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FEATURED ARTICLE

Personalized prediction of progression in pre-dementia patients based on individual biomarker profile: A development and validation study

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[*] Data used in preparation of this article were obtained from the MEMENTO cohort study and the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within both studies contributed to the design and implementation of the respective studies and provided data but did not participate in analysis or writing of this report. A complete listing of MEMENTO investigators can be found at http://memento-cohort.org/ and 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.

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Abstract

Introduction: The prognosis of patients at the pre-dementia stage is difficult to define. The aim of this study is to develop and validate a biomarker-based continuous model for predicting the individual cognitive level at any future moment. In addition to personalized prognosis, such a model could reduce trial sample size requirements by allowing inclusion of a homogenous patient population.

Methods: Disease-progression modeling of longitudinal cognitive scores of pre-dementia patients (baseline Clinical Dementia Rating ≤ 0.5) was used to derive a biomarker profile that was predictive of patient's cognitive progression along the dementia continuum. The biomarker profile model was developed and validated in the MEMENTO cohort and externally validated in the Alzheimer's Disease Neuroimaging Initiative.

Results: Of nine candidate biomarkers in the development analysis, three cerebrospinal fluid and two magnetic resonance imaging measures were selected to form the final biomarker profile. The model-based prognosis of individual future cognitive deficit was shown to significantly improve when incorporating biomarker information on top of cognition and demographic data. In trial power calculations, adjusting the primary analysis for the baseline biomarker profile reduced sample size requirements by ≈10%. Compared to conventional cognitive cut-offs, inclusion criteria based on biomarker-profile cut-offs resulted in up to 28% reduced sample size requirements due to increased homogeneity in progression patterns.

Discussion: The biomarker profile allows prediction of personalized trajectories of future cognitive progression. This enables accurate personalized prognosis in clinical care and better selection of patient populations for clinical trials. A web-based application for prediction of patients' future cognitive progression is available online.

1 | BACKGROUND

Individual Alzheimer's disease (AD) patient prognosis or the power to detect treatment effects in interventional clinical trials in neurodegenerative diseases is often hampered by substantial differences in disease progression on the patient level.[1] In AD dementia stages, it is well established that cognitive ability at baseline is a primary predictor of future rate of decline,[2] due to an increasing rate of

cognitive and functional deterioration along the course of disease.[3] In pre-dementia stages there is typically little or no measurable cognitive deficit with variation in cognitive scores being more related to non–disease-specific differences than disease pathology load. The large variation in disease trajectories between individuals blurs signals of treatment effect and forces AD trials to be extensively large and highly expensive. Sample sizes of up to 2000 patients per arm followed over a duration of 4 years are required to achieve 80% power of a modestly effective drug in preclinical AD.[4] Effective patient stratification could reduce variation of cohorts considerably and increase power to detect treatment effects.[5] For example, it would require ≈600 subjects with mild cognitive impairment (MCI) per arm followed over a 24-month study to reach 80% power for detecting a 25% slowing in the annual rate of decline of Clinical Dementia Rating (CDR)[6] sum of boxes, while an enriched patient population with positive amyloid biomarkers and evidence of brain atrophy would reduce the sample size requirements by 58%.[5]

Traditionally, prognosis of future cognitive progression of individuals has been based on cognitive criteria. However, as more focus has been on selecting patients at early stages of dementia, cognitive cut-offs become of limited value for recruiting a homogeneous patient population as two patients with similar cognitive level could have quite distinct future cognitive progression.[7] Incorporating biomarker information for patient staging and prediction of future cognitive decline have been extensively investigated and shown to have a positive effect on stratification.[1,5,8–12] Accurate predictions of future cognitive decline for pre-dementia patients could be used to detect at-risk patients, to improve clinical trials, and to aid health-care practitioners determine treatment paths for patients, as illustrated in Figure 1. The recently finalized TADPOLE challenge[13] gathered results from 92 algorithms for predicting the future progression of patients at risk of AD on three outcomes: clinical diagnosis, cognitive decline, and ventricle volume. The results showed in general that inclusion of information from diffusion tensor imaging and cerebrospinal fluid (CSF) biomarkers improved predictive performance of the prediction algorithms.

Most works studying the effect of biomarker measures for patient stratification and prediction of future progression rely on discrete grouping of patients. Many use predefined clinical groupings of patients (e.g., cognitively normal, MCI, dementia) and predict these states or transitions between them using biomarkers.[12,14] An alternative approach is to group patients based on abnormality of biomarker measures and study progression of these biomarker-defined groups.[15,16] The recently proposed ATN (amyloid deposition, tauopathy, and neurodegeneration) framework[17] is an example of the latter. The ATN framework divides individuals into eight distinct groups based on biomarker abnormality profiles, with the amyloid-positive profiles being related to different stages of the AD pathological cascade.[18] However, the dichotomization of a continuous biomarker measure into normal or abnormal depends on the modality used to measure the biomarker and results in a loss of predictive power of future decline.[19] In an important recent work, van Maurik et al.[20] used non-dichotomized ATN biomarker profiles to predict dementia risk for individuals with MCI, showing that a combined ATN profile based on both CSF and imaging improved the predictive performance over models including only imaging or CSF biomarkers. This approach avoids the loss of information that would result by dichotomizing biomarker profiles, but it does lose information by using a binary outcome (progression to dementia). A similar approach was used for plasma biomarkers in a recent study that in addition to progression to dementia predicted future cognitive decline.[21]

Disease progression modeling over a time continuum can be used to describe the time evolution of clinical scales and biomarkers on a natural disease time scale.[3,22–24] Compared to conventional approaches for predicting future cognitive trajectories, disease progression modeling enables better use of the data and more stable estimates by assuming that patient trajectories are randomly perturbed observations of the progression along a continuum. Using such approaches, it has previously been demonstrated that individual patient progression along a disease continuum can be predicted using a

