domain nonamnestic MCI (md-MCI – a). When the sample was restricted to 3 years of follow-up (see Table 1 for the baseline characteristics of this restricted sample), the conversion rate was 30.4% (35/115), with 50.0% (32/64) of the patients with md-MCI + a and 10.0% (2/20) of the patients with MCI-A converting to AD (Fisher's exact test [2-sided], *P* = .001).

## EVALUATING THE PREDICTIVE UTILITY OF NEUROPSYCHOLOGICAL TEST MEASURES

### Five A Priori Neuropsychological Measures

In the separate age-stratified Cox predictor models applied to 148 patients, 4 of the 5 a priori measures significantly predicted time to conversion: (1) SRT percent savings from immediate to delayed recall (OR per 1-point decrease, 1.05; 95% confidence interval [CI], 1.03-1.08; $P<.001$); (2) WAIS-R Digit Symbol Test (OR, 1.09; 95% CI, 1.04-1.14; $P=.001$); (3) ANT (OR, 1.04; 95% CI, 1.01-1.08; $P=.02$); and (4) BNT (OR, 1.01; 95% CI, 1.00-1.03; $P=.04$). Moreover, for verbal memory as measured by the SRT, both immediate recall (OR, 1.10; 95% CI, 1.06-1.14; $P<.001$) and delayed recall (OR, 1.09; 95% CI, 1.05-1.12; $P<.001$) were strong predictors of time to conversion. Delayed recall on the WMS-VR test of nonverbal memory was a significant predictor of time to conversion (OR, 1.03; 95% CI, 1.01-1.06; $P=.03$).

When all 5 a priori measures were entered as predictors into a single Cox model, only the SRT percent savings ($P<.001$) and the WAIS-R Digit Symbol Test ($P=.002$) were significant predictors of time to AD conversion.

### Identifying a Subset of "Optimal" Neuropsychological Predictors

Initial screening analyses, in which separate age-stratified Cox models were applied to the demographically adjusted T scores for the measures from the larger battery of tests, yielded 10 measures that were associated with outcome (with multiple tests–adjusted $P$ values $<.10$; a liberal criterion was used for these initial analyses to ensure that all measures associated with risk of conversion would be included in the stepwise procedure): (1) SRT total immediate recall ($P<.001$), (2) SRT delayed recall ($P<.001$), (3) WAIS-R Digit Symbol Test ($P=.001$), (4) BDAE comprehension ($P=.004$), (5) COWAT-CFL ($P=.02$), (6) ANT ($P=.02$), (7) WMS-VR delayed recall ($P=.02$), (8) BNT ($P=.04$), (9) Mattis identities and oddities ($P=.07$), and (10) WAIS-R similarities ($P=.09$). Correlation coefficients between each of these 10 select measures ranged from 0.003 to 0.65, with the highest correlation ($r=0.65$) occurring between SRT immediate and delayed recall.

When these 10 measures were submitted to the stepwise selection procedure with a preset significance level of $P<.10$, only SRT total immediate recall (OR, 1.10; 95% CI, 1.05-1.14; $P<.001$) and the WAIS-R Digit Symbol Test (OR, 1.06; 95% CI, 1.01-1.11; $P=.01$) remained in the final model and were thus selected as the most predictive of time to AD conversion.

Table 2 demonstrates that in addition to SRT immediate recall and WAIS-R Digit Symbol Test ($r=0.05$ between these 2 measures), SRT delayed recall and SRT percent savings from immediate to delayed recall also strongly discriminated between MCI nonconverters and converters ($P<.001$). The intercorrelation matrix between these 3 SRT measures of verbal recall showed correlation coefficients of 0.65 between SRT immediate and SRT delayed recall, 0.49 between SRT immediate recall and SRT percent savings, and 0.92 between SRT delayed recall and SRT percent savings. When all 3 measures were entered as predictors into a single Cox model, only SRT immediate recall was a significant predictor of time to AD conversion ($P<.001$; SRT delayed recall and SRT percent savings, $P=.55$).

