Received: 15 March 2024 | Revised: 29 May 2024 | Accepted: 19 June 2024

DOI: 10.1002/dad2.12621

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Plasma pTau181 enhances the prediction of future clinical decline in amyloid-positive mild cognitive impairment

Viswanath Devanarayan[1,2] | **Daniel A. Llano**[3,4,5] | **Yan Helen Hu**[1] | **Harald Hampel**[1] | **Lynn Kramer**[1] | **Shobha Dhadda**[1] | **Michael Irizarry**[1]

[1]Eisai Inc., Clinical Evidence Generation, Nutley, New Jersey, USA

[2]Department of Mathematics, Statistics and Computer Science, University of Illinois Chicago, Chicago, Illinois, USA

[3]Carle Illinois College of Medicine, Urbana, Illinois, USA

[4]Department of Molecular and Integrative Physiology, University of Illinois Urbana-Champaign, Urbana, Illinois, USA

[5]Beckman Institute for Advanced Science and Technology, Urbana, Illinois, USA

Correspondence
Viswanath Devanarayan, Eisai Inc., Clinical Evidence Generation, 200 Metro Blvd, Nutley, NJ 07110, USA.
Email: viswanath_devanarayan@eisai.com

Funding information
Eisai Inc.

Abstract: Plasma pTau181, a marker of amyloid and tau burden, was evaluated as a prognostic predictor of clinical decline and Alzheimer's disease (AD) progression of amyloid-positive (Aβ+) patients with mild cognitive impairment (MCI). The training cohort for constructing the Bayesian prediction models comprised 135 Aβ+ MCI clinical trial placebo subjects. Performance was evaluated in two validation cohorts. An 18-month $\geq$1 increase in the Clinical Dementia Rating Sum of Boxes was the clinical decline criterion. Baseline plasma pTau181 concentration matched clinical assessments' prediction performance. Adding pTau181 to clinical assessments significantly improved the prediction of an 18-month clinical decline and the 36-month progression from Aβ+ MCI to AD. The area under the receiver operating characteristic curve for the latter increased from 71.8% to 79%, and the hazard ratio for time-to-progression improved from 2.26 to 3.11 ($p < 0.0001$). Baseline plasma pTau181 has the potential for identifying Aβ+ MCI subjects with faster clinical decline over time.

KEYWORDS
blood-based biomarkers, disease progression, machine learning, prognosis

Highlights

- This study assessed pTau181 as a prognostic predictor of 18-month clinical decline and extended progression to Alzheimer's disease (AD) in amyloid-positive patients with mild cognitive impairment (Aβ+ MCI).
- The research findings underscore the promise of baseline plasma pTau181 as a screening tool for identifying Aβ+ MCI individuals with accelerated clinical decline within a standard 18-month clinical trial period. The predictive accuracy is notably enhanced when combined with clinical assessments.
- Similar positive outcomes were noted in forecasting the extended progression of Aβ+ MCI subjects to AD.

1 | BACKGROUND

Implementing blood-based tests for Alzheimer's disease (AD) screening and monitoring offers a faster, easier, and cost-effective alternative to cerebrospinal fluid (CSF) and imaging methods.[1–4] Recent studies have highlighted the relevance of blood-based biomarkers (BBM), such as plasma pTau181, which correlate with brain amyloid burden, tau accumulation, and disease progression in early AD.[5–8]

The prediction of future clinical decline, manifesting as deficits in one or more aspects of cognitive and functional tasks, through convenient and cost-effective assessments at baseline offers substantial benefits in drug development, such as optimizing patient selection and trial design. It is also valuable to real-world clinical practice by furnishing prognostic information for patients and physicians. Several prognostic models for AD progression proposed in the literature rely on CSF biomarkers or amyloid/tau positron emission tomography (PET) imaging, which are difficult to implement at scale due to cost, availability, and perceived invasiveness.[9–15] While recent research advancements in BBM for AD have predominantly focused on disease diagnosis and staging,[16–24] the application of BBM for predicting AD progression is still in its early stages. Although several models have been proposed to forecast disease progression using BBM,[1,5,7,25,26] a prevalent issue is the insufficient validation and evaluation of these models, particularly within clinical trial cohorts.

The growing integration of BBM assessments in contemporary clinical trials and observational research cohorts presents a valuable opportunity to thoroughly assess their effectiveness in predicting AD progression. An example of such a biomarker is pTau181, which has undergone evaluation in multiple AD clinical trials and the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.[27–29] Recent publications on pTau181 and other isoforms [5,7,25] have focused on predicting long-term progression (>3 years) using research cohorts, emphasizing population-level associations over individual predictive performance. They did not combine baseline clinical assessments. Many studies focused on transitioning from mild cognitive impairment (MCI) to AD rather than clinical decline, which may not occur within an 18-month trial.[30] Predicting clinical progression within 18 months is crucial for AD trials and clinical practice. Including data from both trial and observational cohorts would enhance confidence in the prediction model.

