Derivation of a New ADAS-cog Composite Using Tree-based Multivariate Analysis

Prediction of Conversion From Mild Cognitive Impairment to Alzheimer Disease

Daniel A. Llano, MD, PhD, Genevieve Laforet, MD, PhD, and Viswanath Devanarayan, PhD; The Alzheimer's Disease Neuroimaging Initiative

Abstract: Model-based statistical approaches were used to compare the ability of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), cerebrospinal fluid (CSF), fluorodeoxyglucose positron emission tomography and volumetric magnetic resonance imaging (MRI) markers to predict 12-month progression from mild cognitive impairment (MCI) to Alzheimer disease (AD). Using the Alzheimer's Disease Neuroimaging Initiative (ADNI) data set, properties of the 11-item ADAS-cog (ADAS.11), the 13-item ADAS-cog (ADAS.All) and novel composite scores were compared, using weighting schemes derived from the Random Forests (RF) tree-based multivariate model. Weighting subscores using the RF model of ADAS.All enhanced discrimination between elderly controls, MCI and AD patients. The ability of the RF-weighted ADAS-cog composite and individual scores, along with neuroimaging or biochemical biomarkers to predict MCI to AD conversion over 12 months was also assessed. Although originally optimized to discriminate across diagnostic categories, the ADAS. All, weighted according to the RF model, did nearly as well or better than individual or composite baseline neuroimaging or CSF biomarkers in prediction of 12-month conversion from MCI to AD. These suggest that a modified subscore weighting scheme applied to the 13-item ADAS-cog is comparable to imaging or CSF markers in prediction of conversion from MCI to AD at 12 months.

Key Words: random forest, biomarker, fluorodeoxyglucose positron-emission tomography, volumetric MRI, cerebrospinal fluid

(*Alzheimer Dis Assoc Disord* 2011;25:73–84)

There is burgeoning interest in the development of therapeutics for prodromal Alzheimer disease (AD). This is driven by the hypothesis that disease-modifying therapy is most likely to be efficacious in the earliest stages of the pathologic cascade of events leading to neuronal dysfunction and death. Unfortunately, clinical trials of early-stage patients who have not yet met National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)-defined criteria for AD[1] pose special challenges. One difficulty revolves around the most appropriate metric to assess the efficacy of therapeutic interventions in mildly affected patients. Most pharmacotherapy trials of individuals with prodromal AD have used conversion from a cognitively impaired but nondemented state (so-called mild cognitive impairment, or MCI)[2] to AD as an outcome measure because AD has an accepted clinical definition for registration and labeling purposes, and standard cognitive measures, particularly the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog),[3] are not sensitive to change at milder degrees of impairment.[4,5] However, the low rates of conversion of MCI to AD (10% to 15%/y)[6] necessitate either enrolling very large numbers of participants, or following participants for several years to achieve sufficient power to detect a change in the rate of conversion.[7,8]

Several approaches have been used to deal with these issues. One has been to redefine AD to shift the diagnostic threshold to earlier stages of disease by removing the requirement for functional decline and including a requirement for positive biomarker findings.[9] This approach takes advantage of the impressive body of literature showing the utility of biological biomarkers as markers of the underlying disease process in AD, and potentially removes the regulatory hurdle described above, but the problems of

Received for publication April 22, 2010; accepted July 26, 2010.
From Abbott Laboratories, Abbott Park, IL.
Sources of support: Abbott funded the analyses reported in this manuscript.
The Alzheimer's Disease Neuroimaging Initiative: Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu). As such, the investigators within ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available at: http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Manuscript_Citations.pdf.
Disclosures: All individual authors are employees of Abbott, and as such own equity in, receive salary, and other compensation from Abbott and hold Abbott stock and stock options.
The Foundation for the National Institutes of Health (www.fnih.org) coordinates the private sector participation of the $60 million ADNI public-private partnership that was begun by the National Institute on Aging (NIA) and supported by the National Institutes of Health. To date, more than $27 million has been provided to the Foundation for NIH by Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson & Johnson, Eli Lilly and Co., Merck and Co., Inc., Novartis AG, Pfizer Inc., F. Hoffmann-La Roche, Schering-Plough, Synarc Inc., and Wyeth, as well as nonprofit partners the Alzheimer Association and the Institute for the Study of Aging.
Reprints: Daniel A. Llano, MD, PhD, Department of Molecular and Integrative Physiology, 524 Burrill Hall, MC-114407 South Goodwin AvenueUrbana, IL 61801 (e-mail: daniel.llano@abbott.com).
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website, www.alzheimerjournal.com.

poor scale sensitivity remain. In addition, by incorporating biomarker data, such as positive amyloid imaging or depressed levels of cerebrospinal fluid (CSF) amyloid beta (Aβ), this strategy makes a fundamental assumption about the relationship between drug efficacy and the biology of AD that may not be warranted. For example, participants with low CSF Aβ levels may be less sensitive to antiamyloid therapy as it may be more difficult to remove deposited amyloid than to prevent its deposition. Another approach has been to use MCI to AD conversion as an outcome measure, but to "enrich" MCI patient pools by using either cognitive or biomarker data to enroll participants that have a higher likelihood of converting from MCI to AD in a short period of time. The major advantage of this approach compared with the first is that it retains the current regulatory taxonomy and the primacy of functional decline as the outcome measure.

The success of any biomarker-based enrichment scheme depends on the appropriateness and practical applicability of candidate markers. The ideal marker should not only predict short-term conversion from MCI to AD with a high degree of accuracy, but should be suitable for screening a large population to recruit an adequate number of participants. Certain markers, such as ^{11}C-PIB binding, are not widely available, and many imaging modalities are prohibitively expensive to apply across hundreds of potential participants. In addition, some markers, such as loss of hippocampal volume or deposition of amyloid, should be viewed with caution, as they may reflect a state of disease that is too advanced to allow many therapeutic approaches to show efficacy.

In this report, we use data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, which is ideally suited to compare multiple potential markers of disease progression in a population of MCI patients, to develop a tractable strategy to predict over a short period of time (12 mo) the conversion from MCI to AD. Specifically, we use modern forms of multivariate analysis of cognitive data to compare the ability of cognitive measures versus neuroimaging and biochemical biomarkers to predict the conversion from MCI to AD.

METHODS

Alzheimer's Disease Neuroimaging Initiative (ADNI)

ADNI is a naturalistic, longitudinal study of AD onset and progression being conducted at 57 sites in the United States and Canada. ADNI is supported and administered as a public-private partnership involving the Foundation for the National Institutes of Health, members of the pharmaceutical and biotechnology industries, and Alzheimer's advocacy groups. ADNI's aim is to develop validated surrogate markers for early detection and monitoring of disease progression, in order to inform the design and conduct of clinical trials for the development of new AD therapeutics.

The ADNI study was designed to follow over time approximately 200 normal elderly individuals (36 mo), 400 patients with amnestic MCI (36 mo), and 200 with AD (24 mo). ADNI participants undergo evaluation at 6-month to 12-month intervals through a battery of assessments including cognitive and neuropsychological testing, neuroimaging (MRI with or without PET), and plasma and CSF biomarkers. The resultant data are housed in an online database (http://www.loni.ucla.edu/ADNI/) that is freely available to researchers who request access. Data used for the analyses presented here were accessed April 29, 2009 and comprise data from 229 normal, 397 MCI, and 193 AD subjects. Although the ADNI database continues to be updated on an ongoing basis, most newly added data are from later time points (ie, beyond 1 year), in contrast to the early data used in this study.

ADNI Participants

Participants were recruited into ADNI on an ongoing basis over a period of approximately 2 years. Eligible participants were 55 to 90 years of age, fluent in English or Spanish, and had at least 6 years of education. Participants were enrolled into 1 of 3 groups: cognitively normal, amnestic MCI, or AD. Aside from these latter disorders, participants could have no other significant neurologic disease. Normal individuals were free of memory complaints or depression and had a Mini-Mental State Examination (MMSE)[10] score of 24 to 30 and a Clinical Dementia Rating (CDR) score of 0. MCI individuals met Petersen criteria for single-domain or multidomain amnestic MCI[2] with MMSE scores of 24 to 30, CDR of 0.5, and an informant-verified memory complaint substantiated by abnormal education-adjusted scores on the Wechsler Memory Scale Revised—Logical Memory II. Other cognitive domains and everyday functioning were intact. Alzheimer patients fulfilled NINCDS-ADRDA diagnostic criteria for probable AD,[1] with MMSE scores of 20 to 26 and CDR of 0.5 or 1.0.