### Prediction for the 3-Year Follow-up Sample

In a logistic regression model of AD conversion in 3 years (n=114) that included both predictors selected by the stepwise procedure (SRT total immediate recall and WAIS-R Digit Symbol Test), the overall sensitivity, specificity, predictive accuracy, positive predictive value, and negative predictive value were 76%, 90%, 86%, 76%, and 90%, respectively.

## COMMENT

In this study, 39 (26.4%) of 148 MCI patients converted to AD during a mean of 46.6 months. Of the 39 MCI converters, 38 (97.4%) were classified at baseline as amnestic MCI; 36 (41.4%) of 87 multiple-domain amnestic patients (md-MCI+a) and 2 (9.5%) of 21 pure amnestic patients (MCI-A) converted to AD on follow-up. When the sample was restricted to 3 years of follow-up, the conversion rate was 30.4% (35/115), with 50.0% (32/64) of multiple-domain amnestic patients and 10.0% (2/20) of pure amnestic patients converting to AD. These results are consistent with reports from other groups indicating that 12% to 15% of amnestic MCI patients convert annually to AD[1] (40.5% within 3 years in our sample).

These findings support other data[52-54] showing that conversion rates to AD are considerably greater for amnestic MCI patients with multiple cognitive domain deficits than for those with pure memory impairment. This raises the intriguing possibility that these amnestic-"plus" patients constitute a group at high risk for conversion to AD, whereas the pure amnestic MCI patients may not be at such a high risk. However, with longer follow-up the pure amnestic MCI patients may develop multiple cognitive domain deficits and eventually convert to AD. These findings also suggest that testing for deficits in multiple cognitive domains in addition to those in memory will improve the predictive value of neuropsychological testing in MCI patients.[5,32]

Four of the 5 a priori predictors significantly predicted time to conversion to AD. Percent savings from immediate to delayed recall on the SRT, an index of verbal learning and memory, was the strongest predictor. In addition, poor performance on WAIS-R digit symbol coding, animal naming, and confrontational naming also strongly predicted time to conversion. When all 5 predictors were entered into a single model, however, only SRT percent savings and WAIS-R digit symbol coding remained significant predictors.

Based on the stepwise selection procedure, SRT total immediate recall across 6 trials and WAIS-R digit symbol coding were the measures that contributed the most unique variance to prediction. For the 3-year follow-up sample,

**Table 3. Increase in Odds of AD Conversion Within 1 Year Associated With Each 5-Point T Score Decrease on 2 Neuropsychological Measures***

| 5-Point T Score Decreases† | | Odds Ratio (95% CI) | |
|---|---|---|---|
| T Score | SD | SRT Total Immediate Recall (Adjusting for WAIS-R Digit Symbol Test) | WAIS-R Digit Symbol Test Coding (Adjusting for SRT Total Immediate Recall) |
| 45 | 0.5 | 1.56 (1.30-1.88) | 1.36 (1.11-1.81) |
| 40 | 1.0 | 2.43 (1.69-3.53) | 1.85 (1.23-3.28) |
| 35 | 1.5 | 3.80 (2.20-6.65) | 2.52 (1.37-5.93) |
| 30 | 2.0 | 5.92 (2.86-12.49) | 3.42 (1.51-10.73) |

Abbreviations: AD, Alzheimer disease; CI, confidence interval; SRT, Selective Reminding Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised.

*The 2 measures were elected as the best predictors of outcome (see "Evaluating the Predictive Utility of Neuropsychological Test Measures" section for details). Odds are relative to patients with a mean T score of 50.