RESEARCH IN CONTEXT

1. **Systematic review**: Reviewing the literature, we found many studies linking fluid and imaging biomarkers to cognitive status and rate of decline in dementia. However, only a few studies addressed the added value of biomarkers compared to conventional cognitive assessments and fewer studied combinations of biomarkers. Furthermore, almost all the reviewed studies categorized patients in discrete disease stages based on either cognitive cut-offs or biomarker positivity. Such dichotomization disregards the continuously progressive nature of cognitive decline and potentially leads to considerable variation in individual cognitive progression patterns for study populations due to large heterogeneity within the discrete groups.
2. **Interpretation**: Our study refrains from dichotomizing clinical scales and biomarker measures but uses the continuous information to stage patients along a disease continuum. The analyses suggest that including information from a combination of biomarkers improves predictions of patients' current and future progression along the disease continuum, which is highly useful in clinical practice. We validated both internally and externally that the developed biomarker profile improves prediction beyond cognitive scores. In addition to personalized prognosis, this improved knowledge of future cognitive progression of individuals can be used to select more homogeneous cohorts for clinical trials which has potential for decreasing sample size requirements.
3. **Future directions**: Future work should address the value of including alternative biomarkers and confirm the utility of the biomarker profile in the setting of interventional clinical trials.

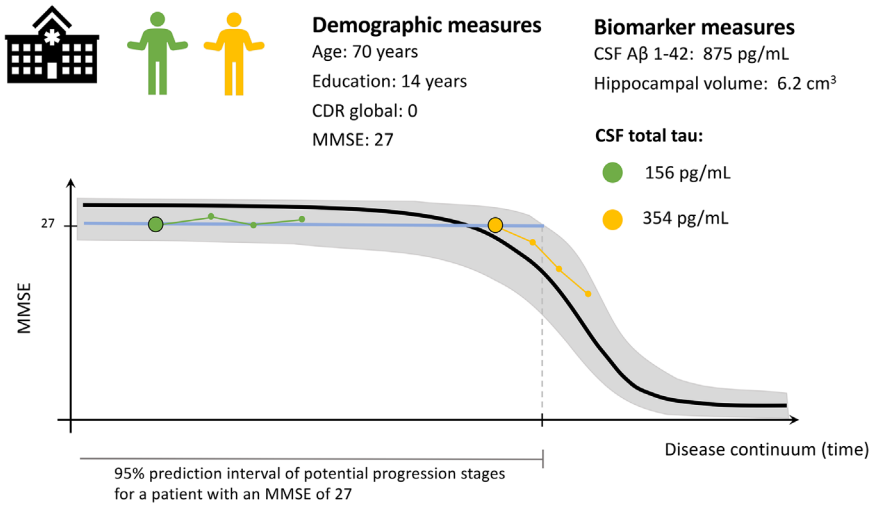

FIGURE 1 Two patients (green and yellow) with identical characteristics, Mini-Mental State Examination (MMSE) scores, and biomarker values except for cerebrospinal fluid (CSF) total tau. Due to the wide prediction interval of possible disease progression stages in pre-dementia, the future cognitive progression cannot be accurately predicted from cognitive scores. Knowledge of differences in biomarkers may improve the staging of patients along the disease continuum. Aβ, amyloid beta; CDR, Clinical Dementia Rating

combination of biomarkers.[3] However, this prediction model required simultaneous collection of CSF, magnetic resonance imaging (MRI), and two positron emission tomography (PET) scans, making it highly impractical for implementation in clinical practice. Furthermore, these prediction results have not been externally validated.

The aim of this study is developing and validating a biomarker-based continuous predictive model allowing reduction in trial sample sizes together with defining the individual cognitive prognosis at any future moment. The model is developed using data from the MEMENTO study[25] and externally validated using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. A web-based application is available for predicting future cognitive decline and location on the disease continuum of a patient based on user-specified demographics and biomarker measures (see https://disease-progression.shinyapps.io/disease_progression/).

2 | METHODS

2.1 | Data description

Patient-level data from the MEMENTO study[25] were used for model development. The MEMENTO cohort includes patients from 26 university-based memory clinics scattered across France. Included subjects either had very mild to mild cognitive impairment (defined by cognitive abilities at least one standard deviation below age, sex, and education level–adjusted norms) or had subjective cognitive complaints and were at least 60 years old. Individuals were required to have a CDR global score of 0 or 0.5 and no diagnosis of dementia at baseline. At the time of their inclusion, participants underwent 3DT1 brain MRI, an optional lumbar puncture, and a fluorodeoxyglucose (^{18}FDG) PET scan.

The development of a biomarker profile predictive of a patient's future cognitive trajectory along the disease continuum included the following baseline biomarker candidates: CSF measures of total tau, phosphorylated tau (p-tau 181), amyloid beta (Aβ)1-42, Aβ1-40, and their ratio Aβ1-42/Aβ1-40 based on the INNOTEST sandwich enzyme-linked immunosorbent assay (Fujirebio); hippocampal volume (volumetric MRI using SACHA software[26]); global FDG-PET uptake; and both AD-signature meta-region of interest (ROI) thickness and volumes[27] (derived using FreeSurfer).

Individuals with complete biomarker data were included in the development set. Study subjects were split into two groups based on their baseline CDR global score: an asymptomatic group with a baseline CDR global score of 0 and a MCI group with a baseline score of 0.5.

The measure for determining cognitive decline was longitudinal Mini-Mental State Examination scores[28] (MMSE; range 30 to 0 with low scores indicating more severe cognitive impairment).

The biomarker profile construct was externally validated using subjects from the ADNI (adni.loni.usc.edu) cohort. Subjects were included in the external validation study if they had the same biomarker measures at baseline and a baseline CDR global score $\leq$0.5. The differences in biomarker assays between MEMENTO and ADNI is described in Table S1 in supporting information. Up to 3 years of follow-up data were included in the analyses.

2.2 | Statistical analysis

Longitudinal MMSE scores were modeled using a nonlinear mixed-effects disease-progression model.[3] The model estimates a population-level cognitive trajectory along the disease continuum based on the observed longitudinal trajectories. This population-level trajectory describes the general progression of cognitive decline that one would expect an individual to have as they progress through the disease continuum. A subject-level random effect is included in the model to describe the deviation in how long the subject is progressed along the population-level disease continuum (horizontal variation). This model structure enables inclusion and tests the predictive ability of biomarkers on patients' progression state along the disease continuum.

