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Identifying Cost-Effective Predictive Rules of Amyloid-β Level by Integrating Neuropsychological Tests and Plasma-Based Markers

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Abstract.
Background: Detecting participants who are positive for amyloid-β (Aβ) pathology is germane in designing prevention trials by enriching for those cases that are more likely to be amyloid positive. Existing brain amyloid measurement techniques, such as the Pittsburgh Compound B-positron emission tomography and cerebrospinal fluid, are not reasonable first-line approaches limited by either feasibility or cost.
Objective: We aimed to identify simple and cost-effective rules that can predict brain Aβ level by integrating both neuropsychological measurements and blood-based markers.
Method: Several decision tree models were built for extracting the predictive rules based on the Alzheimer's Disease Neuroimaging Initiative cohort.
Results: We successfully extracted predictive rules of Aβ level. For cognitive function variables, cases above the 45th percentile in total cognitive score (TOTALMOD), above the 52nd percentile of delayed word recall, and above the 70th percentile in orientation resulted in a group that was highly enriched for amyloid negative cases. Conversely scoring below the 15th percentile of TOTALMOD resulted in a group highly enriched for amyloid positive cases. For blood protein markers, scoring below the 57th percentile for apolipoprotein E (ApoE) levels (irrespective of genotype) enriched two fold for the risk of being amyloid positive. In the high ApoE cases, scoring above the 60th percentile for transthyretin resulted in a group that was >90% amyloid negative. A third decision tree using both cognitive and blood-marker data slightly improved the classification of cases.
Conclusion: Our study demonstrated that the integration of the neuropsychological measurements and blood-based markers significantly improved prediction accuracy. The prediction model has led to several simple rules, which have a great potential of being naturally translated into clinical settings such as enrichment screening for AD prevention trials of anti-amyloid treatments.

Keywords: Amyloid, decision rules, neuropsychological tests, plasma markers, prediction

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INTRODUCTION

Alzheimer's disease (AD) is progressive, fatal neurodegenerative disorder, characterized by memory loss and other cognitive impairments. There is now a scientific consensus that the pathological events in AD initiate decades before clinical symptoms become apparent, and disease-modifying therapies will be most effective at the earliest stages of the disease. A major disease-modifying therapy which holds great promise in preventing AD is anti-amyloid preventative treatment [1], since abnormal amyloid-β (Aβ) deposition has been widely regarded as the initial event in a cascade of pathological processes, leading to synaptic dysfunction and neuronal death, and followed by the development of cognitive impairment and eventually dementia [2]. Despite the promises held by the developing anti-amyloid preventative treatments, the success of their clinical trials requires appropriately selected participants who are positive for Aβ pathology.

The identification of suitable individuals with elevated brain amyloid burden poses a great challenge in terms of feasibility and cost. To date, the advancement of molecular imaging tracers that bind to amyloid, such as Pittsburgh Compound B (PiB), offers a non-invasive *in vivo* method to detect and quantify brain amyloid deposition [3, 4]. However, this approach for pre-symptomatic detection is economically challenging for routine use given the current cost [5]. Similarly, the clinical use of other useful biomarkers such as $A\beta_{1\text{-}42}$ and phosphorylated tau in cerebrospinal fluid (CSF) is also limited, since lumbar puncture carries risks and is met with resistance in elderly subjects. Furthermore, it is unlikely to be used in primary health care centers to routinely screen large number of participants. Given the cost and limited availability of these brain amyloid measurement techniques, they are not reasonable first-line approaches for screening participants at risk of having elevated brain amyloid burden.

Recent studies have revealed the possibility of predicting elevated brain amyloid burden using more cost-effective measurements, such as neuropsychological tests and blood-based biomarkers. Some concurrent relationships between Aβ and cognition [6–8], metabolism decline [9], and brain atrophy [10] have been identified. A few studies have developed models to predict elevated Aβ level or AD, using either neuropsychological measures [11, 12] or blood-based markers [13–16]. On the other hand, although neuropsychological measures and blood-based biomarkers have more practical applicability for routine use and are more cost effective, their predictive capabilities for detection of pre-symptomatic AD are still limited [11–16]. For instance, by relying on neuropsychological measures alone, individuals with very high premorbid intellectual abilities experiencing incipient cognitive decline may go undetected, and false positives are possible in individuals with a low level of intellectual abilities. It is also a well-known fact that the ceiling and floor effects limit the measurement capacity of many neuropsychological instruments [17–19]. Also, the set of blood-based biomarkers that have been reported as associated with AD are largely inconsistent in literature [13–16], probably due to the inherent measurement uncertainty since these markers fluctuate over time [20, 21]. Another possible reason is that univariate statistical methods were used for identifying these blood-based biomarkers, falling short on recognizing the multivariate patterns that may be more robustly and reliably associated with the AD pathology [13–16].