†Demographically adjusted T scores for each patient were derived from 83 normal controls (mean [SD] normative T score, 50 [10]) using the following regression equations (only significant demographic predictors were included). Predicted T scores for SRT total immediate recall = 63.824 + (sex × 3.658) + (age × –0.194), where female is coded as 1 and male as 0, and WAIS-R digit symbol coding = 18.96 + (years of education × 1.877). One can use the following 2 regression equations to calculate a patient's T score on SRT immediate recall and/or WAIS-R digit symbol coding: SRT total immediate recall = 50 + {10[(SRT immediate recall score – predicted score)/6.329]} and WAIS-R digit symbol coding = 50 + {10[(Digit Symbol Test score – predicted score)/10.132]}. The table can then be used to obtain an estimate of the patient's odds of AD conversion during the next year. Take, for example, a 65-year-old woman with 18 years of education who scores 46 on SRT total immediate recall. The predicted score for this patient is: 63.824 + (1 × 3.658) + (65 × –0.194) = 54.87. The corresponding T score is 50 + {10[(46 – 54.87)/6.329]} = 35.99. Table 3 shows that, based on a decrease in SRT immediate recall alone, this patient has approximately a 3.80-fold increase in the odds of converting to AD during the next year relative to a patient with a T score of 50. A similar calculation can be conducted for WAIS-R digit symbol coding.

sensitivity (76%), specificity (90%), predictive accuracy (86%), positive predictive value (76%), and negative predictive value (90%) were strong, suggesting potential clinical applicability. However, these indicators of prediction were not robust enough for these measures to be used as the sole early markers of conversion from MCI to AD.

The increase in odds of AD conversion during a 1-year period associated with each 5-point T score decrease on SRT total immediate recall, after adjusting for WAIS-R digit symbol coding, and vice versa, was considerable. **Table 3** shows that patients with a T score of 35 (1.5 SDs below the normative mean) on either of these measures had an approximately 3-fold increase in the odds of AD conversion during the next year. For a given patient, this table provides an initial model that can be used to transform raw scores from either of these 2 measures into T scores and to estimate the corresponding increase in odds of AD conversion during the first 1-year follow-up period (see the example in the footnote to Table 3).

Previous studies[7,15,18,55] have consistently shown that the ability to acquire and recall new verbal information over several consecutive trials is the best and possibly the earliest neuropsychological predictor of who will convert to AD. Hence, it is not surprising that SRT total immediate recall was a strong predictor that contributed the most unique variance to prediction based on stepwise regression analyses. However, SRT delayed recall and SRT percent savings from immediate to delayed recall also strongly discriminated between MCI nonconverters and converters ($P<.001$), indicating that these measures of verbal memory are also useful predictors of AD conversion.

Studies[11,24,30,31,56-58] have also shown that WAIS-R digit symbol coding is strongly associated with AD conversion. This task requires efficient performance in several cognitive domains, including psychomotor speed, attention, and executive function.[39] In the present study, other measures of attention and psychomotor speed (ie, digit span and timed cancellation tasks) did not discriminate MCI nonconverters from converters. This indirectly suggests that specific processing components related to executive function abilities (eg, self-monitoring, set shifting, and working memory) most likely accounted for the predictive value of the WAIS-R Digit Symbol Test. Together, these findings corroborate those of other groups[7] reporting that episodic memory and executive function deficits are among the most robust and earliest predictors of AD.

The present study had a number of limitations. First, the results from this study can be applied to outpatient clinic settings in which patients present to the psychiatry or neurology department because of memory and cognitive difficulties, but may not be generalizable to other settings. Second, our neuropsychological test battery did not include tests specifically designed to assess executive function, although we were able to draw on a range of tests that incorporate executive function abilities. Third, the neuropsychological scores that were included in the diagnostic process were also used to predict time to AD conversion, raising the issue of circularity. However, expert raters made diagnoses on the basis of all the clinical research information and not solely on the neuropsychological tests. Critically, there were marked differences between MCI converters and nonconverters in progression on several global measures of cognitive functioning (MMSE, WAIS-R full-scale IQ, and WMS memory quotient) over time, thereby validating the diagnostic outcome. Fourth, the primary outcome (conversion to AD) contained some error because some patients classified as MCI nonconverters may convert to AD with longer follow-up.