Assume n subjects have been included for analysis and the ith subject has been assessed at m_i time points $t_{i1} < t_{i2} < \ldots < t_{im_i}$

(e.g., at baseline/0 months, 6 months, 12 months). The number of observed time points m_i and observation times may vary across subjects. Let $y_i = (y_{i1}, \dots, y_{im_i})$ denote the vector of longitudinally observed MMSE scores for the ith subject and in addition let x_i be a time-invariant covariate vector for subject i with associated unknown model parameters β. In the following analyses the considered covariates will be demographic information and baseline biomarker measures. The longitudinal progression of the MMSE scores are modeled as

$$y_{ij} = \mu\left(t_{ij} - x_i^T\beta - z_i\right) + \varepsilon_{ij},\ i = 1, \dots, n,\ j = 1, \dots, m_i,$$

where μ is a function modeling the population-level time-evolution of cognitive decline, $z_i \sim N(0, \tau^2)$ is the random subject-specific variation in progression along the continuum, and $\varepsilon_{ij} \sim N(0, \sigma^2)$ is independent identically distributed Gaussian noise.

The population-level cognitive trajectory μ is modeled as a generalized logistic function

$$\mu(t) = A + \frac{K - A}{(1 + \exp(-Bt))^v}$$

where A and K are the lower and upper asymptotes, respectively; B describes the rate of progression; and v controls where the maximal rate of decline occurs. Because MMSE scores are restricted to values within [0, 30], the lower asymptote A was fixed at 30 (no measurable cognitive deficit) and the upper asymptote K was fixed at 0 (severe cognitive deficit). The shape parameters B, v were estimated from the data. Specifically, the rate of progression could depend on covariates $B = B_0 + x_{B,i}^T\beta_B$.

At each observed time point, t_{ij}, representing a visit of patient i, the model assumes that patient i will be progressed to location $t_{ij} - x_i^T\beta - z_i$ on the disease continuum, which is described by the population-level disease trajectory μ. The model predicts these individual locations of patients along the disease continuum such that the observed trajectory of MMSE scores aligns with the population level of decline. The individual location of subject i at baseline $t_{i1} = 0$ is split into a fixed effect $x_i^T\beta$ that depends on covariates (e.g., age, level of education, biomarkers) and a subject-specific random effect z_i that models the residual variation in the positioning that cannot be attributed to covariate effects. This prediction of location of a patient along the disease continuum can be considered a continuous way of staging patients. Usually patients are staged by categorizing them into discrete groups, but in the present study, we estimate a full disease continuum and predict the relative staging of patients based on their disease severity in a fully continuous manner.

All model parameters were estimated using maximum-likelihood estimation, and predictions of progressions along the disease continuum were the maximum a posteriori prediction of the fitted model based on each individual's baseline scores and covariates.

In the development study, four models were compared for investigating the effect of different biomarker modalities for outlining the disease continuum. All four models included a covariate effect of baseline CDR global score on the location along the continuum. The base model used forward selection to estimate the covariate effects of education level, sex, and age, on both the rate of decline, B, and disease progression. The three other models were built from the base model and used forward selection to include covariate effects of baseline biomarker observations. The three models were: a model including MRI biomarkers, a model including CSF biomarkers, and the full biomarker model including both MRI and CSF biomarkers as well as FDG PET. The forward selection procedure was based on the Akaike information criterion.[29]

To investigate the effect of cut-offs for dichotomizing amyloid and tau positivity based on CSF Aβ1-42 and p-tau, two additional CSF models were evaluated. The first model used the continuous biomarker values for predicting the location of subjects on the disease continuum, and the second model used amyloid and tau positivity based on prespecified cut-offs for its prediction. In addition to CSF p-tau and Aβ1-42, both models included the terms from the base model.

2.3 | Internal and external validation

The findings in the development study were validated internally and externally. Individuals not included in the development set due to partially missing biomarker data, but who had complete biomarker data for the selected biomarker profile, were used as an internal validation set. The internal validation investigated the predictive performance of the models on this held-out validation set in MEMENTO. The external validation study evaluated the identified biomarker models from the development study on data from the ADNI cohort. Because of differences in the CSF biomarker assays in ADNI and MEMENTO (see Table S1), CSF biomarkers were normalized to ensure that parameters were comparable across cohorts. Because ADNI includes subjects with no cognitive deficit, the normalization was based on the distribution of the subgroup with a CDR global score 0.5 to ensure comparability across cohorts. The normalization process consisted of independently shifting and scaling each biomarker variable in each cohort such that the minimal normalized value in the group of subjects with CDR global score of 0.5 at baseline was 0 and the maximal value was 1.

The predictive power for patients' future cognitive decline measured via MMSE trajectories with and without biomarker profiles were evaluated by the root mean squared error (RMSE). Differences in predictive performance between base and biomarker models were tested using paired Wilcoxon rank sum tests.

2.4 | Exploratory analyses

The normalization procedure for CSF biomarker values assumes that the subgroups with CDR global score 0.5 in the MEMENTO and ADNI cohorts are comparable and that the measures from the different assays are equivalent up to a linear transformation. Furthermore, it was assumed that volumentric MRI measures were directly comparable between cohorts. To explore if these assumptions impacted the results in the external validation study, a sensitivity analysis was done

in which original biomarker values were used, but the coefficients were recalibrated. The details and results of this analysis based on the base and full biomarker model are available in the supporting information.

To investigate the correlations between biomarker and predicted patient progression on the disease continuum, partial correlation analyses were performed in both the MEMENTO and ADNI cohorts. The partial correlations measure the degree of association between pairs of variables when adjusting for all other observed variables. The analysis included patient characteristics, biomarkers, and predicted disease progression obtained from base models with parameters estimated separately for each cohort. The analyses assessed the independent contribution of each biomarker to the correlation with the predicted disease progression. These contributions were compared across cohorts.