To date, we are aware of no prior work that has explicitly sought to identify these multivariate patterns which integrates both neuropsychological tests and blood-based markers, as existing research works focus on either neuropsychological tests or blood-based markers alone. As it is becoming increasingly apparent that univariate biomarkers are not sufficiently sensitive or specific for the diagnosis of complex, multifactorial disorders such as AD [22], it is more promising to consider applying multivariate data mining approaches to combine the neuropsychological measures and blood-based biomarkers and allow them to complement with each other, in order to identify biomarker signatures which are consistent with preclinical AD and specifically associated with amyloid pathology. Such an approach will be more practical for clinical use and be germane in designing large-scale prevention trials by enriching for those cases that are more likely to be amyloid positive by positron emission tomography (PET) imaging. This would then require smaller numbers of individuals to be screened to populate anti-amyloid secondary prevention trials.

Therefore, our aim is to investigate the feasibility of extracting cost-effective, simple predictive rules of brain Aβ positivity for enriching the study population for clinical trials of anti-amyloid treatments, by integrating neuropsychological tests and blood-based markers. We explore different strategies for building our prediction models, and compare their predictive performances. Moreover, rather than focusing on predictive regression models as in most of the relevant existing studies [11–16], we use the decision tree

model since it can lead to simple decision rules that can be naturally translated into the clinical settings for detecting amyloid positive cases. Furthermore, these rules will permit some individuals to be classified on the basis of only one, or at most a few, measurements, whereas scores derived from regression-based prediction models, such as logistic regression or support vector machine, require that all covariates are available.

MATERIALS AND METHODS

Subjects

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians in developing new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years. For up-to-date information, see http://www.adni-info.org/.

Analysis data-set

Data used for the analyses presented here were accessed on May 11, 2013 and comprise data from 50 normal old adults and 168 MCI subjects for which blood proteomics data and Aβ status were available. Normal individuals were free of memory complaints or depression and had a Mini-Mental State Examination (MMSE) score of 28 to 30 and a Clinical Dementia Rating (CDR) score of 0. MCI individuals met Petersen criteria for single-domain or multi-domain amnestic MCI with MMSE scores of 24 to 27, 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.

The variables included in this study are as follows. For neuropsychological measurements, we used the standard 11-item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), including: word recall, commands, construction, naming, ideational praxis, orientation, word recognition, recall instructions, spoken language, word finding, comprehension, and two additional items (delayed word recall and number cancellation). We also included the total scores from both the 11-item and 13-item versions. For blood-based markers, we used the proteomics data set that was produced by the Biomarkers Consortium Project "Use of Targeted Multiplex Proteomic Strategies to Identify Plasma-Based Biomarkers in Alzheimer's Disease" [23]. We used 146 blood-based markers from the proteomic data downloaded from the ADNI website. For measurements of amyloid burden, we used both the PiB-PET imaging and the CSF beta amyloid 1-42 ($A\beta_{1\text{-}42}$) level. The subjects were then dichotomized into either PiB positive (PiB retention summary measure >1.5) or PiB negative (PiB retention summary measure <1.5), based on a threshold used in [24]. The CSF samples were acquired from these subjects by the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center. The subjects were then dichotomized into either CSF $A\beta_{1\text{-}42}$ positive (CSF $A\beta_{1\text{-}42}$ level of <=192 pg/mL) or CSF $A\beta_{1\text{-}42}$ negative (CSF $A\beta_{1\text{-}42}$ level of >192 pg/mL), based on a threshold used in [25]. Finally, a subject is classified as amyloid positive if this subject is positive either by PiB-PET or CSF $A\beta_{1\text{-}42}$ or both.