ADNI Assessments

Participant cognitive status was evaluated at baseline and at 6 to 12 month intervals using the MMSE and the ADAS-cog.[3] The standard 11-item version of the ADAS-cog was augmented with 2 additional items (delayed word recall and number cancellation), and results from both the 11-item and 13-item versions were included in the ADNI dataset.

Participants were assessed by neuroimaging at baseline, 6, 12, and 24 months. MCI individuals had additional evaluations at 18 and 36 months; normal individuals were also evaluated at 36 months. All participants received 1.5 Tesla (T) structural magnetic resonance imaging (MRI). In addition, approximately 25% also received 3.0 T MRI. Fluorodeoxyglucose-positron emission tomography (FDG-PET) was conducted on approximately half of the participants. Cognitive assessments and neuroimaging procedures were carried out within 2 weeks of each other.

All analyses in the present publication were done using processed imaging data from the ADNI database. More detailed information regarding ADNI neuroimaging instrumentation, procedures, regions of interest, and data processing is publicly available on the UCLA Laboratory of Neuroimaging (LONI) website (www.loni.ucla.edu).

In approximately 35% of MCI individuals, CSF samples were obtained at baseline and 12 months. CSF was frozen for subsequent batch analysis at the ADNI Biomarker Core laboratory at the University of Pennsylvania. Levels of amyloid beta ($A\beta_{1-42}$), total tau, and phosphorylated tau (P-tau_{181}) were determined using Innogenetics' INNO-BIA AlzBio3 immunoassay on a Luminex xMAP platform (see Shaw et al 2009 for methodologic details and results from baseline biochemical biomarker analyses).[11]

Derivation of a Weighted ADAS-cog Composite

Baseline cognitive data from the ADNI database on AD, MCI and elderly control participants were used to derive a new weighted ADAS-cog. Weights for the ADAS-cog components were derived using the Random Forests (RF) tree-based algorithm[12,13] that compared the 3 diagnostic categories (AD, MCI, and Normal). In this algorithm, 10,000 bootstrap datasets of the same size as the original data are drawn randomly by sampling with replacement. In this sampling process, some samples get repeated multiple times, and approximately one-third of the original data get left out; these left-out data corresponding to each bootstrap dataset are referred as the Out-Of-Bag (OOB) datasets. Classification Trees are grown to the maximum possible depth for each of the 10,000 bootstrap datasets. At each tree node, only a small random subset of the ADAS-cog components is used to split that node. Predictions of the diagnostic categories for each sample in the omitted OOB datasets are then made using majority vote from the 10,000 Trees. The predictive accuracy of this RF model on all the ADAS-cog components is then obtained by comparing the predictions with the true diagnosis of the OOB samples.

The weight for each ADAS-cog component was derived as follows. First, each component was replaced by noise, one at a time. The RF model was then fit on this noise component and the remaining ADAS-cog components using the algorithm described above. The predictive accuracy of the OOB samples was then derived and compared with the predictive accuracy determined from the RF model on all ADAS-cog components. The resulting drop in predictive accuracy became the importance score and this became the "weight" for the component that was replaced by noise. This was repeated for each ADAS-cog component, resulting in weights for all the components. These weights were then used to calculate a weighted average of all the 13 components. The resultant new ADAS-cog composite is referred to as ADAS.Tree.

The significance of the ADAS-cog components and composites between the three diagnostic categories (AD, MCI, and Normal) was assessed using a Kruskal-Wallis nonparametric test.

Evaluation of Cognitive and Imaging Markers for Prognostication of Disease Progression

We determined the prognostic performance of *baseline* cognitive markers (ADAS-cog components, ADAS-cog composites, MMSE), CSF amyloid/tau markers ($A\beta_{1-42}$, total tau, and phospho-tau) and imaging markers (FDG-PET and volumetric MRI) in MCI individuals to correctly identify those that progressed to AD and those that did not over a 1-year period. PIB amyloid imaging was not included in this analysis because baseline data were not available. The primary objectives of these analyses were as follows:

1. Evaluate the relative usefulness of ADAS.Tree, ADAS.All, ADAS.11, MMSE, and the individual ADAS-cog components to predict conversion from MCI to AD over 1 year.
2. Identify an optimal subset of markers (called "signature") from the ADAS-cog domain, CSF amyloid/tau domain, FDG-PET domain and the MRI domain for predicting MCI-AD progression (separately for each domain, and then in combination). This will help determine how much value is added by the baseline CSF and imaging markers over and above the performance of baseline signatures from the cognitive markers, and in particular, the relative usefulness of ADAS.Tree and ADAS.All.

FDG-PET, volumetric MRI and CSF data were not available on all MCI patients at baseline. To enable "apples-to-apples" comparison, separate datasets were created for these analyses; one in which the ADAS-cog and CSF data were available in all patients (called Cog-CSF dataset), another in which the ADAS-cog and FDG-PET data were available in all patients (called Cog-PET dataset), and a third in which the ADAS-cog and MRI data were available on all patients (called Cog-MRI dataset).

To address objective no.1, the significance of each of the baseline cognition composites and components was determined separately using the nonparametric Wilcoxon test. This was compared with the significance of the individual CSF and imaging markers.

To address objective no. 2, multivariate analyses were done to determine the optimal subset of markers (called "signature") that best detects the progression of MCI to AD. For the Cog-PET dataset, this analysis was done separately for the cognition markers alone, FDG-PET markers alone, and the cognition and FDG-PET markers together. This was similarly repeated for the Cog-MRI dataset and Cog-CSF datasets. From all these analyses, the performance of the optimal subset of markers to predict MCI-AD progression was determined and compared. This helped determine whether the CSF and imaging markers added value over and above the cognition components and composites, and also the relative usefulness of ADAS.Tree and ADAS.All in this context.

For each dataset (eg, Cog-PET dataset), and for each subgroup of markers (cognition alone, FDG-PET alone, and cognition together with FDG-PET), optimal signatures were derived by first filtering out the most significant markers using a robust version of the Student *t*-test. The optimal signatures were derived using one of the following methods: (1) Relative importance scores from Random Forests algorithm described above, and (2) Simulated Annealing. These derived signatures were then used in one of the following classification algorithms: (1) Linear Discriminant Analysis, (2) Diagonal Linear Discriminant Analysis, (3) Diagonal Quadratic Discriminant Analysis, (4) Random Forests, (5) Support Vector Machines, (6) Neural Network, and (7) k-Nearest Neighbor method.

The predictive performance from these classification algorithms on the optimal signatures was evaluated using 10 iterations of a 5-fold stratified cross-validation. This was carried out by first dividing the original dataset randomly into 2 equal parts, stratified to ensure that each of these parts had the same balance between disease progressors and nonprogressors as was found in the original dataset. Then each part was left out one at a time (test-set), and the remaining four parts were used as a training set to derive the optimal signature and fit the classification model described above. The models on the training sets were then used to predict the test-sets, and the predictions from all the five test-sets were pooled together to estimate the performance measures, sensitivity (ability to correctly identify MCI-AD progression) and specificity (ability to correctly identify nonprogressors). This entire procedure was iterated

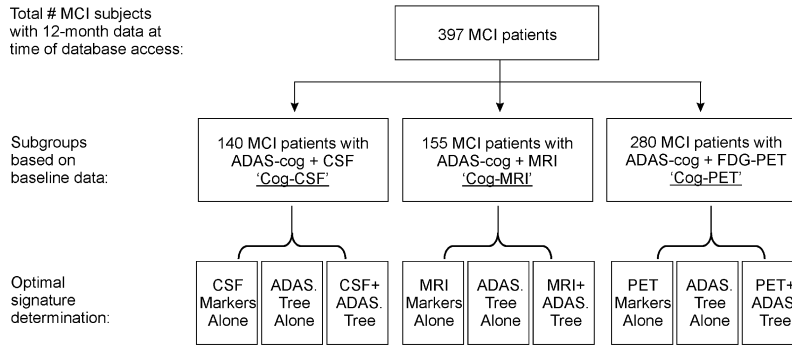

FIGURE 1. Diagram of data flow for characterization of performance of cognitive, CSF and imaging markers for prediction of MCI to AD conversion. The total pool of MCI participants was divided into partially overlapping subgroups that contain participants for which baseline ADAS-cog and candidate marker data were available. The next stage of processing involved the selection of the optimum composite for each marker individually, or coupled with ADAS.Tree, using several multivariate approaches (see Methods for details).