2.5 | Clinical trial power analyses

For power calculations, we selected ADNI subjects with complete 13-item Alzheimer's Disease Assessment Scale-Cognitive subscale[30] (ADAS-Cog) scores at baseline, 6, 12, and 24 months (follow-up times required to be within 2 months of visit time). We modeled trial power under two different inclusion criteria. The first group, CDR 0.5, included subjects with baseline CDR global score 0.5. The second group, Biomarker profile cut, included subjects with biomarker-based predicted progression within the interquartile range of the CDR 0.5 group, but no requirement on CDR global score to evaluate if this resulted in a more homogenous patient group.

In each of the above scenarios, we estimated the standard deviations of ADAS-Cog changes at 6, 12, and 24 months separately using two different linear regression models. The first adjusted for baseline ADAS-Cog score, baseline CDR global score (only in the second scenario), actual time since baseline, age, sex, and education level. The second model adjusted for baseline ADAS-Cog score and the biomarker-profile–based prediction of disease progression $(B_0 + x_{B,i}^T \beta_B)(t_{ij} - x_i^T \beta)$ at the follow-up time t_{ij}. Based on the estimated standard deviations, we computed the number of patients needed to achieve 90% power for detecting a 1-point treatment effect on the 13-item ADAS-Cog.

3 | RESULTS

3.1 | Development and internal validation

The MEMENTO cohort included 2323 subjects. The distribution of available biomarker measures within patients is shown in Figure S1 in supporting information. Three hundred eleven patients formed the development set used to fit the disease progression models. Figure 2 shows the consort diagram for the MEMENTO cohort. The median age was 69.5 years (range 42 to 91), with 54% women. The median number of years of education was 16 (range 13 to 18). The internal validation set used to examine generalizability of the model's predictive performance consisted of 59 subjects. These 59 subjects were similar to the subjects in the development set on all measures. Baseline characteristics are given in Tables S2 and S3 in supporting information.

The base model was fitted to the development dataset. The forward selection search included effects of education and age on the patient's progression stage along the disease continuum and rate of cognitive progression. No effect of sex was found for either parameters.

The results suggested that patients with higher level of education had better cognitive scores in the early disease stages, but slightly accelerated decline in the later stages and that younger patients declined slower than older (Figure S2 in supporting information). While earlier onset of AD has often been associated with increased rate of cognitive decline,[2] the current study had no requirements for the etiology of symptoms that led to a subject visiting a memory clinic. Thus, the apparent contradictory finding of slower rate of decline in younger patients is likely due to differences in etiology, which is corroborated by an observed Spearman correlation of −0.34 ($P < .0001$) between CSF Aβ1-42 to Aβ1-40 ratio and age.

Three biomarker models were fitted using forward selection to include normalized biomarker values to explain variation in predicted future cognitive trajectories in the base model. The MRI model included measures of hippocampal volume, AD-signature meta-ROI thickness and AD-signature meta-ROI volume. The CSF model included CSF measures of total tau, Aβ1-42, and Aβ1-40 and after the selection procedure the full biomarker model included total tau in CSF, hippocampal volume, Aβ1-42 in CSF, AD-signature meta-ROI thickness, and Aβ1-40 in CSF. For an overview of the models and included variables see Table 1.

Parameter estimates, model diagnostics, and instructions for doing the calculations for predicting a patient's future cognitive decline is available in the supporting information (pp. 2–3 and Table S4).

The predictive performance of all four models (base, MRI, CSF, and the full biomarker model) were compared for both the development and internal validation set. Figure 3 shows the model fit and predicted progression of patients on the disease continuum for the base and biomarker model in the development and internal validation set. Examples of the difference between subject-specific predicted locations for the two models are shown in Figure 4. The predictions in both figures included the baseline MMSE score. The results of the predictions excluding baseline MMSE are shown in Figure S3. The results in Table 2 show that including information from the full biomarker profile significantly improved predictions in the validation set compared to the base model ($P = .0004$ without MMSE; $P < .0001$ with MMSE). This was not the case for the MRI model, which showed comparable results with the base model on the validation set ($P = .91$ without MMSE; $P = .33$ with MMSE). The CSF model was significantly better at predicting future cognitive decline compared to the base model ($P = .0077$ without MMSE; $P < .0001$ with MMSE). Compared to the full biomarker profile, the CSF model performed worse on the development set ($P = 0.0042$ without MMSE; $P < .0001$ with MMSE) but showed comparable results on the internal validation set ($P = .20$ without MMSE; $P = .31$ with MMSE). Table S5 in supporting information presents the difference in RMSE for the MRI and CSF models relative to the full biomarker model.