Statistics

Data for the 50 normal and 168 MCI are used for estimating the prediction models. As mentioned in the introduction, we explored different strategies for integrating the neuropsychological tests and blood-based markers, and compared the predictive

performances of these integrated prediction models with the single-modality prediction models that are built on either neuropsychological tests or blood-based markers. Specifically, we: 1) evaluated the predictive performance of the neuropsychological measurements; 2) evaluated the predictive performance of the blood-based biomarkers; 3) evaluated the predictive performances if the neuropsychological measurements and blood-based biomarkers are combined.

Therefore, we generated three decision tree models: model 1 (M1) built a decision tree that only uses ADAS-cog; model 2 (M2) built a decision tree that only uses blood-based markers; and model 3 (M3) built a decision tree that uses both ADAS-cog and blood-based markers. For estimating each of the decision tree models, the conditional recursive partitioning technique [26] was used. This technique is a nonparametric methodology that creates a decision tree with respect to risk factors and their interactions that are most important in determining the outcome. Basically, it consists of three steps. The first step is tree building. A group of subjects (represented as a node on the tree) would split into child nodes if the testing statistic that measures the group differences between the two child nodes was significant for any variable beyond the 0.05 probability level. The significance level was adjusted for the number of multiple comparisons by Bonferroni method. The cut-off point that determined the splitting of the node for a continuous variable was the point that maximized the test statistic with the smallest p-value. Each splitting resulted in the definition of two homogeneous subgroups, that is, subjects in the same subgroup have a similar outcome, i.e., either amyloid positive or negative. The second step is termination of the tree building. There are multiple criteria that have been demonstrated effective in the termination of the tree building. One approach that was adopted in our study was to terminate the tree building when there were only a pre-specified number of observations in each of the leaf nodes, i.e., the number as 30 observations was used in our study. The third step was tree pruning that revised and reduced the size of the obtained tree after step 2. The main purpose of tree pruning was to achieve the optimal balance between the tree complexity (i.e., a tree with too many layers and leaf nodes will be cumbersome to use) and maintenance of prediction accuracy (by deleting the leaf nodes that do not substantially improve accuracy). A simple but effective strategy recommended in the literature is to select the smallest tree whose model error falls within the one standard error rule [26], which was adopted in our study. The decision tree analysis has been found valuable in many biomedical studies. For example, it was used for a cancer study to divide patients into homogenous groups based on the length of survival [27]. It has an advantage over the regression models in identifying prognostic factors because it relies on fewer modeling assumptions and has an established procedure that adapts to missing data through the use of surrogate measures. Also, because the method is designed to divide subjects into groups based on the heterogeneity of clinical outcome of interest, it defines groupings for outcome classification whereas regression models do not. Moreover, there is no need to explicitly include covariate interactions or transformations because of the recursive splitting structure of tree model construction. Analyses were performed using R, version 2.12 (http://www.r-project.org/), and the contributed libraries for the different machine-learning methods were used in our analyses, such as the "party", and "pROC".

Evaluation of predictive performances of different models

In attempt to evaluate the predictive performances of these models, first, we randomly split the whole dataset into two subsets of two-third and one-third size. The validation was conducted upon the one-third dataset once a decision tree model was estimated from the two-third dataset. This division resulted in similar numbers of control/ MCI and amyloid positive/negative cases in the two groups. The decision tree model was applied to the one-third dataset, and thereby, the classification accuracy, sensitivity, and specificity of each model was estimated. Sensitivity refers to the ability to correctly classify the subjects who are amyloid positive. Specificity refers to the ability to correctly classify the subjects who are amyloid negative.

RESULTS

Demographics

Characteristics of the 218 participants that are used in our study are summarized in Table 1 (so are the characteristics of the training and testing dataset that are generated by randomly splitting the 218 participants). Participants are well matched for age ($p = 0.4866$, Kruskal-Wallis test) and education. There are more men than women (60.0%, 71%, for normal and MCI, respectively), and the proportion of men is greater in the MCI group.

Table 1
Demographics of the 218 participants

	NC (Total)	MCI (Total)	Training NC	Training MCI	Validation NC	Validation MCI
Number	50	168	37	108	13	60
Age	83.82 (6.3)	82.06 (6.9)	85.32 (5.2)	81.5 (6.9)	79.5 (7.6)	83.1 (7.0)
Education	15.9 (3.03)	16.2 (2.56)	15.8 (3.0)	16.2 (2.6)	16.3 (3.1)	16.2 (2.6)
Gender (% male)	0.6	0.71	0.59	0.71	0.62	0.72
MMSE	29.28 (0.93)	26.98 (1.99)	29.16 (0.93)	26.98 (1.99)	29.62 (0.87)	27 (2.01)

NC, normal controls; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam.