10 times to yield robust estimates of sensitivity and specificity. Such a rigorous derivation of optimal signatures is recommended also for high throughput datasets such as genomics,[14] and it provides a more accurate reflection of the true performance in a future cohort of MCI patients. For example, when the cross-validation is done only in the final model fitting step after the signatures are derived from the entire dataset, estimates of sensitivity and specificity will be significantly biased upward.[15] Therefore, performance measures reported by different publications should be compared with caution.

The optimal signature from the list of several signatures that were derived as described above was selected on the basis of Matthews Correlation Coefficient (MCC),[16] sensitivity and specificity. Unlike the usual means of describing overall classification accuracy, such as area under the curve (AUC) measurements from receiver-operator curves (ROC), MCC takes into consideration the different number of participants in each class. This is appropriate for this study, as only approximately 20% of participants progressed from MCI to AD over the 12 month period. MCC values are expressed as percentages. A diagram of the dataflow for these analyses is shown in Figure 1.

Analyses were done with R (http://www.R-project.org), version 2.7, and the contributed libraries for different machine learning methods used in our analyses. AUC values were compared using a χ^2 statistic[17] implemented with a web-based tool.[18]

TABLE 1. Demographic Data

	Normal N = 229	MCI N = 397	AD N = 193
Sex			
Female, n (%)	110 (48%)	141 (36%)	91 (47%)
Male, n (%)	119 (52%)	256 (64%)	102 (53%)
ApoE genotype			
ApoE4, n (%)	61 (27%)	212 (53%)	127 (66%)
Non-ApoE4, n (%)	168 (73%)	185 (47%)	66 (34%)
Age (y), mean (SD)	75.9 (5.0)	74.8 (7.5)	75.2 (7.5)
Education (y), mean (SD)	16.0 (2.9)	15.7 (3.1)	14.7 (3.1)

RESULTS

Demographics

Data from a total of 819 participants were analyzed in this study. Baseline demographic data are shown in Table 1. Participants were well matched for age ($P = 0.4866$, Kruskal-Wallis test). As expected, AD patients had the lowest number of years of education ($P < 0.0001$, Kruskal-Wallis test) and greatest proportion of participants that were APOE4 positive ($P < 0.0001$, likelihood-ratio test). In all 3 diagnostic groups, there were more men than women (52.0%, 64.5%, 52.8%, for Normal, MCI and AD, respectively), and the proportion of men was greatest in the MCI group ($P = 0.002$, likelihood-ratio test).

Analysis of Baseline ADAS-cog Data

We analyzed baseline ADAS-cog data (the routine subscales, ie, ADAS.11, plus delayed word recall and number cancellation, ie, ADAS.All) from 197 AD patients, 397 MCI patients and 229 elderly control individuals in the ADNI database. In the ADNI dataset, the subscales are given the labels Q1 to Q12, and Q14, and we have kept this nomenclature. Figure 2 shows the distributions of the scores of each of the subscales. All the components are highly significant ($P < 0.0001$, Kruskal-Wallis test) in their ability to distinguish diagnostic categories. However, these box plots show an uneven capacity of the components to separate the different diagnostic categories. For example, Word Recall and Delayed Word Recall show clearly separable modal values among the 3 diagnostic categories (test statistics = 359.37 and 431.57, respectively). In contrast, other tests, such as Commands and Ideational Praxis, have scores that cluster near the lowest values, suggestive of prominent ceiling effects in these populations (test statistics = 48.7 and 41.85, respectively). This implies that weighting these components equally by simply summing them up to define the composite, as presently done for the traditional ADAS-cog, might not provide an optimal diagnostic for AD.

As described in the statistical methods section, the relative importance (rank) of each of the 13 components and composites for differentiating AD, MCI, and Normal at baseline was assessed within the framework of the Random Forests multivariate tree-based algorithm. These are plotted in Figure 3, expressed as mean decrease in

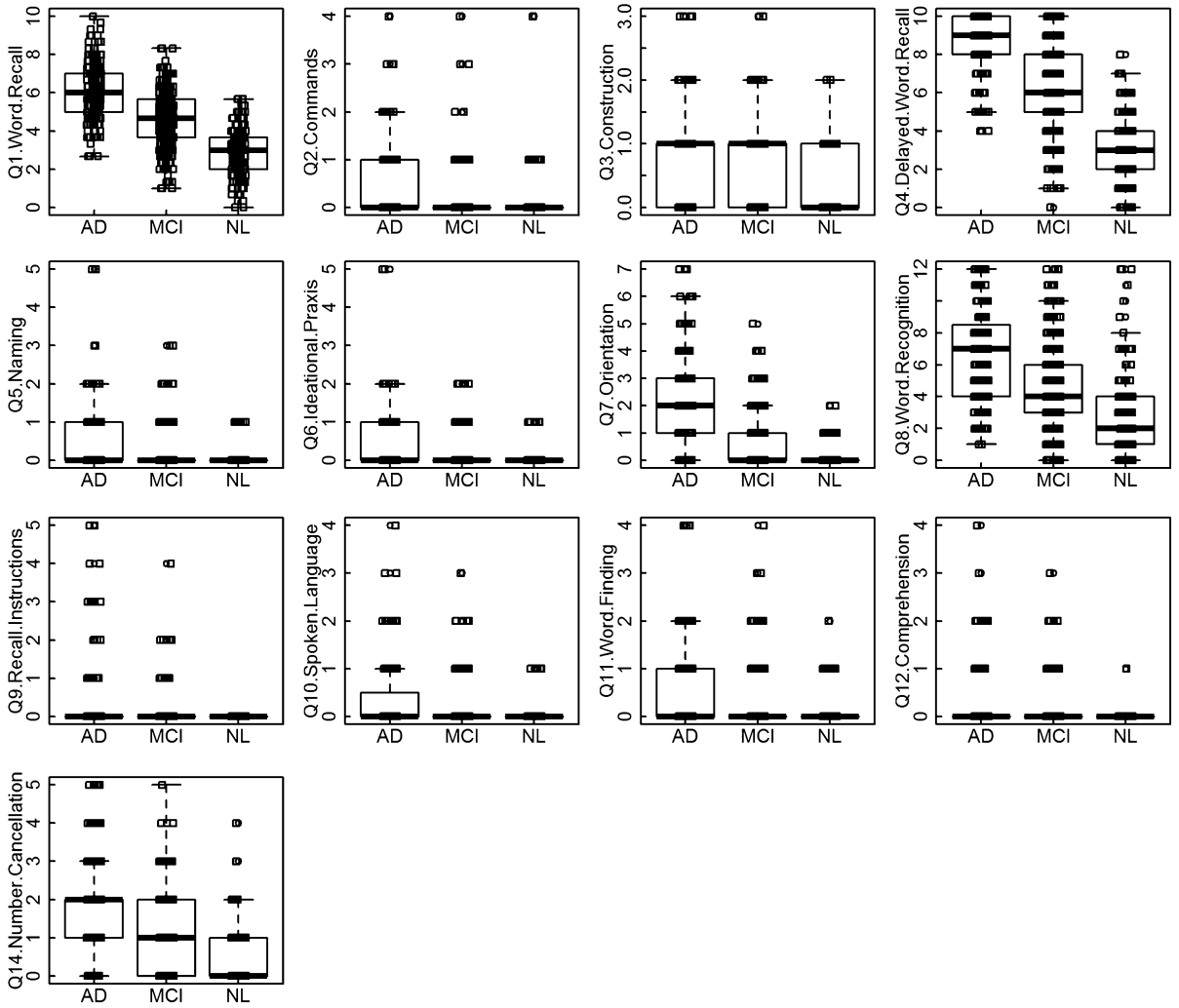

FIGURE 2. Series of box plots showing the distributions of scores on the 13 items of the full ADAS-cog across the 3 diagnostic categories: AD, MCI and Normal (NL).