In this study, our primary objective was to investigate the prognostic potential of baseline plasma pTau181 concentration, along with demographics and apolipoprotein E (*APOE*) $\varepsilon 4$ allelic count, as predictors for the 18-month clinical decline in MCI subjects showing significant amyloid accumulation (ie, amyloid-beta [Aβ] positive, denoted as Aβ+). Subsequently, we examined whether the inclusion of pTau181 alongside routine baseline clinical assessments could enhance the prediction performance. The prediction models were initially developed using a clinical trial cohort and then validated in an independent clinical trial cohort and an observational research cohort. Given that the research cohort had a more extended clinical follow-up, we also explored the capability of these clinical progression models to forecast longer-term disease progression ($\geq$3 years) from MCI to AD.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature utilizing PubMed and recent meeting abstracts. Relevant research on screening and monitoring individuals with blood-based tests for Alzheimer's disease (AD) is cited. Plasma pTau181 is a marker of brain amyloid and tau burden as well as clinical decline. However, an improved ability to predict AD progression would be useful for clinical trials and in clinical practice.
2. **Interpretation**: Our findings demonstrate that baseline plasma pTau181 is a prognostic marker for identifying amyloid-beta (Aβ)+ mild cognitive impairment (MCI) individuals who may experience faster clinical decline over a typical 18-month duration of a clinical trial. Combining it with baseline clinical assessments significantly improved the prediction accuracy. This is also true for predicting the longer-term progression from MCI to AD.
3. **Future directions**: Further research may include the reconstruction of our models using other fluid biomarkers and clinical tools, including those that are more readily available in clinical practice.

2 | METHODS

2.1 | Database

The training cohort (TC) for constructing the prediction models comprised 135 Aβ+ MCI subjects from the placebo arm of two identically designed clinical trials that were part of the elenbecestat phase-3 program (A Placebo-Controlled, Double-Blind, Parallel-Group, 24 Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat [E2609] in Subjects with Early Alzheimer's Disease; NCT02956486, MissionAD1 and NCT03036280, MissionAD2).

The first validation cohort (VC-1) for testing the performance of the prediction models included 115 Aβ+ MCI subjects from the placebo arm of an 18-month clinical trial of another program (A Study to Evaluate Safety, Tolerability, and Efficacy of Lecanemab in Subjects with Early Alzheimer's Disease; NCT01767311).[31] The trials in TC and VC-1 were approved by the Institutional Review Board or independent ethics committee at each center, and all the participants provided written informed consent.

The second validation cohort (VC-2) for further assessment of the prediction models included 177 Aβ+ MCI subjects with at least three years of clinical follow-up and the relevant cognitive and functional clinical assessments from the ADNI-2 and ADNI-GO phases of the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether

serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. For up-to-date information, see www.adni-info.org. The study was approved by the Institutional Review Boards of all of the participating institutions and informed written consent was obtained from all participants. Data used for the analyses presented here were accessed on December 18, 2023.

Aβ+ status in TC and VC-1 was determined via PET visual read. A positive visual read scan shows more amyloid in gray matter, while a negative read maintains contrast between gray and white matter. In VC-2, amyloid positivity was determined using the PET standardized uptake value ratio (SUVR) of the cortical composite region normalized by the whole cerebellum with a threshold of 1.11 as recommended by ADNI.[32] In TC, the majority (64%) received florbetaben, while 24% and 12% received florbetapir and flutemetamol respectively. In VC-1, 83% received florbetapir, and the remainder (17%) received flutemetamol. All VC-2 subjects received florbetapir.

In TC and VC-1, subjects with mild AD dementia were classified as Aβ+ and at an early disease stage.[33] Aβ+ MCI subjects met the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria, indicating symptomatic individuals without dementia but with AD characteristics.[34] Assessments used the Mini-Mental State Examination (MMSE), global Clinical Dementia Rating (CDR) score (0.5 for MCI and 1 for mild AD), and delayed word recall impairment. VC-2 used similar criteria.

Plasma pTau181 was analyzed by the single-molecule array (Simoa) technique in all three cohorts, using the same assay in TC and VC-1 and a different assay in VC-2. For TC and VC-1, Simoa Advantage V2 assay kit #103714 (immunoassay) provided by Quanterix Corporation was used to generate the data.[35] For VC-2 (ADNI), an in-house assay developed in the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden, was used. Due to the different assay used in VC-2, to make the data comparable across the training and validation cohorts, the concentration values were log-transformed and then standardized to have similar means and variances by first subtracting the concentration value of each subject from the mean concentration of all subjects from the corresponding cohort and then dividing this difference by the standard deviation. All subsequent analyses on plasma pTau181 were carried out using these standardized log-transformed values.

TC and VC-1 included an 18-month clinical follow-up, and VC-2 included a 3- to 10-year follow-up. An increase from baseline in the CDR Sum of Boxes (CDR-SB) at 18 months of $\geq$1 was used as a criterion for faster clinical decliners. Subjects with slower clinical decline who dropped out before month 18 were excluded from the training and validation cohorts. A summary of some key demographics and clinical characteristics of the subjects in these three cohorts is included in Table 1.