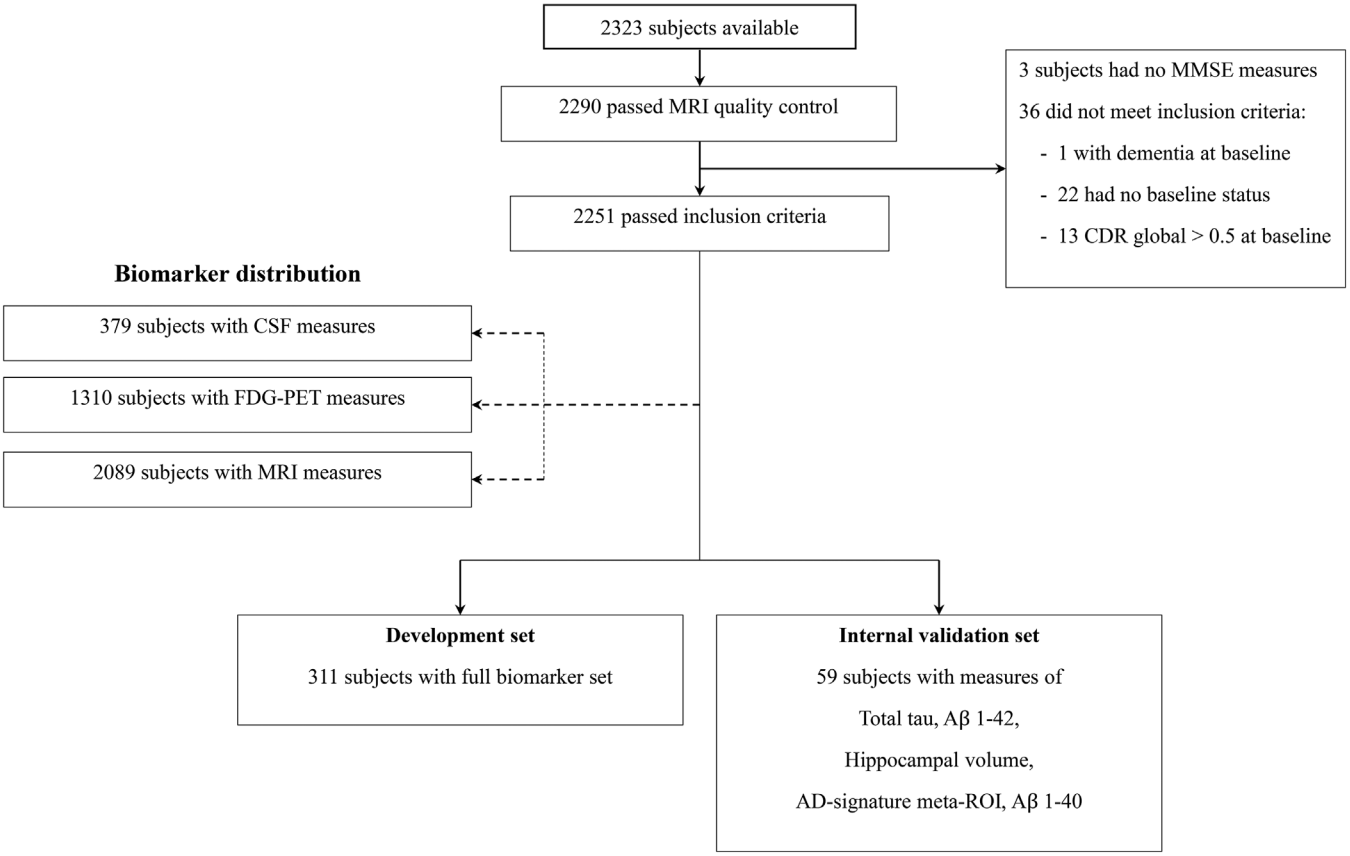

FIGURE 2 Consort diagram for the MEMENTO cohort. Aβ, amyloid beta; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; ROI, region of interest

TABLE 1 Overview of the presented models and which variables are included for predicting the future cognitive decline and continuous staging of patients

	Demographics		MRI			CSF			
	Education	Age	AD-signature thickness	Hippocampal volume	AD-signature volume	Total tau	p-tau	Aβ1-42	Aβ1-40
Base	X	X							
MRI	X	X	X	X	X				
CSF	X	X				X		X	X
Full biomarker	X	X	X	X		X		X	X
CSF continuous	X	X					X	X	
CSF discrete	X	X					X	X	

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging

The effect of using continuous measures of Aβ1-42 and p-tau compared to classifications of amyloid and tau positivity on the predictive performance are presented in Table 3. The results of the models were very similar suggesting only small differences in using the discrete measures of CSF Aβ1-42 and p-tau compared to the continuous biomarker values for predicting future cognitive decline in a pre-dementia population.

For further comparison of the proposed disease progression model's predictive performance, a random forest and a slope model were fitted to the development set and predictions were made on the development and validation sets with and without biomarker information (Table S6 in supporting information). The biomarker models included the five biomarkers that were selected for the full biomarker profile. For all models the predictive performance improved when including