predictive accuracy when each parameter was removed from the model and replaced by noise, and sorted by importance scores. These relative importance scores defined the weights for these components, and a weighted sum of these components was used to define a new composite: ADAS.Tree. Note that Delayed Word Recall and Number Cancellation are excluded from the usual clinical endpoint (ADAS.11), but these are among the most powerful components for differentiating AD, MCI, and Normal. Construction and Ideational Praxis do not add significant predictive value to the composite, so these received negligible weight. The weights given for the 12 components (Fig. 3), in order from Q1 to Q12 and Q14, are 1.05, 0.38, 0, 1.17, 0.61, 0.13, 1.13, 0.41, 0.54, 0.49, 0.69, 0.39, and 0.68, respectively.

The performance of the MMSE, ADAS.11, ADAS.All, and ADAS.Tree composite scores was evaluated for the separation of the diagnostic categories of Normal, MCI and AD (n = 229, 397 and 193 for Normal, MCI and AD respectively). All of these measures achieved highly significant ($P < 0.0001$) separation of diagnostic categories, with the ADAS.Tree generating the numerically highest test statistic of the 4 scales (Fig. 4). We also assessed the performance of these composite scores on a dataset separate from the training dataset. In this case, we used the 24 month data for all participants for whom such data were available (n = 197, 284 and 135 for Normal, MCI and AD respectively). We again found that all of these measures were highly statistically significant ($P < 0.0001$) and found that the test statistic was highest for ADAS.Tree (test statistics = 401.1, 393.3, 378.9, and 368.8 for ADAS.Tree, ADAS.All, ADAS.11 and MMSE, respectively).

Prediction of MCI to AD Conversion

We examined the relationship between the individual ADAS-cog subscales and the composite ADAS measures and the likelihood of conversion from MCI to AD over 12 months. The overall rate of conversion in one year was 18% (66/349). The number of MCI-AD progressors and non-progressors in the Cog-CSF, Cog-PET and Cog-MRI datasets was (34, 140), (13, 74), and (64, 279) respectively.

Table 2 shows the *P*-values from the nonparametric (Wilcoxon) tests for each of the subscales or composite measures for differentiating MCI to AD converters versus

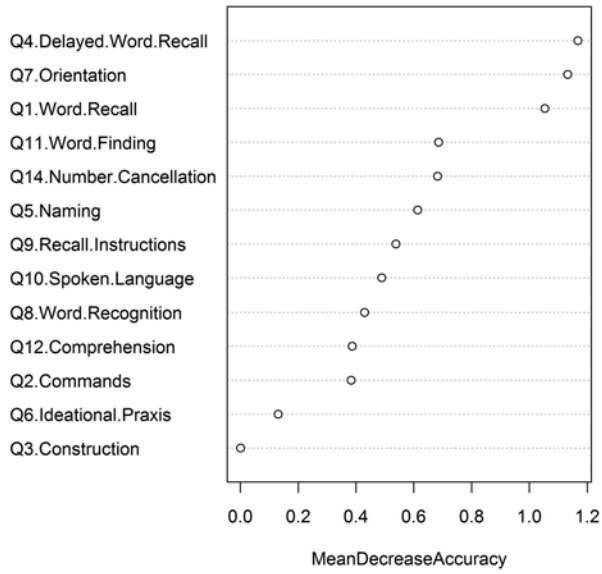

FIGURE 3. Plot of the relative importance of each of the individual components of the ADAS-cog, as determined using a tree-based multivariate modeling algorithm. The plot shows the decrease in predictive accuracy of each of the components as each component is replaced, one at a time, by noise.

nonconverters. The predictor with the lowest *P*-value was the ADAS.Tree ($P = 6.23 \times 10^{-10}$). Note again that Delayed Word Recall ($P = 7.06 \times 10^{-7}$) and Number Cancellation ($P = 3.1 \times 10^{-5}$) were among the best of the individual subscales in predicting decline. Other subscales, such as Comprehension ($P = 0.961$) and Ideational Praxis ($P = 0.756$), showed no differences between converters and nonconverters. Univariate comparisons were made among the composite measures (ADAS.Tree, ADAS.All, ADAS.11, and MMSE) for the prediction of MCI-AD conversion and the ROC curves for these comparisons are shown in Figure 5. The AUCs for prediction of MCI-AD conversion were 0.746, 0.730, 0.696 and 0.589 for the ADAS.Tree, ADAS.All, ADAS.11 and MMSE, respectively. Pairwise comparison of the ADAS.Tree to the other composites using a χ^2 statistic[16] showed marginal superiority over ADAS.All ($P = 0.124$), and that it was superior to ADAS.11 ($P = 0.027$) and MMSE ($P = 0.00024$).

We assessed the relationship between baseline ADAS.Tree and the probability of conversion from MCI to AD, which is shown in Figure 6. Logistic regression on the relationship between ADAS.Tree and the probability of progression yields the sigmoidal function shown in Figure 6, such that for each one unit increase on the baseline ADAS.Tree, the odds ratio for conversion from MCI to AD is 1.223 ($P = 2.49 \times 10^{-9}$). Given this, and the distribution of baseline ADAS.Tree values [mean (SD) = 15.98 (5.14), dotted line, Figure 6], one can compute the number of participants needed to screen to enroll a group of individuals with a desired rate of 12-month MCI-AD conversion.

We also compared the ability of individual ADAS-cog components and ADAS-cog composite measures versus individual imaging or CSF biomarker values to predict conversion from MCI to AD over 12 months. Table 3 lists the results of univariate analysis of the 3 CSF markers and the ratio of total tau and p-tau$_{181}$ to A$\beta_{1\text{-}42}$. The most robust predictor of MCI-AD conversion is the ratio of *P*-tau$_{181}$ to A$\beta_{1\text{-}42}$ ($P = 0.006$). Table 4 lists the top 10 FDG-PET biomarkers and Table 5 lists the top 10 volumetric MRI biomarkers [for a full list of *P*-values for all 85 FDG-PET and 142 volumetric MRI markers, (Supplemental Table 1 http://links.lww.com/WAD/A9) and (Supplemental Table 2 http://links.lww.com/WAD/A8), respectively]. Note that the *P*-value of even the most highly predictive imaging marker (TEMPINFL_uas, left inferior temporal cortex) is almost 3 orders of magnitude higher than the most predictive cognitive subscale (Word Recall) and 4 orders of magnitude higher than the most predictive cognitive composite score (ADAS.Tree). Among the CSF markers, A$\beta_{1\text{-}42}$ and p-tau$_{181}$ were significantly associated with conversion to AD, but these associations were several orders of magnitude less significant than the best cognitive and imaging markers.

We then compared the MCI to AD prediction accuracy of the ADAS.Tree to optimized composite markers from each of the three other biomarker domains: CSF, FDG-PET, and volumetric MRI. To do this, we applied machine-learning predictive modeling methods to determine the optimal subset of markers ("signature") that best detects the 12-month progression of MCI to AD (see statistical methods section for details).

Comparisons between the ADAS-cog and imaging or biochemical biomarkers for the prediction of MCI to AD conversion are shown in Table 6. For the Cog-CSF dataset, the optimal signature from the CSF markers alone had 62.65% sensitivity and 54.2% specificity (MCC = 13.4%). The optimal signature from the cognitive markers alone had 76.5% sensitivity and 63.9% specificity (MCC = 32.2%), and the optimal signature from the CSF and cognitive markers had 76.8% sensitivity and 63.9% specificity (MCC = 32.5%). Thus, the performance of cognitive markers alone was superior to the CSF markers alone, and the addition of CSF markers to the cognitive markers did not substantially improve the predictive performance.