2.2 | Cognitive function assessments

While the clinical decline was defined in terms of the change from baseline in the CDR-SB, a variety of cognitive and functional assessments at baseline were also considered as potential predictors for constructing the prediction models. These include the MMSE, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog-13), CDR-SB, Functional Activity Questionnaire (FAQ), and all their subscores.

2.3 | Data analysis

A predictive model distinguishing between slower and faster 18-month clinical decline, where faster decline is defined by the increase in CDR-SB of at least 1, was initially constructed using baseline plasma pTau181. The Bayesian logistic lasso regression (BLLR) was employed in model construction, mirroring a process detailed in a recent publication.[36] Subsequently, a parallel model was developed including baseline clinical assessments, encompassing the MMSE, CDR-SB, ADAS-Cog-13, and FAQ composites, along with their respective subscores. Lastly, a comprehensive model integrating baseline clinical assessments and plasma pTau181 was established. *APOE* ε4 allelic count and demographic variables, including gender and age, were considered for selection in all the models.

BLLR, a regularization method utilizing a spike and slab mixture double-exponential prior, reduces model complexity, preventing overfitting and improving generalizability.[37] It moderates predictor variable weights, emphasizing crucial ones and shrinking less significant ones. Standardization, ensuring interpretability and comparability of odds ratios, involved subtracting the mean and dividing by the standard deviation. The final model reports key predictors with their odds ratios and 95% confidence intervals for a comprehensive summary.

The performance of the models was first assessed through 10 iterations of 10-fold stratified cross-validation within the TC.[38] Subsequently, the predictive ability for distinguishing fast versus slow 18-month clinical decline was evaluated in the two independent validation cohorts (VC-1 and VC-2). Given the extended clinical follow-up in VC-2, the models were further assessed for their ability to predict the progression from Aβ+ MCI to AD at 36 months. This longer timeframe was chosen due to the relatively low prevalence of MCI subjects converting to AD within 18 months. Evaluation metrics included sensitivity, specificity, and the area under the receiver operating characteristic curve (AUROC). Model comparisons based on the AUROC were conducted using DeLong's test.[39]

In VC-2, we compared time-to-progression to AD between Aβ+ MCI subjects predicted to experience faster versus slower clinical decline. This utilized Kaplan-Meier analysis with up to 10 years of follow-up data, deriving estimates of median and quartiles for progression time. Additionally, the Cox proportional hazards model estimated hazard ratios, indicating the increase in the instantaneous risk of MCI to AD progression at any given time. The Cox model's proportional hazards assumption was assessed using a chi-squared test. Hazard ratio estimates were compared between prediction models using Student's *t*-test for dependent samples.[40]

All analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing),[41] along with the packages BhGLM,[42] pROC,[43] survival,[44] and survcomp.[40]

TABLE 1 Demographics and clinical data summary of training and validation cohorts.

		TC N = 135		VC-1 N = 115		VC-2 N = 177	
Patient characteristics		Slower CD N = 66	Faster CD N = 69	Slower CD N = 52	Faster CD N = 63	Slower CD N = 51	Faster CD N = 126
APOE ε4 status	ε4 homozygous; N (%)	11 (17%)	10 (14%)	6 (11%)	13 (21%)	4 (8%)	23 (18%)
	ε4 heterozygous; N (%)	28 (42%)	39 (57%)	31 (60%)	35 (55%)	24 (47%)	72 (57%)
	Non-ε4; N(%)	27 (41%)	20 (29%)	15 (29%)	15 (24%)	23 (45%)	31 (25%)
Gender	Female; N(%)	31 (47%)	34 (49%)	24 (46%)	40 (63%)	22 (43%)	56 (44%)
	Male; N(%)	35 (53%)	35 (51%)	28 (54%)	23 (37%)	29 (57%)	70 (56%)
Age	Mean (SD)	71.8 (6.7)	73.9 (6.9)*	71.1 (7.7)	71.3 (9.9)	71.5 (7.0)	72.7 (6.4)
MMSE	Mean (SD)	26.6 (2.7)	25.4 (2.8)*	27.4 (2.0)	26.0 (2.3)*	28.4 (1.7)	27.4 (1.8)*
ADAS-Cog-13	Mean (SD)	17.5 (5.2)	21.8 (6.6)*	15.9 (4.6)	21.1 (5.9)*	11.4 (5.1)	19.5 (6.9)*

Note: Some key demographic and clinical characteristics of the subjects in the training cohort (TC) and the two validation cohorts (VC-1 and VC-2) are summarized here. An increase from baseline in the Clinical Dementia Rating Sum of Boxes score at 18 months of > = 1 was used as a criterion for faster clinical decliners. Subjects with faster clinical decline (CD) are significantly older in the TC ($p < 0.05$). Baseline MMSE is significantly lower in subjects with faster clinical decline in all three cohorts ($p < 0.05$). Other characteristics are not significantly different.