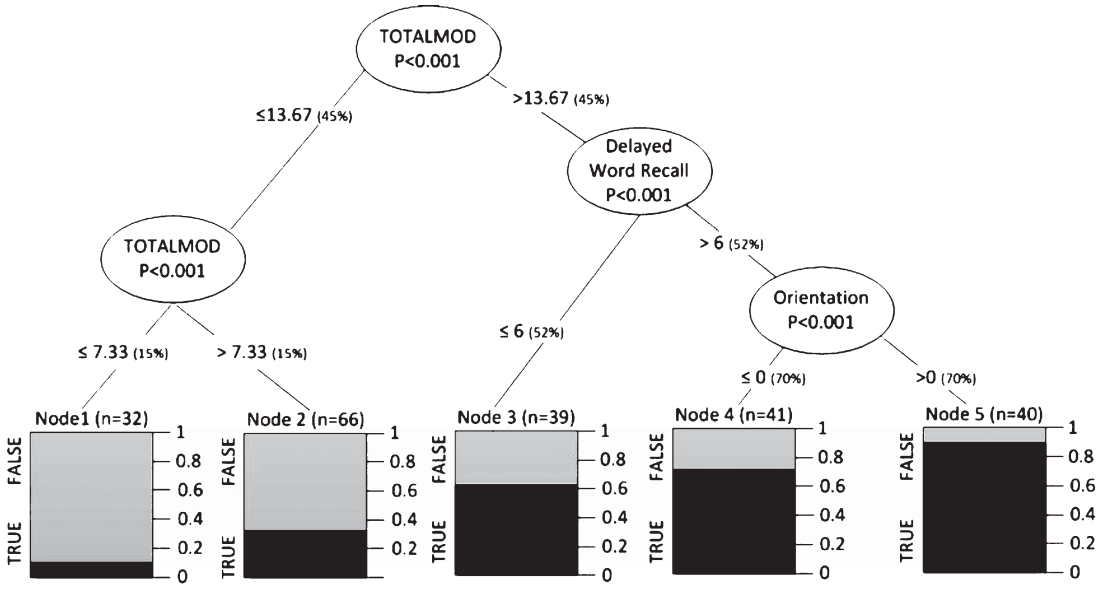

Fig. 1. The decision tree model of ADAS-cog (M1); note that the decision tree is estimated only using the training data, but the classification results of all 218 subjects (including both the training dataset and testing dataset) are presented. The dark section of each bar represents the proportion of cases that are amyloid-positive and the white section represents amyloid negative cases.

Estimation of the three models based on the training dataset

The three models were estimated using the two-third training data. The estimated model of M1, using only the cognitive function data, is shown in Fig. 1, together with the classification results of all the 218 subjects (including both the training dataset and testing dataset). Here, M1 identified three variables from the ADAS-cog tests, which are Delayed Word Recall, Orientation, and the TOTALMOD (the 85 point total score including the ADAS-cog, Delayed Word Recall, and Number Cancellation). M1 identified two homogenous subgroups, Node 1 (majority is amyloid negative) and Node 5 (majority is amyloid positive). These two subgroups are characterized by two rules, M1_Rule1: TOTALMOD <=7.33, M1_Rule2: TOTALMOD >13.67 AND Delayed Word Recall >6 AND Orientation >0, respectively. Note that, Node 4 also implies a relatively homogenous subgroup where the majority is amyloid positive.

Model M2 (as shown in Fig. 2) automatically identified five blood-based markers that were predictive of the amyloid-positivity out of the 146 blood-based markers. These five markers are APOE (Apolipoprotein E), PAP (Prostatic Acid Phosphatase), TTR (Transthyretin), MMP10 (Matrix Metalloproteinase-10), and MYOGLOBN (Myoglobin). M2 also identified two homogenous subgroups, Node 1 (majority is amyloid negative) and a merge of Node 5 and Node 6 (majority is amyloid positive). These two subgroups are characterized by two rules, M2_Rule1: APOE >1.785 AND TTR >2.569, M2_Rule2: APOE <=1.785 AND PAP <=−0.638 AND MMP10 >−1.481, respectively.