For the Cog-PET dataset, the optimal signature from the PET markers alone had 55.4% sensitivity and 85.5% specificity (MCC = 36.4%). The optimal signature from the cognitive markers alone had 63.1% sensitivity and 82.2% specificity (MCC = 37.8%), and the optimal signature from the PET and cognitive markers had 56.9% sensitivity and 83.7% specificity (MCC = 34.7%). Thus, the performance of cognitive markers alone was quite comparable to the PET markers alone, and the addition of PET markers to the cognitive markers did not result in substantial improvement.

For the Cog-MRI dataset, the optimal signature from the MRI markers alone had 57.5% sensitivity and 62.3% specificity (MCC = 15.6%). The optimal signature from the cognitive markers alone had 67.3% sensitivity and 67.4% specificity (MCC = 27.7%), and the optimal signature from the MRI and cognitive markers had 66.6% sensitivity and 66.5% specificity (MCC = 26.3%). Thus, the performance of cognitive markers alone was superior to the MRI markers alone, and the addition of MRI markers to the cognitive markers did not improve predictive performance.

Lists of the most frequently occurring cognitive and CSF, MRI, and PET markers in the signatures from 10 repetitions of 5-fold cross-validation (out of $10 \times 5 = 50$ signatures) are summarized in Figures 7A to C, respectively. ADAS.Tree plays the most prominent role among

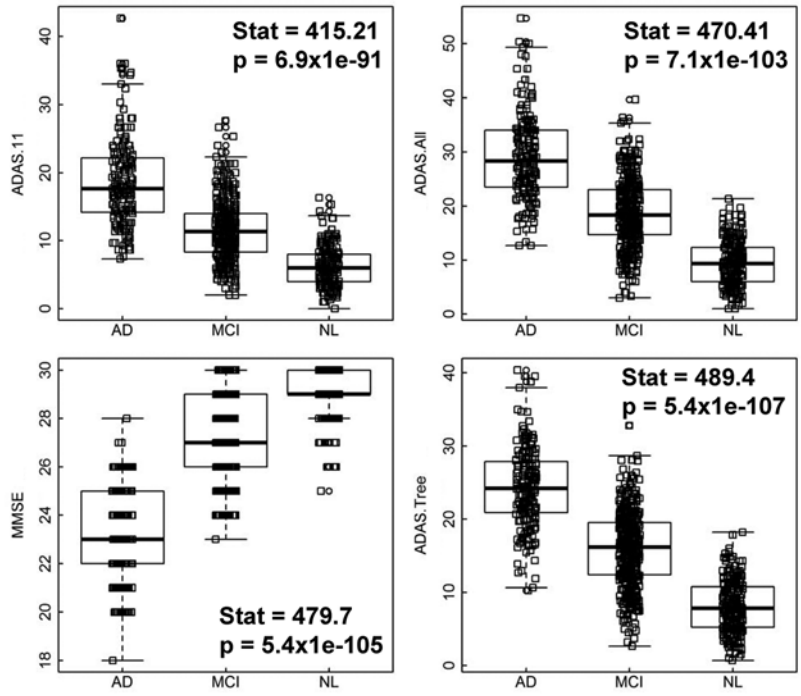

FIGURE 4. Box plots of the distributions of the traditionally weighted composite scores (ADAS.11, ADAS.All and MMSE), and the composite score weighted using a tree-based algorithm (ADAS.Tree). The Kruskal-Wallis χ^2 test statistic (Stat) and *P*-value (*P*) are shown for each comparison.

the cognition markers. ADAS.All, MMSE and some specific ADAS-cog components such as Q1 (Word Recall), Q4 (Delayed Word Recall), and Q7 (Orientation) feature fairly prominently as well. Most importantly, we continued to observe that the primary endpoint, ADAS.11, has considerably less predictive value relative to the other cognitive composites considered and also relative to some of the specific ADAS-cog components.

TABLE 2. Significance of Each Component of the ADAS-cog and Composite ADAS-cog Scores for Identifying MCI Patients That Progressed to AD Over a 12-month Period

Marker	*P*
Q1. Word recall	8.17E-09
Q2. Commands	0.725
Q3. Construction	0.785
Q4. Delayed word recall	7.06E-07
Q5. Naming	0.437
Q6. Ideational praxis	0.756
Q7. Orientation	0.0042
Q8. Word recognition	0.0005
Q9. Recall instructions	0.0119
Q10. Spoken language	0.121
Q11. Word finding	0.136
Q12. Comprehension	0.961
Q14. Number cancellation	3.10E-05
ADAS.All	7.46E-09
ADAS.11	4.61E-07
MMSE	0.0188
ADAS.Tree	6.23E-10

Gray shading denotes components or composites with $P < 0.05$.
ADAS.All indicates 13-item version Alzheimer's Disease Assessment Scale-cognitive subscale; MMSE, Mini-Mental State Examination.

DISCUSSION

Multivariate modeling using a Random Forests approach applied to the ADNI dataset showed that modified weighting of the subscales of the 13-item ADAS-cog (ADAS.Tree) is better able to separate the diagnostic

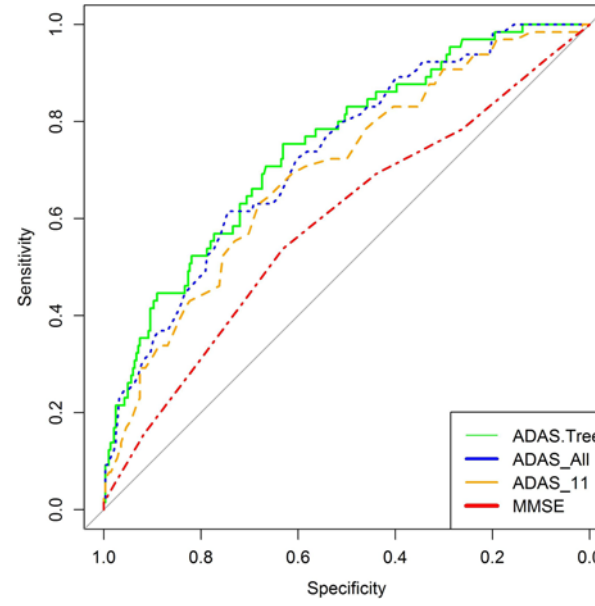

FIGURE 5. ROC curves for all composite cognitive measures assessed for the conversion of MCI patients to AD. AUC values for the composites were 0.746 for ADAS.Tree, 0.730 for ADAS.All, 0.697 for ADAS.11 and 0.589 for MMSE.

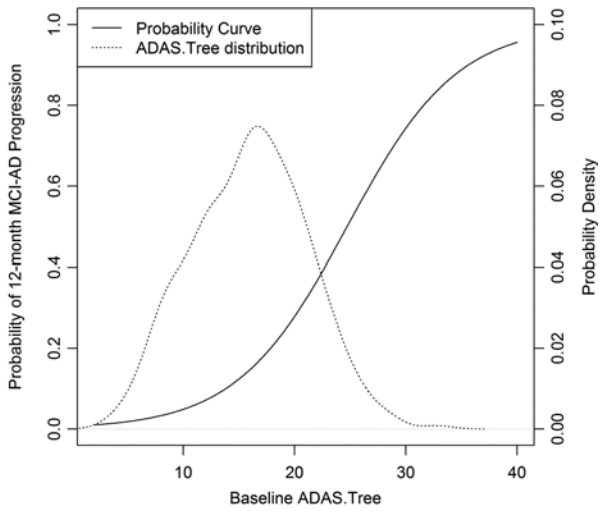

FIGURE 6. Solid sigmoid curve represents the probability of conversion from MCI to AD as a function of baseline ADAS.Tree score. Regression equation: Probability of conversion $=[1+\exp(4.979-0.202*\text{ADAS.Tree})]^{-1}$. Ordinate is on the left. The dashed curve represents the fitted probability density for the distribution of baseline ADAS.Tree values for MCI participants in the study. Summary statistics for this distribution: Min: 3.22, Q1 (25th percentile)=12.16, Q2 (median)=16.11, Q3 (75th percentile)=19.57, Max=32.79, Mean±SD=15.96±5.14 Ordinate is on the right.

categories of elderly control, MCI, and AD than the traditional version of the ADAS-cog. Furthermore, we showed that ADAS.Tree provides at least comparable predictive power for 12-month conversion from MCI to AD when compared with optimized biomarker profiles derived from volumetric MRI, FDG-PET, or CSF analysis. Much of the predictive power of the ADAS.Tree model is derived from the Delayed Word Recall task, with a lesser, but significant, contribution from the Number Cancellation task, both of which are not typically included in the ADAS-cog when used as a primary outcome measure for registration trials. It is important to note that the ADAS.Tree, which was optimized to discriminate between diagnostic categories, not to predict MCI to AD conversion, performed as well as composite imaging signatures that were optimized for the conversion from MCI to AD. These data suggest that a modified weighting system of the expanded ADAS-cog may play a role in an optimal screening algorithm for the prediction of MCI to AD conversion.