Abbreviations: *APOE* ε4, apolipoprotein E gene ε4 allele; ADAS-Cog-13, Alzheimer's Disease Assessment Scale–Cognitive Subscale; CD, clinical decline; MMSE, Mini-Mental State Examination; TC, training cohort; VC-1, first validation cohort; VC-2, second validation cohort.

*$p < 0.05$.

3 | RESULTS

3.1 | Demographics

Data in the training and two validation cohorts (TC, VC-1, and VC-2) included 135, 115, and 177 Aβ+ MCI subjects, respectively. A summary of some key demographic and clinical characteristics (gender, age, *APOE* ε4 status, MMSE and ADAS-Cog-13 scores) is presented in Table 1. As anticipated, the baseline MMSE is lower, and the baseline ADAS-Cog-13 is higher in subjects with accelerated clinical decline across all cohorts ($p < 0.05$). Furthermore, subjects with faster clinical decline are significantly older in the TC ($p < 0.05$), which aligns with the lower MMSE and higher ADAS-Cog-13 scores in this subgroup. Age, MMSE, and ADAS-Cog-13 were compared using the Kruskal–Wallis test, while gender and *APOE* ε4 status were assessed using the chi-squared test. Baseline plasma pTau181 is markedly elevated in subjects experiencing rapid clinical decline across all three cohorts, and the distribution of standardized log-transformed plasma pTau181 appears consistent between the three cohorts, with means and variances showing no significant differences (Supplementary Figure S1).

3.2 | Prediction models

The prediction model, incorporating baseline plasma pTau181, demographics, and *APOE* ε4 allelic count, identified pTau181 ($p = 0.042$) as the singular key predictor. Conversely, the model integrating baseline clinical assessments, demographics, and *APOE* ε4 allelic count revealed a more comprehensive set of baseline predictors. These encompassed CDR-SB, ADAS-Cog-13, and CDR-global composites, alongside functional activities associated with preparing a balanced meal, assembling, heating water, making coffee, and personal care. Similarly, the ADAS-Cog-13 tasks for spoken language ability (ADCSL) and number cancellation (ADCNC) were significant contributors.

Adding baseline plasma pTau181 to clinical assessments preserved most of the same predictors in the resulting model. The rank order, odds ratio estimates, and 95% confidence intervals for these predictors are summarized in Figure 1. Top predictors with $p < 0.05$ included CDR-SB, ADAS-Cog-13, meal preparation (FAQ06), and plasma pTau181. Another tier of predictors with relatively less significant influence ($p < 0.2$) included activities like heating water (FAQ05), assembling (FAQ02), personal care (CDR0106), and cognitive tasks like speech (ADCSL) and number cancellation (ADCNC). Although not attaining individual statistical significance, the multivariate model recognizes their contribution to overall prediction accuracy.

3.3 | Performance evaluation of the prediction models

In predicting the 18-month clinical decline, the model utilizing baseline plasma pTau181 alone demonstrated comparable performance to the one relying solely on baseline clinical assessments, with AUROC values in VC-1 of 64.8% and 70.6%, respectively ($p = 0.2$), while in VC-2, both models achieved an AUROC of 69.5%. Similarly, for predicting the 36-month MCI to AD progression in VC-2, the AUROC was 72.5% for plasma pTau181 and 71.8% for clinical assessments alone ($p = 0.56$). Additional details can be found in Table 2.