Model M3 (as shown in Fig. 3) used all the ADAS-cog variables and the blood-based markers as potential predictors. It identified one ADAS-cog

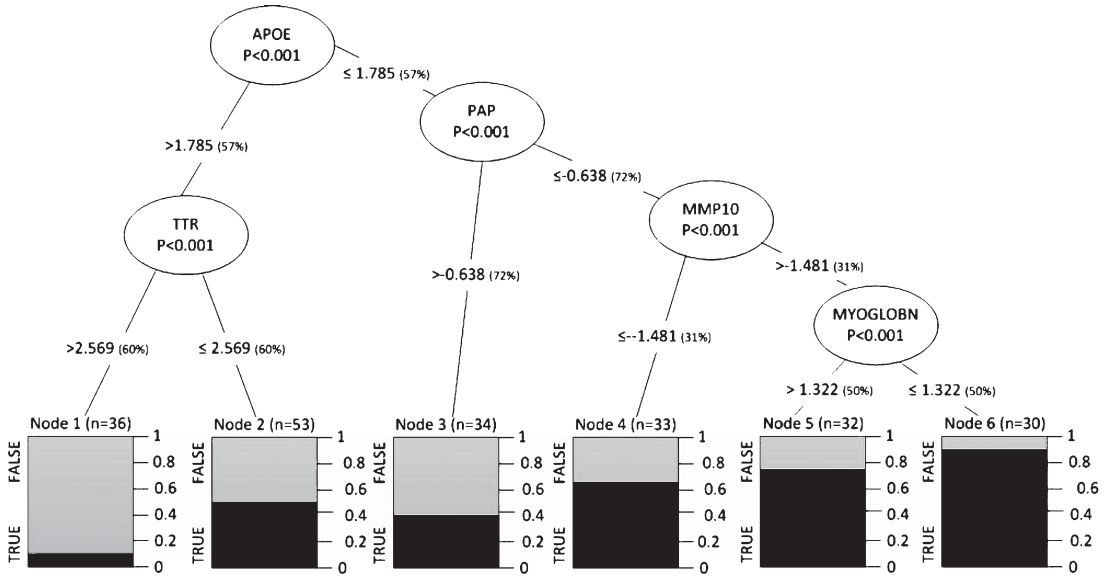

Fig. 2. The decision tree model of blood-based markers (M2); note that ithe decision tree is estimated only using the training data, but the classification results of all the 218 subjects (including both the training dataset and testing dataset) are presented.

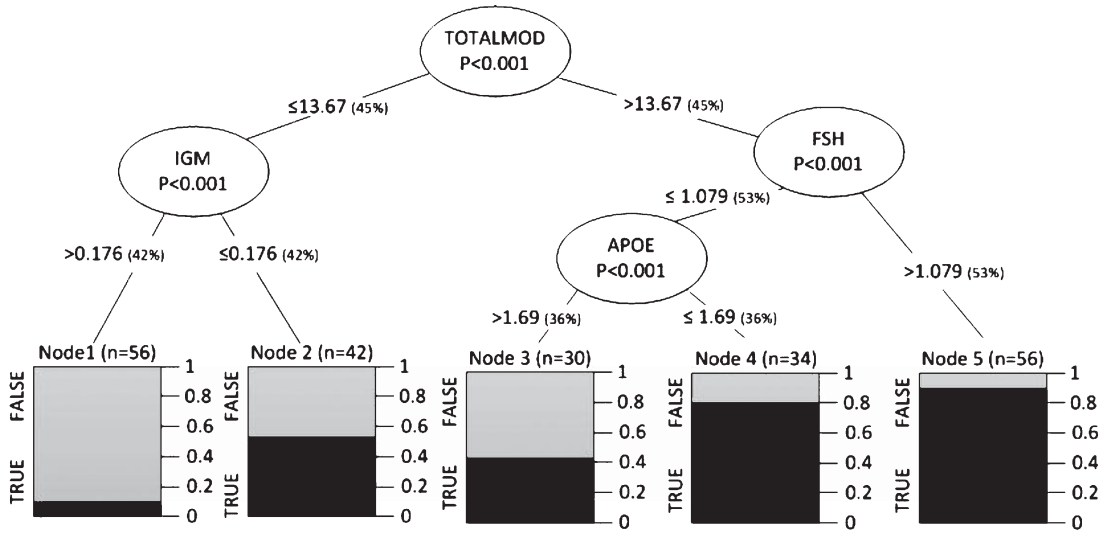

Fig. 3. The decision tree model of both ADAS-cog and blood-based markers (M3); note that it is estimated only using the training data, but the classification results of all the 218 subjects (including both the training dataset and testing dataset) are present.