Multiple previous studies have identified prognostic markers for progression of MCI to AD. Deficits in episodic memory and/or executive function,[19] total ADAS-cog,[20] abnormal CSF [low Aβ (total or subtypes), high tau and/or high *P*-tau],[21] whole brain or regional volume changes,[22,23] decreases in brain metabolic activity,[24,25] brain PIB binding,[26,27] or combinations of the above,[28] can predict the conversion from MCI to AD. However, few studies have compared CSF or imaging markers with cognitive markers. One example is Fleisher et al[29] who studied 129 MCI participants over 36 months, and found that the optimal prediction model consisted of delayed 10-word recall, the NYU delayed paragraph recall and the ADAS-cog. Addition of volumetric MRI did not increase the performance of the model. Similarly, Jack et al[30] found that baseline free and cued selective recall performed as well as baseline hippocampal volume in the prediction of conversion of MCI to AD. These studies are consistent with our findings that cognitive assessments perform similarly to imaging biomarkers in the prediction of MCI to AD conversion. In contrast, Anchisi et al[31] found that a composite of several volumes of interest in temporoparietal regions and posterior cingulate cortex was a better predictor than any of several individual cognitive tests, with the California Verbal Learning Test-long delay being the best cognitive predictor (AUC from the ROC curve for FDG-PET = 0.863 vs. 0.783 for CVLT-long delay). In addition, Devanand et al[31] found that a model that contained demographic data and the Selective Reminding Test and the WAIS-Digit-Symbol test (encompassing similar cognitive domains as the Delayed Word Recall and Number Cancellation Task, tested here), had 80% sensitivity (at a fixed specificity of 80%) for prediction of conversion from MCI to AD over 3 years. Addition of baseline hippocampal and entorhinal cortex volumes enhanced sensitivity to 83.3%.

In interpreting the findings from the present analyses, it should be noted that the MCI participants in ADNI were selected to meet Petersen criteria for amnestic MCI, and as such, represent a more advanced point in the disease spectrum than MCI participants in some other studies. This may account in part for the predictive value of the number cancellation task, which is more attuned to later-stage MCI patients. Our analyses may well have yielded different ADAS-cog weightings and predictive biomarkers if applied to an earlier MCI population.

Our approach differs from many of the other approaches in 2 important respects. First, we have focused on the short-term (12-mo) conversion rates from MCI to AD, whereas many of the others have looked at longer

TABLE 3. Significance of Each CSF Marker and Marker Ratios for Identifying MCI Patients That Progressed to AD Over a 12-month Period

Rank	ADNI Marker	Common Name	N1	N2	*P*
1	PTAU181p_upe/ABETA142_upe	ptau 181/amyloid beta 1-42	140	35	0.006
2	ABETA142_upe	Amyloid beta 1-42	140	35	0.036
3	PTAU181p_upe	ptau 181	140	35	0.080
4	TAU_upe/ABETA142_upe	Total tau/amyloid beta 1-42	140	35	0.17
5	TAU_upe	Total tau	140	35	0.259

ADNI Marker indicates name of marker, as listed in ADNI dataset. Three-letter suffix refers to site where analysis took place. Common name = typical name of marker; N1 = number of MCI patients for whom baseline CSF data and 12-mo clinical data are available; N2 = number of MCI patients that converted to AD over a 12-mo period.

upe indicates University of Pennsylvania.

TABLE 4. Significance of Top 10 FDG-PET Markers for Identifying MCI Patients That Progressed to AD Over a 12-month Period

Rank	ADNI Marker	Common Name	N1	N2	*P*
1	PRECUNL01_bai	Left precuneus 1	146	23	0.0004
2	OCCMIDR04_bai	Right mid-occipital cortex 4	80	14	0.0020
3	PRECUNL02_bai	Left precuneus 2	104	20	0.0020
4	Angular.Left_ucb	Left angular gyrus	155	23	0.0021
5	PARIINFR01_bai	Right inferior parietal cortex	104	20	0.0022
6	PRECUNR02_bai	Right precuneus 2	146	23	0.0023
7	TMPMIDR04_bai	Right mid-temporal cortex 4	80	14	0.0024
8	TMPMIDR01_bai	Right mid-temporal cortex 1	104	20	0.0026
9	CINGPSTL02_bai	Left posterior cingulum 2	146	23	0.0027
10	OCCMIDL01_bai	Left mid-occipital cortex 1	104	20	0.0031

ADNI Marker, name of marker, as listed in ADNI dataset. Three-letter suffix refers to site where analysis took place. Common name = typical name of marker; N1 = number of MCI patients for whom baseline FDG-PET data and 12-mo clinical data are available; N2 = number of MCI patients that converted to AD over a 12-mo period.

bai indicates Banner Alzheimer's Institute; ucb, University of California at Berkeley.

TABLE 5. Significance of Top 10 Volumetric MRI Markers for Identifying MCI Patients that Progressed to AD Over a 12-month Period

Rank	ADNI Marker	Common Name	N1	N2	*P*
1	TEMPINFL_uas	Left inferior temporal cortex	280	65	4.29E-06
2	TEMPPLSUPL_uas	Left superior temporal pole	280	65	1.24E-05
3	HIPPL_uas	Left hippocampus	280	65	1.62E-05
4	TEMPINFR_uas	Right inferior temporal cortex	280	65	7.39E-05
5	TEMPMIDL_uas	Left middle temporal cortex	280	65	8.69E-05
6	LEFTHIPPO_sf2	Left hippocampus	214	45	8.90E-05
7	R_MID_TEMPORAL_ucd	Right middle temporal cortex	157	31	9.03E-05
8	L_MID_TEMPORAL_ucd	Left middle temporal cortex	157	31	9.73E-05
9	AMYGDR_uas	Right amygdala	280	65	0.0001
10	AMYGDL_uas	Left amygdala	280	65	0.0002

ADNI Marker, name of marker, as listed in ADNI dataset. Three-letter suffix refers to site where analysis took place. Common name = typical name of marker; N1 = number of MCI patients for whom baseline CSF data and 12-mo clinical data are available; N2 = number of MCI patients that converted to AD over a 12-mo period.

sf2 indicates University of California at San Francisco; uas, University of Arizona; ucd, University of California at Davis.