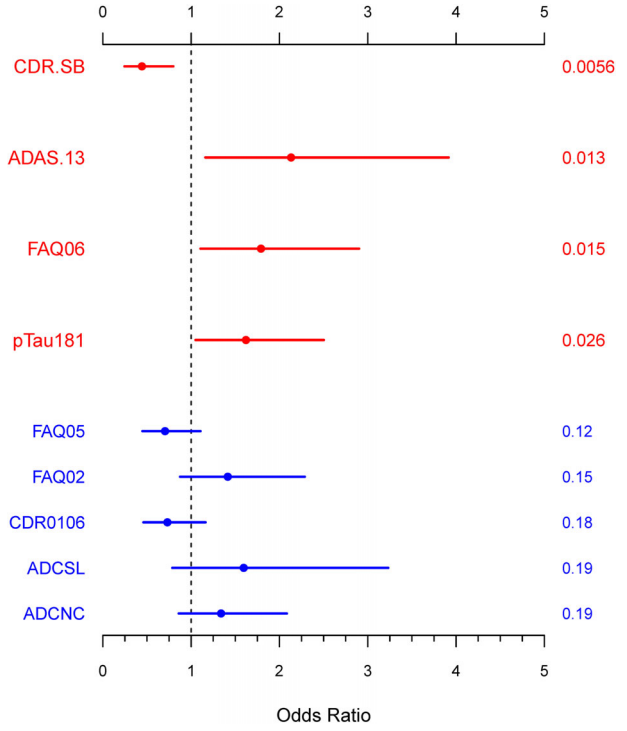

FIGURE 1 Key predictors among baseline plasma pTau181 and baseline clinical assessments in the Bayesian logistic lasso regression model for predicting the 18-month clinical decline in amyloid-positive mild cognitive impairment patients are shown here with odds ratio estimates, 95% confidence intervals, and *p*-values. Significant predictors ($p < 0.05$) are highlighted in red. Although the rest of the predictors are not statistically significant ($p < 0.2$) in this model, they are selected by the model as they help improve the overall prediction accuracy. Notation used for the predictors is as follows: ADAS.13, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCNC, ADAS.13 number cancellation; ADCSL, ADAS.13 tasks for spoken language ability; CDR0106, Clinical Dementia Rating item for personal care; CDR.SB, CDR Sum of Boxes; FAQ02, Functional Activity Questionnaire (FAQ) item for assembling; FAQ05, FAQ items for heating water, making coffee, turning off the stove; FAQ06, FAQ item for preparing a balanced meal.

Upon incorporating baseline plasma pTau181 into the model with baseline clinical assessments, a significant enhancement in the prediction of 18-month clinical decline was observed. The AUROC increased from 70.6% to 74.2% in VC-1 ($p = 0.01$) and from 69.5% to 75.3% in VC-2 ($p < 0.001$). The improvement was also evident in predicting the 36-month MCI to AD progression in VC-2, where the AUROC rose from 71.8% to 79% ($p < 0.0001$). Refer to Table 2 and Figure 2A-C for further details.

Longitudinal clinical data spanning 3 to 10 years in VC-2 was utilized to investigate future time-to-progression to AD among Aβ+ MCI subjects. Specifically, it focused on individuals initially identified at baseline as fast or slow clinical decliners through prediction models. Table 3 summarizes metrics from Kaplan-Meier analysis for time-to-progression and hazard ratios, with 95% confidence intervals from Cox proportional hazards models. The proportionality of hazards assumption was verified by the chi-squared test. Comparable performance was observed in models employing baseline plasma pTau181 alone versus baseline clinical assessments, yielding hazard ratios of 2.88 and 2.26, respectively ($p = 0.17$). Integrating pTau181 into the prediction model alongside clinical assessments significantly improved performance, with the hazard ratio increasing from 2.26 to 3.11 ($p < 0.0001$), underscoring the value of incorporating plasma pTau181 data. Figure 3A–C depicts the nuanced difference in hazard ratios, particularly in Figure 3C, highlighting accelerated future progression among Aβ+ MCI subjects initially predicted as fast progressors. This empirical evidence reinforces the utility of the predictive model, discerning and anticipating varying progression rates in the validation cohort.

As the amyloid positivity of the subjects in the training and validation cohorts was determined via PET assessments, the association of baseline amyloid levels measured via PET Centiloid (CL) with clinical decline and progression was explored. While baseline CL levels were associated with the 18-month clinical decline (AUROC = 58%), unlike plasma pTau181, adding CL to clinical assessments did not significantly enhance the AUROC (70.6% vs 71.1%, $p = 0.479$).

TABLE 2 Performance summary for predicting clinical decline and progression in the two validation cohorts.

	Validation Cohort 1 (Clinical trial)				Validation Cohort 2 (ADNI)					
	18-month clinical decline (CD)				18-month clinical decline (CD)				36-month MCI to AD progression	
Scenarios	Sensitivity	Specificity	AUROC	*p*-value	Sensitivity	Specificity	AUROC	*p*-value	AUROC	*p*-value
pTau181	60.3%	59.6%	64.8%		67.3%	57.5%	69.5%		72.5%	
Clinical	68.3%	63.5%	70.6%	0.01	75.0%	51.7%	69.5%	<0.001	71.8%	<0.0001
pTau181 + Clinical	66.7%	67.3%	74.2%		75.0%	61.7%	75.3%		79.0%	

Note: The performance of the models constructed using the Bayesian logistic lasso regression algorithm for predicting 18-month clinical decline (CD) in Validation Cohorts 1 and 2, and the 36-month progression from MCI to AD in Validation Cohort 2 is summarized here, along with the *p*-value for assessing the improvement in the overall prediction accuracy from adding plasma pTau181 to the clinical assessments in the model. "Clinical" includes baseline cognitive and functional assessments such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale, Clinical Dementia Rating Sum of Boxes, Functional Activity Questionnaire, Mini-Mental State Examination, and their subscores. Age, gender and apolipoprotein E gene ε4 allelic count were considered for selection in all the scenarios.

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; AUROC, area under the receiver operating characteristic curve; CD, clinical decline; MCI, mild cognitive impairment.