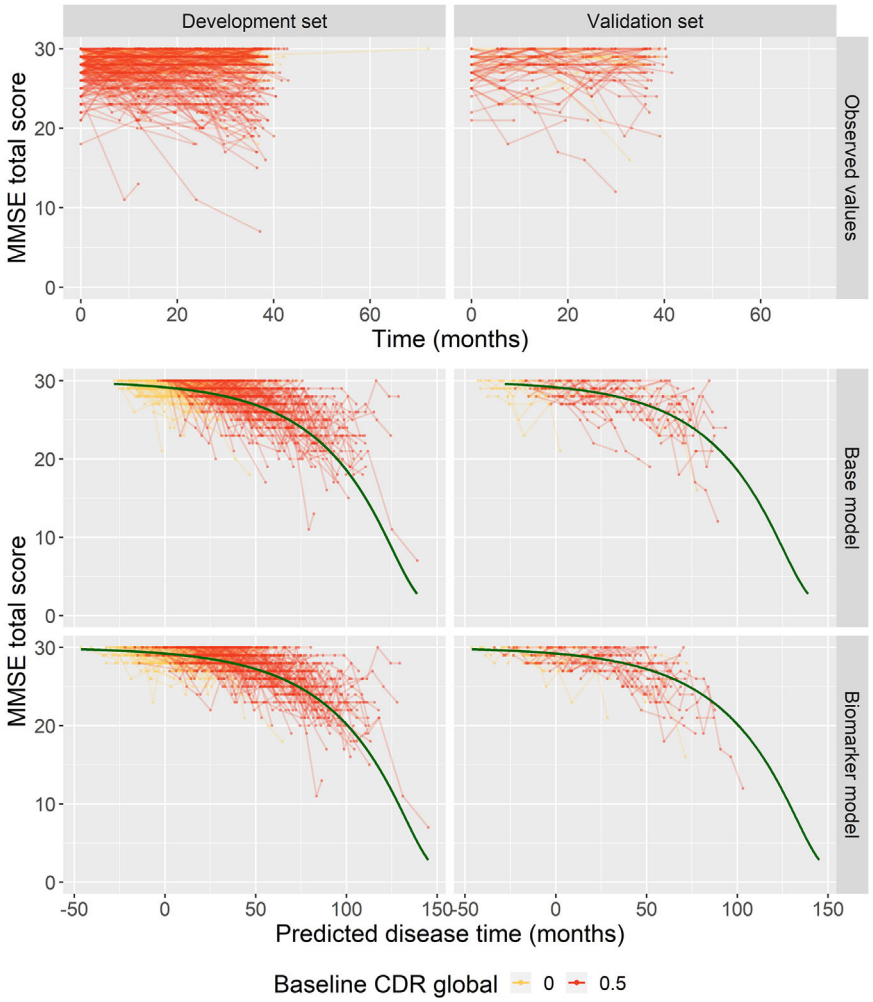

FIGURE 3 Results for the MEMENTO cohort for development and validation set (left and right column, respectively) Top row, The observed Mini-Mental State Examination (MMSE) scores plotted against months since baseline. Middle row, Predicted disease progression stages along the disease continuum of base model and estimated mean trajectory (green). Bottom row, Predicted disease progression stages of the biomarker model and estimated mean trajectory (green). Time zero on the disease continuum is defined as the average predicted disease time at baseline of subjects with a baseline level of Clinical Dementia Rating (CDR) global at 0

biomarker information, and on the internal validation set, the proposed parametric disease progression model including baseline biomarker profile and MMSE score performed best among all models.

3.2 | External validation on ADNI

The developed biomarker model was externally validated on individuals from the ADNI cohort. The external validation set consisted of 610 patients (Figure 5). Baseline characteristics of the individuals in the external validation set are given in Table S2.

The RMSEs of the ADNI predictions calculated based on the developed base, MRI, CSF, and full biomarker model are given in the right-hand column of Table 2. The results validated that incorporating different biomarker modalities gave the greatest improvement of the predictive performance relative to the base model ($P < .0001$ both with and without baseline MMSE). The CSF model did also significantly improve prediction of future cognitive decline compared to the base model ($P < .0001$ without baseline and $P = .0013$ without baseline MMSE); however, the MRI model was only significantly better when incorporating the baseline MMSE measure ($P = .28$ without baseline and $P = .0002$ with baseline MMSE). The full biomarker model showed significantly better performance compared to the MRI and CSF model (full biomarker model vs. MRI model with baseline MMSE $P = .0345$; all other $P < .0001$). The RMSEs are presented in Table S5. Figure 6 shows the predicted progression stages along the disease continuum for patients based on the base and biomarker model for the ADNI cohort. Three patients are highlighted for comparison.

The external comparison of the continuous CSF model compared to the discrete model showed a significant improvement of the continuous model ($P < .0001$) when incorporating the baseline MMSE score for prediction of future cognitive decline. The RMSEs are shown in Table 3.

3.3 | Exploratory analyses

Results of the recalibration analysis suggested little to no gain of recalibrating the full biomarker model in ADNI. The recalibration results are available in the supporting information.

The base model was fitted independently on the MEMENTO and ADNI cohorts. Partial correlations between patient characteristics,

TABLE 2 Root mean squared errors measuring the model performance of predicting future cognitive decline in MEMENTO and ADNI

		MEMENTO				ADNI			
		Relative to base model				Relative to base model			
		Base	ΔMRI	ΔCSF	ΔFull	Base	ΔMRI	ΔCSF	ΔFull
Without baseline MMSE	Development	2.37 (2.19, 2.57)	−0.11 (−0.16, −0.06)	−0.16 (−0.23, −0.08)	−0.28 (−0.36, −0.21)	-	-	-	-
	Validation	2.74 (2.22, 3.28)	−0.075 (−0.19, 0.06)	−0.17 (−0.30, −0.01)	−0.28 (−0.45, −0.09)	2.66 (2.46, 2.87)	0.019 (−0.03, 0.07)	−0.22 (−0.34, −0.09)	−0.46 (−0.55, −0.38)
With baseline MMSE	Development	2.37 (2.16, 2.60)	−0.11 (−0.14, −0.08)	−0.14 (−0.18, −0.11)	−0.24 (−0.29, −0.19)	-	-	-	-
	Validation	2.21 (1.98, 2.45)	−0.081 (−0.19, 0.03)	−0.29 (−0.41, −0.16)	−0.31 (−0.45, −0.18)	2.25 (2.08, 2.43)	−0.11 (−0.18, −0.04)	−0.082 (−0.12, −0.04)	−0.23 (−0.29, −0.18)

Notes: MMSE values were predicted up to 3 years after baseline. Predictive performance of four models are shown: the base model including effects of education and age, the MRI model including additionally two MRI measures, the CSF model based on three CSF measures, and the full model including both information from MRI and CSF measures for predicting patient location on the disease continuum and future cognitive progression. Negative Δ-values indicate better prediction than the Base model. Bootstrapped 95%-CIs are shown in parentheses.
Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CI, confidence interval; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

FIGURE 4 Examples of future predicted decline of three patients in the development set for both base and biomarker model. The observed Mini-Mental State Examination (MMSE) scores of patients are shown with dashed colored lines and the model predicted scores by the colored solid lines. The black dashed lines represent marginal 95% prediction intervals for each model conditional on the continuous staging. The continuous staging is determined by including the baseline MMSE score

biomarkers, and predicted disease progression stages are compared across cohorts and shown in Table 4. There were substantial partial correlations (i.e., explained variation after adjusting for all other biomarkers) between the CSF measures (all partial correlation magnitudes >0.3), which may be partially ascribed to the biomarkers being measured from the same physical sample. Additionaly, there were negative partial correlations between age and hippocampal volume and composite thickness score, suggesting an age-related reduction of the corresponding brain areas that is independent of the biomarkers and predicted disease progressions. The effects were comparable across cohorts. The biomarkers with greatest independent effects on patient progressions in the MEMENTO cohort were hippocampal volume, Aβ1-42, and total tau. In comparison, the biomarkers with the largest effects on progressions in the ADNI cohort were total tau, AD-signature meta-ROI thickness, and Aβ1-40. These apparent differences are partially due to correlations between biomarkers (see Table S7 in supporting information), which is corroborated by the agreement across cohorts of the directional effects of biomarkers on the predicted progression stages in the partial correlation analysis that adjusts for these correlations (Table 4).