TABLE 6. Performance Summary of the Optimal Signatures for Cog-CSF, Cog-PET, and Cog-MRI Datasets

	No. Pre-Filtered	Signature Size	Model	Sensitivity (SE) (%)	Specificity (SE) (%)	AUC (SE) (%)	MCC (SE) (%)
CSF							
CSF alone	None	3	DLDA	62.65 (1.24)	54.21 (0.33)	58.43 (0.66)	13.38 (1.04)
Cog alone	None	3	DQDA	76.47 (0.62)	63.86 (0.22)	70.16 (0.29)	32.21 (0.46)
CSF + Cog	None	3	DQDA	76.76 (0.53)	63.93 (0.29)	70.35 (0.22)	32.51 (0.34)
PET							
PET alone	30	5	DLDA	55.38 (1.54)	85.54 (0.99)	70.46 (1.04)	36.41 (2.21)
Cog alone	None	10	DQDA	63.08 (1.54)	82.16 (1.19)	72.62 (0.92)	37.76 (1.85)
PET + Cog	30	25	DQDA	56.92 (3.08)	83.64 (0.71)	70.29 (1.45)	34.66 (2.26)
MRI							
MRI alone	50	10	DLDA	57.50 (1.09)	62.26 (0.50)	59.88 (0.62)	15.63 (0.98)
Cog alone	None	10	DLDA	67.34 (0.37)	67.38 (0.14)	67.36 (0.23)	27.73 (0.36)
MRI + Cog	80	5	DLDA	66.56 (1.31)	66.45 (0.45)	66.51 (0.58)	26.29 (0.88)

The number of markers prefiltered (if any), final signature size, fitted model, and the corresponding sensitivity, specificity, AUC, and MCC from the 10 repetitions of fully embedded 5-fold stratified cross-validation are shown. Standard Errors (SE) are derived from these 10 repetitions.

DLDA indicates Diagonal Linear Discriminant Analysis; DQDA, Diagonal Quadratic Discriminant Analysis.

periods. Indeed, many other types of biomarkers such as CSF Aβ/p-tau[21] or combinations of CSF and brain blood flow[33] have shown a very impressive ability to predict conversion from MCI to AD over a 4-year to 5-year follow-up period. However, in both of these studies, review of the 12-month conversion data shows very modest separation at best. The second major difference is the use of a novel multivariate approach to generate a weighting system for the ADAS-cog. Multivariate approaches coupled with machine learning algorithms provide a powerful means to

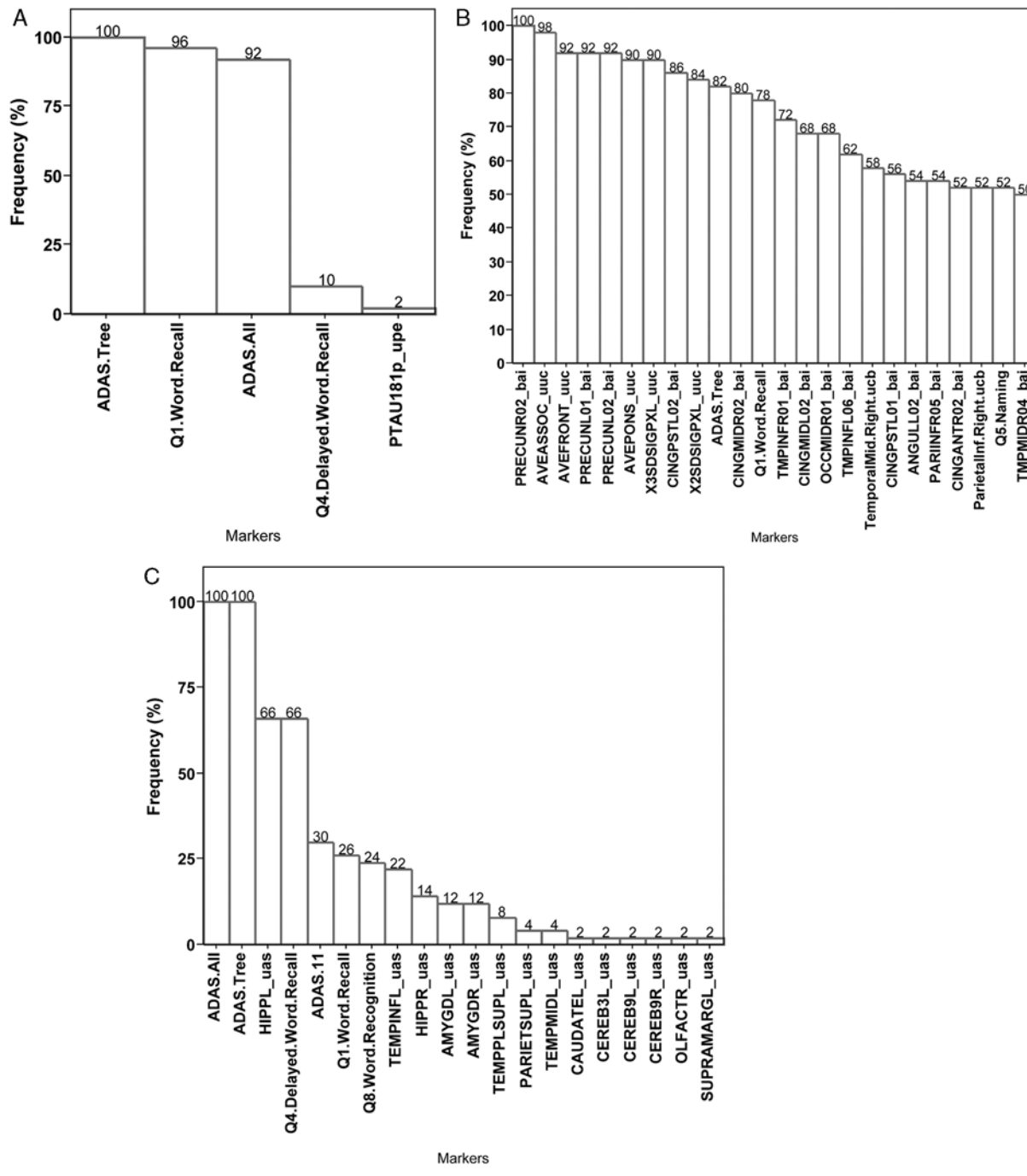

FIGURE 7. Summary of the % frequency of cognitive and CSF markers (A), cognitive and FDG-PET markers (B) and cognitive and MRI markers (C) that appear in the signatures across 10 repetitions of 5-fold cross-validation ($10 \times 5 = 50$ signatures) from the optimal model for predicting 12-month progression from MCI to AD.

explore a massive dataset (such as ADNI) for optimal and robust combinations of predictors. In this study, the ADAS.Tree, whose components were weighted using a Random-Forest-based algorithm, outperformed the unweighted ADAS.All by nearly an order of magnitude. This is consistent with other work demonstrating a substantial advantage of the use of machine-based multivariate analyses.[34,35]

There are several advantages to an enrichment scheme based on cognitive testing, rather than imaging or CSF biomarkers. First, from a pragmatic and cost-containment point of view, cognitive testing is clearly superior. Unlike proposals to use imaging and CSF biomarkers as outcome measures, which could potentially be feasible when applied to satellite populations,[36] assessing all potential participants through volumetric MRI, FDG-PET, or lumbar

puncture for purposes of enrichment could severely limit the number of participants screened for a study. In addition, screening participants through a biological marker such as Aβ deposition (eg, as imputed indirectly based on low concentrations of CSF $A\beta_{1-42}$), may enrich for a population that is less sensitive, for any given level of cognitive performance, to drug effects as the pathology may be further along its destructive cascade. It may also be argued that CSF or imaging biomarkers add specificity to the prediction of MCI to AD conversion. However, we found that the addition of these markers did not substantially alter the model's specificity for progression from MCI to AD.

We have relied on processed data from the ADNI dataset to derive our predictive models. It is possible that other approaches to processing the raw imaging data may produce more robust predictors of MCI to AD conversion. This is suggested by this study, where similar anatomical regions that were processed differently (eg, left precuneus in Table 4) are seen more than once, but with different *P*-values for prediction of MCI to AD conversion. It is also possible that markers that combine modalities, such as CSF + imaging or genotype + imaging may provide better predictors of MCI to AD conversion. However, on the latter point, it is worth noting that combination biomarker approaches that cross domains (eg, imaging + CSF), place a high burden on the conduct of the study, such that enhanced predictive power may be of very little practical value.

Another important methodologic issue raised by this study is that of cross-validation. Many studies of the predictive and diagnostic utility of AD biomarkers report sensitivity and specificity values, or ROC AUC values, based on the application of a decision rule onto the same set of data from which that model was generated. This may generate inflated values of specificity and sensitivity.[15] By contrast, we have used a form of cross-validation, described in the Methods section, to determine the sensitivity and specificity of our predictive models. For this reason, the values of sensitivity and specificity reported in this study are lower than those typically reported in other studies that have not used cross-validation. Clearly, the optimum form of validation will involve testing our model on a novel database, and this external validation will be pursued in the future.