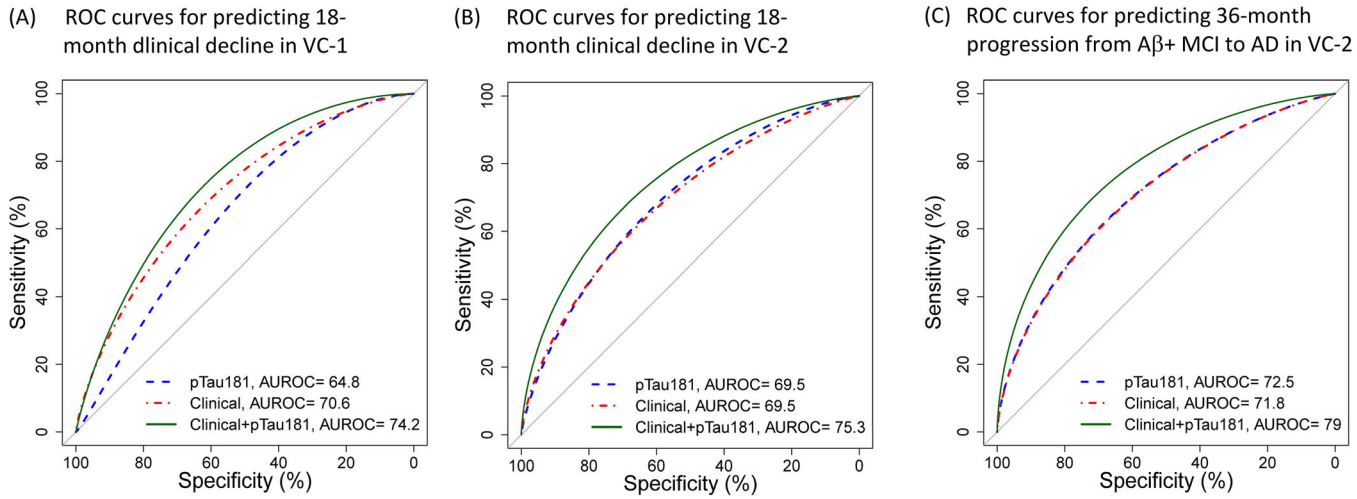

FIGURE 2 The receiver operating characteristic (ROC) curves for predicting the 18-month clinical decline in VC-1 and VC-2 and for predicting the 36-month progression from Aβ+ MCI to AD in VC-2 are shown here in panels A, B, and C, respectively, along with the area under the ROC curves for the different prediction models. The prediction model using baseline plasma pTau181 alone (blue) achieved similar performance as the model using baseline clinical assessments (red). Adding baseline plasma pTau181 to baseline clinical assessments in the model (green) significantly improves the prediction performance. Aβ+, amyloid-positive; AD, Alzheimer's disease; AUROC, area under the receiver operating characteristic curve; MCI, mild cognitive impairment; ROC, receiver operating characteristic; VC-1, first validation cohort; VC-2, second validation cohort.

TABLE 3 Performance summary for predicting the time-to-progression from MCI to AD in the second validation cohort.

	Predicted fast progressor				Predicted slow progressor					
		T2P (months)				T2P (months)				
Scenarios	*N*	Q1	Q2	Q3	*N*	Q1	Q2	Q3	Hazard ratio (95% CI)	
pTau181	88	13	27	73	89	46	87	113	2.88	(1.9, 4.3)
Clinical	100	22	35	87	77	48	83	>120	2.26	(1.5, 3.4)
pTau181 + Clinical	88	13	25	77	89	61	84	>120	3.11	(2.0, 4.7)

Note: Estimates of the median (Q2), first quartile (Q1), and 3rd quartile (Q3) of the time-to-progression (T2P) to AD over the 10-year clinical follow-up period are summarized here along with the hazard ratio estimates for the amyloid-positive mild cognitive impairment subjects in the second validation cohort who were predicted by the models to be either fast or slow progressors. "Clinical" includes baseline cognitive and functional assessments such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale, Clinical Dementia Rating Sum of Boxes, Functional Activity Questionnaire, Mini-Mental State Examination, and their subscores. Demographics (age, gender, body mass index) and apolipoprotein E gene ε4 allelic count were considered for selection in all the scenarios. Abbreviations: AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment; T2P, time-to-progression.

4 | DISCUSSION

In this study, we constructed prognostic models to forecast the pace of clinical decline, defined as fast or slow, among Aβ+ MCI patients within the standard 18-month duration of a clinical trial. These models relied on the baseline clinical (cognitive and functional) assessments and plasma pTau181 measurements. The models were constructed using the BLLR machine-learning algorithm with a TC of 135 placebo-arm subjects pooled from two clinical trials.

When predicting 18-month clinical decline within the validation cohorts, baseline plasma pTau181 showed comparable performance to using baseline clinical assessments alone. Adding plasma pTau181 to the clinical assessments significantly improved the AUROC for predicting 36-month clinical progression from Aβ+ MCI to AD. It also contributed to a more pronounced divergence in the future time-to-progression between those predicted at baseline to be either fast or slow decliners over the follow-up period, highlighting the model's robustness. Although tau PET is more effective than plasma pTau markers,[45] we developed a model using clinical assessments and plasma pTau181, which are more accessible and cost-effective.