variable, the TOTALMOD, and three blood-based markers, APOE, FSH (Follicle-Stimulating Hormone), and IGM (Immunoglobulin M), which were predictive of cases that were the amyloid pathology. M3 identified three homogenous subgroups, Node 1 (majority is amyloid negative), Node 4 (majority is amyloid positive), and Node 5 (majority is amyloid positive). These three subgroups are characterized by three rules, M3_Rule1: TOTALMOD <=13.67 AND IGM >0.176, M3_Rule2: TOTALMOD >13.67 AND FSH <=1.079 AND APOE <=1.69, M3_Rule3: TOTALMOD >13.67 AND FSH >1.079, respectively.

Application of the three models to the pseudo-external validation dataset

All the three models were estimated using the two-third training dataset. The remaining one-third testing data was used to evaluate their predictive performances. The results are shown in Fig. 4. It is evident

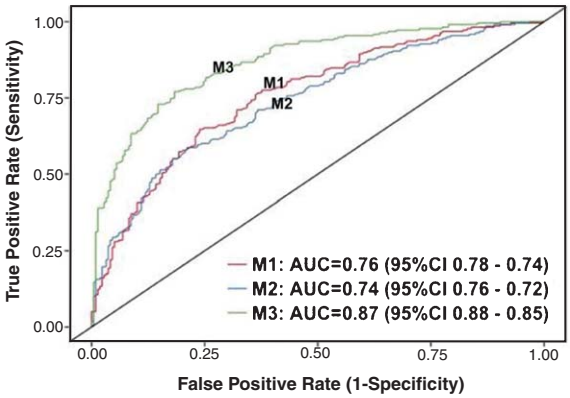

Fig. 4. The receiver operator curves of the three models on the testing dataset.

that all the models were demonstrated to be predictive of the testing data, showing that over-fitting is thereby not likely. It can also be seen that the prediction performance of M3 is superior to the other models, i.e., the 95% CI of the AUC of M3 does not overlap with the 95% CI of the AUC of M1 and M2, which demonstrated that the integration of both the neuropsychological tests with blood-based markers is effective. The sensitivity and specificity can also be extracted by querying Fig. 4. For example, with the specificity being fixed at 0.75, the sensitivities of the three models are approximately 0.61, 0.56, and 0.77, respectively. Note that our cross-validation randomly split the whole dataset into two subsets without intentionally balancing the subsets for amyloid positivity, yet maintained a similar distribution of positive and negative cases (see the characteristics in Table 1). Furthermore, the 10-fold cross-validation is also investigated that showed almost the same performance as this 3-fold cross-validation.

DISCUSSION

Our study identified effective prediction models for detecting subjects with elevated amyloid burden. All the three models identified simple rules that are predictive to brain amyloid level. These rules use cost-effective measurements and also permit some individuals to be classified on the basis of only one, or at most a few, measurements. For example, in M2 (Fig. 2), 43% of the 216 subjects have the ApoE plasma value >1.785, and only 33% of this group are amyloid positive. In contrast, 57% of the 216 subjects have the ApoE plasma value <=1.785, and 67% of this group are amyloid positive. This implies that by implementing the decision rule, ApoE <=1.785, it will enrich the amyloid positive population two fold. Therefore, as long as these rules can be clinically validated, we believe that these simple decision rules can be naturally translated into the clinical settings, such as enrichment screening for AD prevention trials of anti-amyloid treatments.

M1 is the decision tree model that only uses ADAS-cog variables. It is evident from the tree (shown in Fig. 1) that the risk of being amyloid positive increases from the left nodes to the right nodes, while at the same time, the scores of the ADAS-cog items that are used by M1 also increase. This trend is consistent with the nature of ADAS-cog as higher scores of the ADAS-cog variables imply greater cognitive impairment. Also, the item, delayed word recall, has been found to be associated with amyloid pathology in recent studies that used cohorts of cognitively normal subjects which were different from ours [7, 28]. On the other hand, the correlation between the ADAS-cog item, the "orientation", with amyloid pathology, requires further investigation.

