ARTICLE CLASS OF EVIDENCE

Validation of the Alzheimer Disease Dementia Conversion-Related Pattern as an ATN Biomarker of Neurodegeneration

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Abstract

Objective

To determine whether the Alzheimer disease (AD) dementia conversion-related pattern (ADCRP) on [^{18}F]FDG PET can serve as a valid predictor for the development of AD dementia, the individual expression of the ADCRP (subject score) and its prognostic value were examined in patients with mild cognitive impairment (MCI) and biologically defined AD.

Methods

A total of 269 patients with available [^{18}F]FDG PET, [^{18}F]AV-45 PET, phosphorylated and total tau in CSF, and neurofilament light chain in plasma were included. Following the AT(N) classification scheme, where AD is defined biologically by in vivo biomarkers of β-amyloid (Aβ) deposition ("A") and pathologic tau ("T"), patients were categorized to the A–T–, A+T–, A+T+ (AD), and A–T+ groups.

Results

The mean subject score of the ADCRP was significantly higher in the A+T+ group compared to each of the other group (all $p < 0.05$) but was similar among the latter (all $p > 0.1$). Within the A+T+ group, the subject score of ADCRP was a significant predictor of conversion to dementia (hazard ratio, 2.02 per z score increase; $p < 0.001$), with higher predictive value than of alternative biomarkers of neurodegeneration (total tau and neurofilament light chain). Stratification of A+T+ patients by the subject score of ADCRP yielded well-separated groups of high, medium, and low conversion risks.

Conclusions

The ADCRP is a valuable biomarker of neurodegeneration in patients with MCI and biologically defined AD. It shows great potential for stratifying the risk and estimating the time to conversion to dementia in patients with MCI and underlying AD (A+T+).

Classification of Evidence

This study provides Class I evidence that [^{18}F]FDG PET predicts the development of AD dementia in individuals with MCI and underlying AD as defined by the AT(N) framework.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 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://links.lww.com/WNL/B307.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADCRP** = Alzheimer disease dementia conversion-related pattern; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **ANOVA** = analysis of variance; **AUC** = area under the curve; **FAQ** = Functional Activities Questionnaire; **HR** = hazard ratio; **MCI** = mild cognitive impairment; **MCI-c** = patients with mild cognitive impairment who converted to Alzheimer disease; **MCI-nc** = patients with mild cognitive impairment who did not convert to Alzheimer disease; **MMSE** = Mini-Mental State Examination; **NfL** = neurofilament light chain; **NIA-AA** = National Institute on Aging and the Alzheimer's Association; **p-tau** = phosphorylated tau; **PCA** = principal components analysis; **ROI** = region of interest; **SSM** = scaled subprofile modeling; **SUVR** = standardized uptake value ratio; **t-tau** = total tau.

The definition of Alzheimer disease (AD) during lifetime, initially solely based on clinical symptoms, recently shifted from a syndromal to a biological construct. The AT(N) research framework[1] proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) is grounded on imaging and biofluid biomarkers. The framework defines 3 biomarker groups: biomarkers of neuropathology including markers of β-amyloid (Aβ) plaques (labeled "A") and fibrillary tau (labeled "T") and biomarkers of neurodegeneration or neuronal injury ("labeled (N)"), the binarization of which leads to different biomarker profiles. In the AT(N) framework, AD is defined biologically by markers of neuropathology, whereas neurodegeneration and, subsequently, cognitive impairment are treated as sequels and symptoms of the disease rather than defining the disease. Therefore, for the diagnosis of AD in living persons, both Aβ (A) and pathologic tau (T) must be abnormal, independently of clinical symptoms. Aside from its diagnostic value, the AT(N) scheme may be of particular value in patients with mild cognitive impairment (MCI) by providing prognostic information on the risk of progression from MCI to AD dementia as demonstrated by recent studies.[2,3]