As amyloid positivity was determined through PET assessments, we explored the predictive potential of baseline amyloid levels measured via PET CL. Although baseline CL levels were correlated with 18-month clinical decline, adding CL to clinical assessments did not significantly improve predictions. This underscores the absence of a linear or monotonic relationship between brain amyloid and cognitive decline[46–48] and highlights the distinct prognostic utility of plasma pTau181 beyond amyloid status.

In a recent review,[1] it was noted that tau phosphorylation starts early in the Aβ cascade, preceding neurofibrillary tangle

(A) Prediction of time-to-progression to AD of Aβ+ MCI subjects in VC-2 using the model with baseline ***plasma pTau181***

(B) Prediction of time-to-progression to AD of Aβ+ MCI subjects in VC-2 using the model with baseline ***clinical assessments***

(C) Prediction of time-to-progression to AD of Aβ+ MCI subjects in VC-2 using the model with baseline plasma ***pTau181 & clinical assessments***

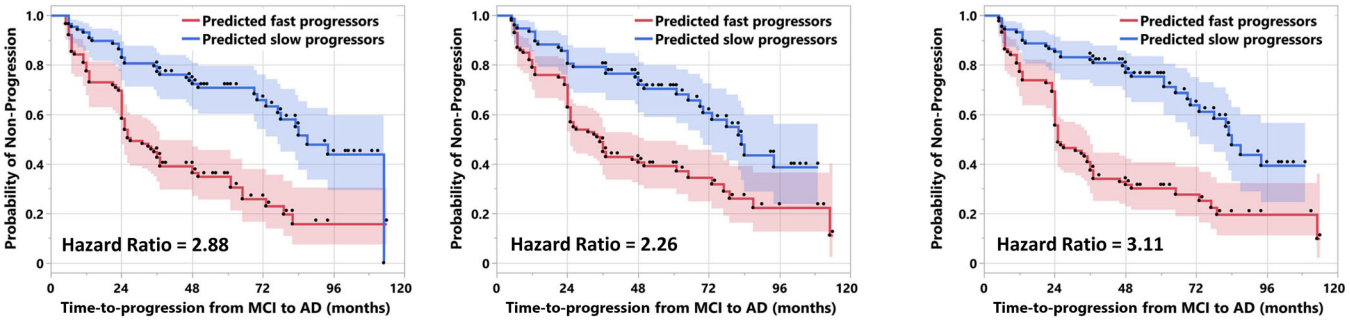

FIGURE 3 Prediction of time-to-progression to AD of Aβ+ MCI subjects in the second validation cohort (VC-2) using the model with baseline plasma pTau181 alone, baseline clinical assessments alone, and both are shown here in panels A, B, and C, respectively, along with the hazard ratio estimates. The prediction models using baseline plasma pTau181 alone achieved similar performance as the model using baseline clinical assessments alone. Adding pTau181 to clinical assessments in the prediction model significantly improved the performance ($p < 0.05$) as visually evident from the greater separation of the time-to-progression curves in panel C, with the hazard ratio increasing from 2.26 to 3.11. Aβ+, amyloid-positive; AD, Alzheimer's disease; MCI, mild cognitive impairment; VC-2, second validation cohort.

accumulation. Elevated pTau isoform levels after Aβ plaque formation may signal disease progression. This study focused on pTau181 due to data limitations, but similar findings are expected with other isoforms, albeit with varied accuracy. Further exploration is planned.

Recent publications have explored the utility of plasma pTau181 and other pTau isoforms for predicting AD progression.[5,7,25] Our prediction models stand out in key ways: (1) They were developed using clinical trial cohorts and validated in both clinical trial and observational research cohorts; (2) They were optimized to predict near-term clinical progression (18 months), relevant for both clinical trials and practice, and effective for predicting longer-term progression (>36 months); and (3) They are based on widely employed baseline clinical assessments and plasma pTau181.

Incorporating individual subscores of the CDR-SB, FAQ, and ADAS-Cog-13 into our prediction models provided insights into specific cognitive and functional domains influencing clinical progression. Key predictors, as shown in Figure 1, indicate that deficits in functional activities such as meal preparation, heating water, assembling, and personal care, along with cognitive tasks related to speech and number cancellation, significantly impact future clinical decline. The BLLR algorithm's selection of these tasks aligns with our definition of clinical decline, incorporating changes from baseline in the CDR-SB. This comprehensive approach ensures a nuanced understanding of the factors contributing to clinical decline.

In light of the restricted number of predictors and the imperative for streamlined and interpretable models conducive to clinical trials and practical application, the choice was made to employ the BLLR machine algorithm for this analysis. The inherent simplicity of the BLLR model, presented in the form of logistic regression coefficients and odds ratio estimates for each selected predictor in the final model, significantly amplifies its interpretative clarity. This simplicity not only fosters a clearer comprehension of the model's outcomes but also renders it pragmatic for seamless integration into both clinical trials and clinical practice. Ensemble machine-learning algorithms such as regularized random forests (RRF) generated comparable predictive factors to BLLR but did not outperform it in the two validation cohorts. The AUROC for models using plasma pTau181 and clinical assessments was 73.7% and 72.7% for RRF, not surpassing those of the BLLR (Table 2).