TABLE 3 Root mean squared errors measuring the model performance of predicting future cognitive decline in MEMENTO and ADNI

		MEMENTO		ADNI	
		Dichotomized CSF	ΔContinuous CSF	Dichotomized CSF	ΔContinuous CSF
Without baseline MMSE	Development	2.27 (2.09, 2.45)	−0.028 (−0.066, 0.012)	–	–
	Validation	2.50 (2.03, 2.99)	0.033 (−0.031, 0.10)	2.49 (2.31, 2.68)	−0.019 (−0.07, 0.03)
With baseline MMSE	Development	2.30 (2.10, 2.51)	−0.031 (−0.048, −0.013)	–	–
	Validation	1.96 (1.72, 2.18)	−0.01 (−0.076, 0.061)	2.20 (2.04, 2.36)	−0.072 (−0.097, −0.048)

Notes: Comparison of predictive performance of models using dichotomized versus continuous measures of p-tau and Aβ1-42. Negative Δ-values indicate better prediction than the dichothomized model. Bootstrapped 95%-CIs are shown in parentheses.
Abbreviations: Aβ, amyloid beta; ADNI, Alzheimer's Disease Neuroimaging Initiative; CI, confidence interval; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination.

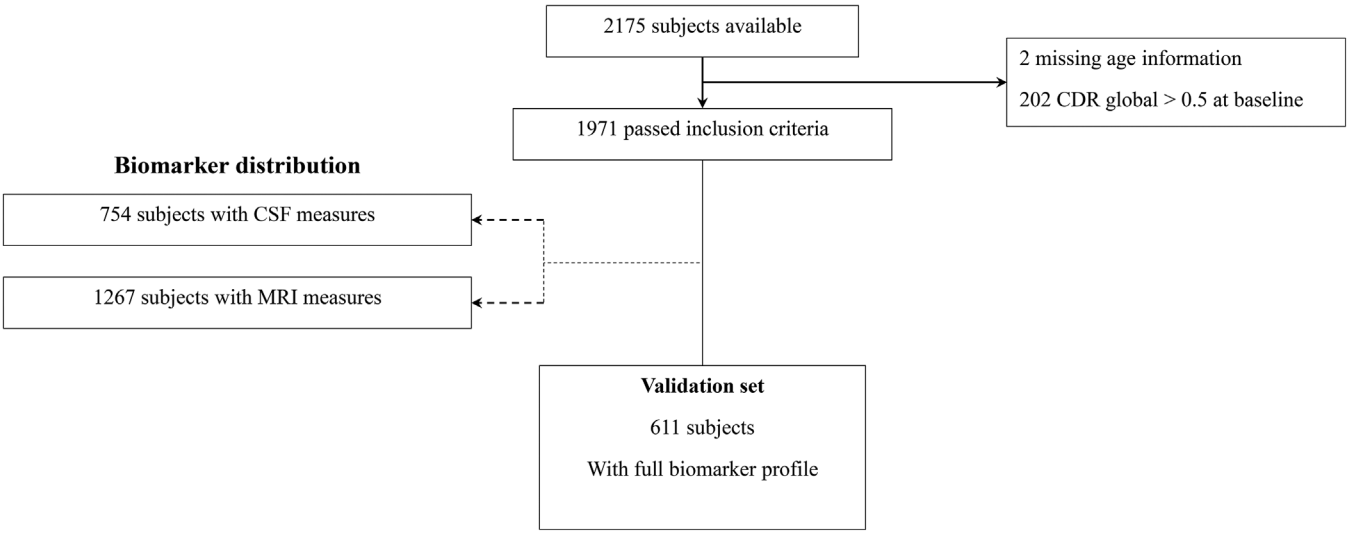

FIGURE 5 Alzheimer's Disease Neuroimaging Initiative (ADNI) consort diagram. CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging

TABLE 4 Partial correlations between the predicted disease progression and biomarker observations

	Education	Age	Total tau	Hippocampal volume	Aβ1-42	AD-signature meta-ROI thickness	Aβ1-40
Education							
Age	0.0579 (0.0273)						
Total tau	0.0260 (−0.0609)	−0.112 (−0.00502)					
Hippocampal volume	0.207 (0.125)	−0.232 (−0.212)	−0.0788 (−0.130)				
Aβ1-42	0.154 (0.0874)	−0.149 (−0.0431)	−0.427 (−0.527)	−0.0937 (0.0375)			
AD-signature meta-ROI thickness	0.0259 (0.0727)	−0.209 (−0.221)	−0.123 (−0.102)	0.206 (0.307)	−0.108 (−0.00562)		
Aβ1-40	−0.000941 (0.0131)	0.162 (0.0795)	0.653 (0.727)	0.0350 (0.101)	0.380 (0.507)	0.0501 (0.113)	
Education	0.204 (0.338)	0.293 (−0.0885)	0.164 (0.254)	−0.269 (−0.148)	−0.198 (−0.0996)	−0.153 (−0.206)	−0.100 (−0.177)

Notes: The predicted disease progression is estimated via fitted base models on both the MEMENTO and ADNI cohort. The partial correlations from the ADNI cohort are shown in parentheses.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ROI, region of interest.