This study also raises questions about the overall utility of the traditional ADAS-cog as a metric of cognitive function. The ADAS-cog has not changed in form since it was first introduced in 1984. Although it has gained popularity, primarily driven by its ability to detect drug effects in the pivotal trials of the cholinesterase inhibitors, it has well-recognized ceiling effects that limit its usefulness in patients with MCI or mild AD.[4] It is clear from Figure 2 that most MCI participants cluster toward the low end of the scale across several domains (eg, naming, ideational praxis and orientation), producing prominent ceiling effects for these participants in these categories. This could potentially be overcome by either reweighting the scale to deemphasize the less informative subscales, as was essentially done here, although in this case indexed to maximize separation between diagnostic categories. Another approach could be to tailor the less informative scales to increase their dynamic ranges (ie, altering the difficulty of tests based on the presence of floor or ceiling effects), or indexing scores based on their precision and performance relative to global performance (eg, Rasch analysis).[37] In this light, it is important to distinguish between the work presented here, which uses the ADAS-cog as a screening tool, and the work by Hobart, Cano and others, who have analyzed the ability of the ADAS-cog to serve as a reliable metric of cognitive function. For example, Hobart et al (2009) reported that the additional two components included in the ADAS-cog 13 (Delayed Word Recall and Number Cancellation) add very little to the metric properties of the 11-item ADAS-cog in AD patients.[38] Our findings are not inconsistent with this, as there are prominent floor effects seen with Delayed Word Recall in AD patients, as shown in Figure 2. This suggests that different components of the ADAS-cog may be most suitable for different needs (eg, serving as an outcome metric vs. serving as a screening tool).

Our findings suggest that relatively simple modifications of the ADAS-cog enhance its ability to predict conversion from MCI to AD in a time period that is tractable for clinical trials. It is important to emphasize that imaging and/or CSF biomarkers still play a key role in AD drug development as markers of disease state and progression risk. However, for the particular application described herein, the modified ADAS-cog may have practical advantages, driven by the wide experience with this test, its multilingual and multicultural validations, and its ease of administration. Further, the multivariate approach used to optimize the ADAS-cog weights may be tailored for other applications, potentially expanding the utility of the ADAS-cog for other patient populations.

ACKNOWLEDGMENTS

The authors thank Regula E. Egli, PhD, of Abbott, for technical review and copyediting assistance during the preparation of this manuscript.

REFERENCES

1. McKhann G, Drachman D, Folstein M, et al. 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.
2. Petersen RC, Smith GE, Waring SC, et al. Mild Cognitive Impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56:303–308.
3. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356–1364.
4. Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. *Am J Psychiatry*. 1994;151: 390–396.
5. Benge JF, Balsis S, Geraci L, et al. How Well Do the ADAS-cog and its Subscales Measure Cognitive Dysfunction in Alzheimer's Disease? *Dement Geriatr Cogn Disord*. 2009;28:63–69.
6. Mitchell AJ, Shiri-Feshki M. Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis. *J Neurol, Neurosurg Psychiatr*. 2008;79:1386–1391.
7. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and Donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352:2379–2388.
8. Salloway S, Correia S, Richardson S. Key lessons learned from short-term treatment trials of cholinesterase inhibitors for amnestic MCI. *Int Psychogeriatr*. 2008;20:40–46.
9. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *The Lancet Neurol*. 2007;6:734–746.

10. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
11. Shaw L, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Annals Neurol*. 2009;65: 403–413.
12. Breiman L. Random Forests. *Machine Learning*. 2001;45:5–32.
13. Liaw A, Wiener M. Classification and regression by random Forest. *R News*. 2002;2:18–22.
14. Shi L, Campbell G, Jones WD, et al. The MicroArray Quality Control (MAQC)-II study of common practices for the development and validation of microarray-based predictive models. *Nat Biotechnol*. 2010;28:827–838. [Epub 2010 Jul 30].
15. Dupuy A, Simon RM. Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting. *J Natl Cancer Inst*. 2007;99:147–157.
16. Matthews BW. Comparison of the predicted and observed secondary structure of T4 phage lysozyme. *Biochim Biophys Acta*. 1975;405:442–451.
17. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
18. Vergara I, Norambuena T, Ferrada E, et al. StAR: a simple tool for the statistical comparison of ROC curves. *BMC Bioinformatics*. 2008;9:265.
19. Knopman DS, Ryberg S. A verbal memory test with high predictive accuracy for dementia of the Alzheimer Type. *Arch Neurol*. 1989;46:141–145.
20. Rozzini L, Vicini Chilovi B, Bertoletti E, et al. The importance of Alzheimer disease assessment scale-cognitive part in predicting progress for Amnestic mild cognitive impairment to Alzheimer disease. *J Geriatr Psychiatry Neurol*. 2008;21:261–267.
21. Ewers M, Buerger K, Teipel SJ, et al. Multicenter assessment of CSF-phosphorylated tau for the prediction of conversion of MCI. *Neurology*. 2007;69:2205–2212.
22. Chételat G, Landeau B, Eustache F, et al. Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. *NeuroImage*. 2005;27:934–946.
23. Risacher SL, Saykin AJ, West JD, et al. Baseline MRI Predictors of Conversion from MCI to Probable AD in the ADNI Cohort. *Curr Alzheimer Res*. 2009;6:347–361.
24. Lisa M, Alberto P, Mony JDL. Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's Disease. *Annals N Y Acad Sci*. 2008;1147:180–195.
25. Habeck CG, Ng T, Muraskin J, et al. Univariate and multivariate FDG markers for early diagnosis of Alzheimer's disease in data from the Alzheimer's Neuroimaging Disease Initiative. Program No. 17.1. 2009 Neuroscience Meeting Planner. Chicago, IL. Society for Neuroscience, 2009. Online. 2009.
26. Okello A, Koivunen J, Edison P, et al. Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology*. 2009;73:754–760.
27. Morris JC, Roe CM, Grant EA, et al. Pittsburgh compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. *Arch Neurol*. 2009;66: 1469–1475.
28. Bouwman FH, Schoonenboom SNM, van der Flier WM, et al. CSF biomarkers and medial temporal lobe atrophy predict dementia in mild cognitive impairment. *Neurobiol Aging*. 2007;28:1070–1074.
29. Fleisher AS, Sun S, Taylor C, et al. Volumetric MRI vs clinical predictors of Alzheimer disease in mild cognitive impairment. *Neurology*. 2008;70:191–199.
30. Jack CR Jr, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 1999;52:1397–1407.
31. Anchisi D, Borroni B, Franceschi M, et al. Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer disease. *Arch Neurol*. 2005; 62:1728–1733.
32. Devanand DP, Pradhaban G, Liu X, et al. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. *Neurology*. 2007;68:828–836.
33. Hansson O, Buchhave P, Zetterberg H, et al. Combined rCBF and CSF biomarkers predict progression from mild cognitive impairment to Alzheimer's disease. *Neurobiol Aging*. 2009;30: 165–173.
34. Karam JA, Lotan Y, Karakiewicz PI, et al. Use of combined apoptosis biomarkers for prediction of bladder cancer recurrence and mortality after radical cystectomy. *Lancet Oncol*. 2007;8:128–136.
35. Shahrokh FS, Pierre IK, Raheela A, et al. Multiple biomarkers improve prediction of bladder cancer recurrence and mortality in patients undergoing cystectomy. *Cancer*. 2008;112:315–325.
36. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. Aug 4, Epub ahead of print.
37. Wouters H, van Gool WA, Schmand B, et al. Revising the ADAS-cog for a More Accurate Assessment of Cognitive Impairment. *Alzheimer Dis Assoc Disord*. 2008;22: 236–244.
38. Hobart J, Posner H, Aisen P, et al. The ADAS-cog's performance as a measure-lessons from the ADNI study: part 3-do the scale modifications add value? 2009;5:P256.