The BLLR algorithm identified crucial predictors through a lasso-based regularization method, using the spike and slab double-exponential prior.[37] This approach streamlined model complexity by shrinking features with marginal contributions to clinical decline to zero, mitigating overfitting, and enhancing generalizability and performance across new datasets. Importantly, our algorithm provided an unbiased identification of predictive features, eschewing preselection biases.

As these prognostic models use only the baseline (initial visit) clinical assessments and plasma pTau181 to predict the clinical decline and progression of Aβ+ MCI patients, there are wide-ranging applications for these models across drug development and real-world clinical practice. In drug development, utilizing these models at baseline can effectively enrich clinical trials with subjects anticipated to undergo mild to moderate clinical decline. This targeted enrichment substantially reduces sample size requirements, as highlighted in recent publications,[49,50] with reported reductions of up to 50%. Despite notable variability, as one study reported an R^2 of 0.29[49] and another showed an AUROC of 72%,[50] their impact on clinical trial design remains significant. Considering our models achieve similar prediction performance, with AUROC values reaching 74.2% and 75.3% in the two validation cohorts (Table 2), we anticipate a comparable impact on clinical trial enrichment. Additionally, these models offer opportunities for patient stratification within clinical trials, allowing for post hoc evaluation of treatment effects in subgroups predicted to experience varying rates of progression.

A limitation of the proposed models is that certain cognitive and functional assessments may not be accessible in all settings. Assessments like FAQ might be omitted in some clinical trials, and ADAS-Cog-13 and CDR-SB are not routinely conducted in clinical practice. While the direct application of the proposed models may face constraints in settings where specific assessments are absent, a notable strength is their adaptability. In instances where certain assessments are unavailable, the models can be reconstructed using available assessments, with performance reevaluated. This study's methods provide a framework for customization, accommodating variations in available data.

Another limitation is the prediction accuracy of the models for plasma pTau181 when using different assay formats. While standardizing pTau181 concentration ensured comparability and robust performance across cohorts, caution is needed with different assay formats. Evaluation on a case-by-case basis is advisable, and the models may need reconstruction using data from alternative assay formats to maintain predictive efficacy.

In summary, this study highlights baseline plasma pTau181 as a prognostic indicator, particularly for identifying Aβ+ MCI subjects likely to experience accelerated clinical decline within an 18-month clinical trial. Integrating this biomarker with initial clinical assessments substantially enhances outcome predictions, including forecasting Aβ+ MCI progression to AD over 36 months and overall time-to-progression. This approach can be adapted to other biomarkers as they undergo evaluation in clinical studies.

ACKNOWLEDGMENTS

The authors thank the patients, their families, and the sites who participated in these studies. The authors also thank Leema Krishna Murali, Kiran Putti, Saad Anbari, Huihong Chen, Malathi Reddy, and Michio Kanekiyo for their help with the preparation or understanding of clinical data files. The authors are grateful to the anonymous reviewers for their constructive and helpful comments, which have improved the quality and clarity of the manuscript. The authors are grateful to Professor Danielle Harvey from the University of California, Davis, for her invaluable guidance related to the ADNI database. The authors would like to acknowledge the editorial support from Lisa Yarenis (Eisai Inc.) and JD Cox, PhD, and Mayville Medical Communications, funded by Eisai Inc. and in compliance with Good Publication Practice 4 ethical guidelines (DeTora et al., Ann Intern Med 2022; August 30, 2022 [epub ahead of print]). Collection and sharing of one of the datasets used in this project were obtained from the ADNI database (adni.loni.usc.edu) and thereby funded by ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). As such, the investigators within the 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 can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; Euroimmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Funding for the studies, analyses, and editorial support was provided by Eisai Inc.

CONFLICT OF INTEREST STATEMENT

VD, YH, HH, LK, SD, and MI are employees of Eisai Inc. HH is a Reviewing Editor and previously a Senior Associate Editor for the journal *Alzheimer's & Dementia*, and he was not involved in the editorial process. There are no competing disclosures to report for DAL. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All the participants in the studies used for the training and validation cohorts in this manuscript provided written informed consent.

CLINICALTRIALS.GOV IDENTIFIERS

NCT02956486 (MissionAD1), NCT03036280 (MissionAD2), NCT01767311 (Lecanemab Study 201)

ORCID

Viswanath Devanarayan https://orcid.org/0000-0003-2059-9252
Yan Helen Hu https://orcid.org/0000-0003-3269-4505
Harald Hampel https://orcid.org/0000-0003-0894-8982

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Devanarayan V, Llano DA, Hu YH, et al. Plasma pTau181 enhances the prediction of future clinical decline in amyloid-positive mild cognitive impairment. *Alzheimer's Dement*. 2024;16:e12621. https://doi.org/10.1002/dad2.12621