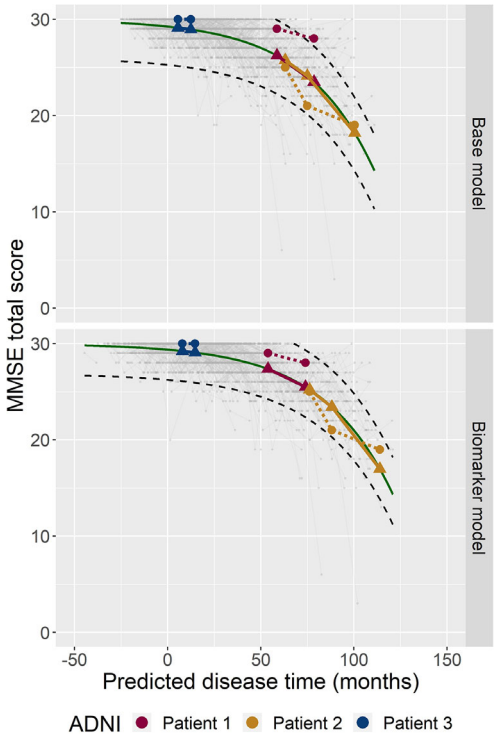

FIGURE 6 Examples of future predicted decline of three Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects in the development set for both base and biomarker model developed in the MEMENTO cohort. The observed Mini-Mental State Examination (MMSE) scores of patients are shown with dashed colored lines and the model predicted scores by the colored solid lines. The black dashed lines represent marginal 95% prediction intervals for each model conditional on the continuous staging. The continuous staging is determined by including the baseline MMSE score

3.4 | Clinical trial analyses

The estimated sample sizes needed to achieve 90% power to detect a 1-point treatment effect on ADAS-Cog are given in Table S8 in supporting information. In the CDR 0.5 group, adjusting for the biomarker-profile–based prediction of disease progression resulted in sample size reductions of 10% to 11% for 6-, 12-, and 24-month studies compared to the adjustment for individual demographic variables. For the Biomarker profile cut group, the reductions associated with adjusting for biomarker-profile–based prediction of disease progression were smaller (1% to 8%) due to increased homogeneity in progression. Compared to the CDR 0.5 group, sample requirements were smaller in all cases. For a 24-month study, including patients based on the biomarker profile prediction of disease progression and adjusting the analyses for this resulted in an additional 20% reduction, leading to a total reduction of 28% or 171 fewer patients required per arm compared to not adjusting for the biomarker profile.

4 | DISCUSSION

In this study we have developed a disease prediction model using age, education, measures of Aβ and total tau in CSF, and volumetric MRI measures from participants of the French MEMENTO cohort. We showed that incorporating individual biomarker profiles significantly improved the ability to predict patients' future course of cognitive decline. The model was externally validated on subjects from ADNI and shown to give a similar improvement in predicting patient-level future cognitive trajectories. An application derived from this model to offer personalized prognosis of any patient at the time of diagnosis has been developed to illustrate the potential use in clinical practice (https://disease-progression.shinyapps.io/disease_progression/). The application provides an estimate of both future cognitive progression and the location on the disease continuum via specified demographics and biomarker levels based on the full biomarker model. We further showed that this model could be used to optimize power of clinical trials by defining inclusion criteria leading to a more homogeneous patient population, which in turn decreases sample size requirements.

The developed biomarker profile included Aβ1-40, Aβ1-42, and total tau in CSF, and hippocampal volume and AD-signature meta-ROI thickness measured from MRI. Both MRI and CSF collection are routinely done in some clinical settings and often required at screening or baseline visits in AD clinical trials. In these settings, the proposed biomarker profile would enable better prognosis of patients' future progression path at no additional cost and aid selection of more homogeneous trial cohorts. A statistical power analysis suggested that this could reduce sample size requirements for clinical trials by up to 28%. Furthermore, such predictions could for example be used in adaptive trials to dynamically adjust sample size, or to improve power of interim analyses by comparing the progression of study participants to observed progression patterns of patients at matching disease stages from external cohorts. The proposed biomarker profile only included a subset of biomarkers available. Future work should investigate a larger variety of biomarkers for even better prognosis of patients' disease progression and explore the value of minimally invasive plasma biomarkers for phospho-tau[31,32] and neurofilament light.[33]

The predictive performance of the developed biomarker profile was compared to single-modality models incorporating either CSF or MRI measures. The full biomarker profile was shown to significantly improve prediction of future cognitive decline over the single-modality MRI model and CSF model. Additionally, we found that dichotomizing CSF measures of Aβ1-42 and p-tau resulted in a slight loss in the model's ability to predict patients' future decline, suggesting a slight information loss associated with dichotomizing amyloid and p-tau measures. This is in line with recent findings of the implications of mapping biomarkers to ATN profiles from Swedish BioFINDER studies.[19]

This study has some limitations. The MMSE scale was used as the outcome measure, but it is primarily sensitive in mild to moderate dementia.[34] While several years' follow-up was used to predict future cognitive decline, other cognitive scales with better sensitivity early in disease could potentially improve the biomarker profile further. Another limitation is that we studied a limited set of biomarkers with a focus on AD pathology, while the goal was to predict cognitive decline and dementia that was not restricted to AD patients. Biomarker profile staging could potentially be improved by inclusion of unspecific markers of neuronal injury such as neurofilament light[33,35] and

vascular biomarkers.[36,37] However, it is worth noting that FDG-PET was not selected in the data-driven model selection, even though it is a non-specific marker of neurodegeneration and potentially a non-specific biomarker of vascular dysfunction.[37] Finally, the differences in CSF biomarker assays between cohorts required normalization of variables in the validation study. The normalization procedure assumed similarity of biomarker distributions across assays. While a recalibration analysis did not find evidence of deviation from this assumption in these cohorts, it may not be satisfied in general. Hence further analyses are required to investigate the impact of assays with differing sensitivities on the personalized predicted disease progression stage.

In summary, our study demonstrates that biomarkers that are routinely collected in some clinical settings have a currently unused potential to improve patient prognosis of future cognitive decline in clinical practice and may be useful for optimizing trial design. Overall, this study reflects that individual patient trajectories can be modeled with continuous measures giving the possibility of predicting future cognitive decline at any time point.

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CONFLICTS OF INTEREST

LK, JLM, and LLR are employees of Lundbeck. All other authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

Line Kühnel and Lars Lau Raket developed the disease progression models and biomarker profile, developed figures and tables, and drafted the first version of the manuscript. All authors contributed to the study design, data interpretation, and finalization of the manuscript and approved the final version

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SUPPORTING INFORMATION

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

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