In conclusion, this study confirms that amnestic MCI patients with additional deficits in other cognitive domains are the ones most likely to convert to AD within 3 years of follow-up. Although SRT total immediate recall across 6 trials and WAIS-R digit symbol coding were optimal predictors on the basis of stepwise regression analyses, SRT delayed recall and SRT percent savings from immediate to delayed recall were also robust predictors (Table 2). These findings corroborate those of other groups[7] reporting that episodic memory and executive function deficits are among the most robust and earliest predictors of AD. Future studies need to replicate these findings and further validate the relationship between memory and specific executive function abilities in MCI, and to evaluate these measures in conjunction with other putative clinical and neurobiological markers in an ef-

fort to derive an optimal predictive algorithm for early detection of AD.

**Submitted for Publication:** September 13, 2005; final revision received December 6, 2005; accepted December 7, 2005.
**Author Affiliations:** Department of Biological Psychiatry, New York State Psychiatric Institute (Drs Tabert, Pelton, and Devanand and Mss Rosenblum, Jacobs, Zamora, and Goodkind), Departments of Psychiatry (Drs Tabert, Pelton, Stern, and Devanand) and Neurology (Drs Manly, Pelton, Bell, Stern, and Devanand), and the Gertrude H. Sergievsky Center (Drs Tabert, Manly, Pelton, Bell, Stern, and Devanand), Columbia University College of Physicians and Surgeons, and Taub Institute for Research on Alzheimer's Disease and the Aging Brain (Drs Tabert, Manly, Pelton, Bell, Stern, and Devanand) and Department of Biostatistics, Mailman School of Public Health (Dr Liu), Columbia University, New York, NY.
**Correspondence:** Matthias H. Tabert, PhD, Department of Psychiatry, Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute, 1051 Riverside Dr, Unit 126, New York, NY 10032 (mht35@columbia.edu).
**Funding/Support:** This study was supported in part by grants AG17761, AG12101, 1K01AG21548, P50 AG08702, and P30 AG08051 from the National Institute on Aging and grants MH55735, MH35636, and MH55646 from the National Institute of Mental Health.