The interpretation of the result in Fig. 4, i.e., that M1 slightly outperforms M2, needs to be interpreted cautiously. First of all, the difference between the prediction performances of M1 and M2 is not statistically significant. Secondly, M1 has lower specificity than M2.

An integration of ADAS-cog with blood-based markers improved the prediction accuracy. From Fig. 4, it is clear that the integrative models, M3, outperforms M1 (ADAS-cog only) and M2 (blood-based markers only). This indicates that the ADAS-cog and blood-based markers provide supplementary predictive information.

The blood-based markers that are found predictive to the amyloid deposition are APOE, PAP, TTR, MMP10, MYOGLOBN, IGM, and FSH. Most of these blood-based markers have been found to be associated with the amyloid pathology or AD in previous studies. For example, the association between the APOE level in plasma with brain amyloid burden has been identified in [16, 29, 30], where Thambisetty et al. [29] used the BLSA cohort that is a different cohort from ours. Our result is consistent with the studies in [16, 29, 30] that showed that the level of APOE in plasma, independent of genotype, is also a marker of risk. The PAP, as an amyloidogenic protein, has been found to form amyloid fibrils independent of those formed by Aβ [31]. IGM has been reported in [32] to be protective in amyloid formation since they may serve as a "buffering system" to keep free potential toxic endogenous peptides and proteins under homeostatic control and lead to their clearance. TTR, the carrier of thyroxine and

retinol, which also binds with Aβ, has been suggested to protect against Aβ deposition [33]. This protective effect is also consistent with the results in M2 (shown in Fig. 2), i.e., the subgroup of node 2, who has lower level of TTR, is more likely to be amyloid positive than the subgroup of node 1, which has higher level of TTR. Also, the evidence shows that matrix metalloproteinases (including the MMP10) play an important role in the pathogenesis of AD and may be involved in the processing pathway of Aβ [34]. It has been shown that the chromogranin peptides are markers for human hippocampal pathways, and have a potential as neuronal markers for synaptic degeneration in AD [35]. Evidence that supports the associations between FSH and MYOGLOBN with amyloid pathology can be found [36, 37].

We also compared our results with the 16 blood-based markers found to associate with brain amyloid burden in [16], and found only the association of APOE with amyloid is mutual. As that study employed univariate linear regression model for identifying the blood-based markers on the ADNI cohort, the associations between these 16 blood-based markers with amyloid burden were reported to be quite weak [16]. These associations were not significant after adjusting for other covariates such as age. On the other hand, our method identified a different set of blood-based markers that were highly predictive of amyloid burden when used in combination as rules, indicating that our method has the advantage of identifying the blood-based markers that are correlated with the amyloid pathology in a nonlinear and multivariate way.

Our study has limitations. First, we only used the ADAS-cog as the representative neuropsychological measurement. Although ADAS-cog is a standard tool in pivotal clinical trials to detect therapeutic efficacy in cognition, it is not considered sensitive enough to measure the disease progression in early disease stages. As our ultimate goal is to identify the enrichment decision model for detecting amyloid positive cases from cognitively normal subjects, a better alternative may be the Neuropsychological Test Battery [38]. Also, since our study relied on one single cohort for estimating and validating the decision tree model, whether the enrichment decision model can be generally applied to other research studies remains to be confirmed. Moreover, we used both normal aging and MCI subjects for analysis, whether the decision tree models can extrapolate to general normal aging subjects needs to be further validated.

Our future work includes a large-scale study that will use all the potential clinical variables rather than ADAS-cog only. We will include a number of AD-related neuropsychological measurements, such as the Mini-Mental State Exam, Boston Naming Test, Verbal Learning Test, and Clinical Dementia Rating scale, to name a few. A recent study has revealed that some of these neuropsychological measurements are predictive of amyloid pathology [11–13]. Existing research has also revealed that some variables measuring the activities of daily living are also associated with AD [39]. We need to validate our enrichment decision model on other cohorts. Moreover, although the integration model, M3, has demonstrated its effectiveness, it is possible that a better integration strategy may exist, which can further boost the prediction accuracy. Overall, the results indicate that the neuropsychological measurements with blood-based markers can lead to effective and accurate prediction model for detecting subjects with elevated amyloid burden. This prediction model has led to several simple rules, which have a great potential of being naturally translated into the clinical settings, such as enrichment screening for AD prevention trials of anti-amyloid treatments.

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Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2465).

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