## REFERENCES

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004; 256:183-194.
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999; 56:303-308.
3. Bruscoli M, Lovestone S. Is MCI really just early dementia? a systematic review of conversion studies. *Int Psychogeriatr*. 2004;16:129-140.
4. Luis CA, Loewenstein DA, Acevedo A, Barker WW, Duara R. Mild cognitive impairment: directions for future research. *Neurology*. 2003;61:438-444.
5. Backman L, Jones S, Berger AK, Laukka EJ, Small BJ. Multiple cognitive deficits during the transition to Alzheimer's disease. *J Intern Med*. 2004;256:195-204.
6. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58:1985-1992.
7. Albert MS, Moss MB, Tanzi R, Jones K. Preclinical prediction of AD using neuropsychological tests. *J Int Neuropsychol Soc*. 2001;7:631-639.
8. Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. *Arch Gen Psychiatry*. 2001;58:853-858.
9. Grober E, Lipton RB, Hall C, Crystal H. Memory impairment on free and cued selective reminding predicts dementia. *Neurology*. 2000;54:827-832.
10. Howieson DB, Dame A, Camicioli R, Sexton G, Payami H, Kaye JA. Cognitive markers preceding Alzheimer's dementia in the healthy oldest old. *J Am Geriatr Soc*. 1997;45:584-589.
11. Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology*. 1994;44:1427-1432.
12. Hanninen T, Hallikainen M, Koivisto K, Helkala EL, Reinikainen KJ, Soininen H, Mykkanen L, Laakso M, Pyorala K, Riekkinen PJ Sr. A follow-up study of age-associated memory impairment: neuropsychological predictors of dementia. *J Am Geriatr Soc*. 1995;43:1007-1015.
13. Schmand B, Jonker C, Hooijer C, Lindeboom J. Subjective memory complaints may announce dementia. *Neurology*. 1996;46:121-125.
14. Korten AE, Henderson AS, Christensen H, Jorm AF, Rodgers B, Jacomb P, Mackinnon AJ. A prospective study of cognitive function in the elderly. *Psychol Med*. 1997;27:919-930.
15. Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y. Neuropsychological detection and characterization of preclinical Alzheimer's disease. *Neurology*. 1995;45:957-962.
16. Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology*. 2000;55:1847-1853.
17. Small BJ, Herlitz A, Fratiglioni L, Almkvist O, Backman L. Cognitive predictors of incident Alzheimer's disease: a prospective longitudinal study. *Neuropsychology*. 1997;11:413-420.
18. Tian J, Bucks RS, Haworth J, Wilcock G. Neuropsychological prediction of conversion to dementia from questionable dementia: statistically significant but not yet clinically useful. *J Neurol Neurosurg Psychiatry*. 2003;74:433-438.
19. Bondi MW, Monsch AU, Galasko D, Butters N, Salmon DP, Delis DC. Preclinical cognitive markers of dementia of the Alzheimer type. *Neuropsychology*. 1994; 8:374-384.
20. Dubois B, Albert ML. Amnestic MCI or prodromal Alzheimer's disease? *Lancet Neurol*. 2004;3:246-248.
21. Backman L, Small BJ, Fratiglioni L. Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain*. 2001;124:96-102.
22. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of alzheimer disease: a 22-year prospective study of the Framingham cohort. *Arch Neurol*. 2000;57:808-813.
23. Tierney MC, Szalai JP, Snow WG, Fisher RH, Nores A, Nadon G, Dunn E, St George-Hyslop PH. Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. *Neurology*. 1996;46:661-665.
24. Devanand DP, Folz M, Gorlyn M, Moeller JR, Stern Y. Questionable dementia: clinical course and predictors of outcome. *J Am Geriatr Soc*. 1997;45:321-328.
25. Smith GE, Bohac DL, Waring SC, Kokmen E, Tangalos EG, Ivnik RJ, Petersen RC. Apolipoprotein E genotype influences cognitive "phenotype" in patients with Alzheimer's disease but not in healthy control subjects. *Neurology*. 1998;50: 355-362.
26. DeCarli C, Mungas D, Harvey D, Reed B, Weiner M, Chui H, Jagust W. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. *Neurology*. 2004;63:220-227.
27. Luis CA, Barker WW, Loewenstein DA, Crum TA, Rogaeva , Kawarai T, St George-Hyslop P, Duara R. Conversion to dementia among two groups with cognitive impairment: a preliminary report. *Dement Geriatr Cogn Disord*. 2004; 18:307-313 E.
28. Tuokko H, Vernon-Wilkinson R, Weir J, Beattie BL. Cued recall and early identification of dementia. *J Clin Exp Neuropsychol*. 1991;13:871-879.
29. Visser PJ, Verhey FR, Ponds RW, Jolles J. Diagnosis of preclinical Alzheimer's disease in a clinical setting. *Int Psychogeriatr*. 2001;13:411-423.
30. Fabrigoule C, Rouch I, Taberly A, Letenneur L, Commenges D, Mazaux JM, Orgogozo JM, Dartigues JF. Cognitive process in preclinical phase of dementia. *Brain*. 1998;121:135-141.
31. Rapp MA, Reischies FM. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). *Am J Geriatr Psychiatry*. 2005;13:134-141.
32. Arnaiz E, Almkvist O. Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. *Acta Neurol Scand Suppl*. 2003;179:34-41.
33. Devanand DP, Michaels-Marston KS, Liu X, Pelton GH, Padilla M, Marder K, Bell K, Stern Y, Mayeux R. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am J Psychiatry*. 2000;157: 1399-1405.
34. Devanand DP, Pelton GH, Zamora D, Liu X, Tabert MH, Goodkind M, Scarmeas N, Braun I, Stern Y, Mayeux R. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Arch Neurol*. 2005;62:975-980.
35. Tabert MH, Albert SM, Borukhova-Milov L, Camacho Y, Pelton G, Liu X, Stern Y, Devanand DP. Functional deficits in patients with mild cognitive impairment: prediction of AD. *Neurology*. 2002;58:758-764.
36. Tabert MH, Liu X, Doty RL, Serby M, Zamora D, Pelton GH, Marder K, Albers MW, Stern Y, Devanand DP. A 10-item smell identification scale related to risk for Alzheimer's disease. *Ann Neurol*. 2005;58:155-160.
37. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*. 1974;24:1019-1025.
38. Wechsler D. *The Wechsler Memory Scale*. San Antonio, Tex: Psychological Corp; 1990.
39. Wechsler D. *Wechsler Adult Intelligence Scale–Revised*. New York: Psychological Corp; 1981.
40. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. Philadelphia, Pa: Lea & Febiger; 1983.

41. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders*. Philadelphia, Pa: Lea & Febiger; 1983.
42. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 1968;114:797-811.
43. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
44. Benton A. *The Visual Retention Test*. New York, NY: Psychological Corporation; 1955.
45. Rosen W. *The Rosen Drawing Test*. Bronx, NY: Veterans Administration Medical Center; 1981.
46. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Karasu TB, eds. *Geriatric Psychiatry*. New York, NY: Grune & Stratton; 1976:77-121.
47. Benton A, Hamsher A. *Multilingual Aphasia Examination*. Iowa City: University of Iowa; 1976.
48. Heaton RK, Grant I, Matthews CG. *Comprehensive Norms for an Expanded Halstead-Reitan Battery*. Odessa, Fla: Psychological Assessment Resources Inc; 1991.
49. Manly JJ, Bell-McGinty S, Tang M-X, Schupf N, Stern Y, Mayeux R. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. *Arch Neurol*. 2005;62:1739-1746.
50. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann Stat*. 2001;29:1165-1188.
51. Wechsler D. *Wechsler Adult Intelligence Scale—Third Edition: Administration and Scoring Manual*. 3rd ed. San Antonio, Tex: Psychological Corporation; 1997.
52. Bozoki A, Giordani B, Heidebrink JL, Berent S, Foster NL. Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Arch Neurol*. 2001;58:411-416.
53. Palmer K, Backman L, Winblad B, Fratiglioni L. Detection of Alzheimer's disease and dementia in the preclinical phase: population based cohort study. *BMJ*. 2003; 326:245.
54. Arnaiz E, Almkvist O, Ivnik RJ, Tangalos EG, Wahlund LO, Winblad B, Petersen RC. Mild cognitive impairment: a cross-national comparison. *J Neurol Neurosurg Psychiatry*. 2004;75:1275-1280.
55. Small SA, Stern Y, Tang M, Mayeux R. Selective decline in memory function among healthy elderly. *Neurology*. 1999;52:1392-1396.
56. Vliet EC, Manly J, Tang MX, Marder K, Bell K, Stern Y. The neuropsychological profiles of mild Alzheimer's disease and questionable dementia as compared to age-related cognitive decline. *J Int Neuropsychol Soc*. 2003;9:720-732.
57. Storandt M, Hill RD. Very mild senile dementia of the Alzheimer type, II: psychometric test performance. *Arch Neurol*. 1989;46:383-386.
58. Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, Foster NL, Jack CR Jr, Galasko DR, Doody R, Kaye J, Sano M, Mohs R, Gauthier S, Kim HT, Jin S, Schultz AN, Schafer K, Mulnard R, van Dyck CH, Mintzer J, Zamrini EY, Cahn-Weiner D, Thal LJ; Alzheimer's Disease Cooperative Study. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol*. 2004;61:59-66.