Unlike neuropathology biomarkers A and T, biomarkers of neurodegeneration or neuronal injury are not required to diagnose AD. The (N) biomarkers are mostly nonspecific for neurodegeneration due to AD and indicate neuronal injury of different etiologies,[1] which limits their diagnostic accuracy. Neurodegeneration biomarkers proposed by the AT(N) framework include hypometabolism on 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) PET, hippocampal atrophy on MRI, abnormal total tau (t-tau) in CSF, and axonal protein neurofilament light chain (NfL) in plasma. Using [^{18}F]FDG PET, we recently proposed an AD dementia conversion-related pattern (ADCRP) that distinguishes converters from MCI to AD dementia from nonconverters.[4] This disease-specific spatial covariance pattern was established by principal components analysis with the scaled subprofile modeling (SSM) approach (SSM/PCA), a well-validated method that has been used extensively to detect and characterize disease-specific network biomarkers in a variety of neurodegenerative disorders.[5–9] The SSM/PCA is entirely data-driven: it provides a set of principal components ordered by effect size in the data (eigenvalue). It also provides expression values for the pattern in each subject (subject score), which can be used for hypothesis testing and statistical inference. In this study, we examined the diagnostic and prognostic value of the subject score of ADCRP within the novel research framework presented by the NIA-AA. We hypothesized that the subject score of ADCRP is differently altered in biologically defined biomarker profile groups (as defined by AT[N] classification scheme without considering clinical diagnosis) and a valid predictor of conversion to AD dementia in patients with MCI with biologically defined AD. In addition, we compared the prognostic value of the subject score of ADCRP to that of t-tau in CSF and NfL in plasma.

Methods

Participant Cohort

The present data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (ClinicalTrials.gov Identifier: NCT00106899; 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 MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. We selected 319 patients with MCI in whom [^{18}F]FDG and [^{18}F]AV-45 PET at the baseline visit were available. We additionally requested presence of phosphorylated tau (p-tau, biomarker of fibrillary tau or T) and t-tau in CSF, and NfL in plasma at baseline visit (n = 38 excluded). The time interval between different examinations was restricted to 12 months (n = 12 excluded). In total, 269 patients were included for the present analysis. Participants were evaluated at baseline and in 6- to 12-month intervals following initial evaluation for up to 6 years. For initial inclusion criteria and characteristics of the cohort, see reference 4. The patients were dichotomized into MCI who converted to AD dementia as labeled by ADNI (MCI converters [MCI-c]) and those who did not convert (MCI nonconverters [MCI-nc]). Of note, none of the patients converted to different type of dementia than AD dementia. Based on the clinical diagnosis provided by ADNI, a total of 66 patients (25%) were MCI-c. Finally, we retrieved information on Mini-Mental State Examination (MMSE), Functional Activities Questionnaire (FAQ) score, and *APOE* ε4 allele status for group characterization.

Standard Protocol Approvals, Registrations, and Patient Consents

Imaging, CSF and plasma measures, and demographic and clinical information of patients was downloaded from the ADNI database (ADNI, ClinicalTrials.gov Identifier: NCT00106899; adni-info.org). The study protocol was approved by all the institutional ethical review boards of all participating centers and written informed consent had been obtained by ADNI from all patients before protocol-specific procedures were carried out (see ADNI protocols).

PET Acquisition and Preprocessing

PET acquisitions and data preprocessing were performed as previously described.[4] In brief, dynamic 3D PET scans were downloaded from ADNI (adni.loni.usc.edu), motion-corrected to the first frame, and added into a sum file. The resulting images were spatially normalized to in-house templates in Montreal Neurologic Institute space constructed of [^{18}F]FDG PET (n = 35) and [^{18}F]AV-45 PET (n = 16, both amyloid-positive and amyloid-negative) scans of cognitively healthy elderly control patients from the ADNI cohort.

For [^{18}F]FDG PET (acquired 30–60 minutes p.i.), we quantified subject scores for the previously validated ADCRP. The ADCRP was constructed by voxel-based SSM/PCA[5] on a combined group of MCI-c and MCI-nc (n = 272), showing most prominent decreases of relative metabolic activity in MCI-c compared to MCI-nc in the temporoparietal cortex as well as precuneus/posterior cingulate cortex.[4] Subject scores were then computed by the voxel-wise topographic profile rating algorithm to quantify the degree of similarity between the obtained pattern and PET images in individual patients. The theoretical foundation and computing routines of the analysis have been described in detail elsewhere.[5,10,11] In case of [^{18}F]AV-45 PET (acquired 50–70 minutes p.i.), we calculated the mean standardized uptake value ratio (SUVR) in regions with the highest Aβ burden in AD (Pittsburgh compound B region mask; regions were taken from Frings et al.[12]) using cerebellar cortex as reference.

As a supplemental analysis and in analogy to the PCA-based approach, we also examined a region of interest (ROI)–based measure as a conventional [^{18}F]FDG PET-based biomarker of neurodegeneration within AT(N) classification scheme. Here, mean normalized [^{18}F]FDG uptake (cerebellar vermis and pons as reference region) was derived from the composite ROI of regions with AD-typical hypometabolism proposed by Landau and colleagues[13] that comprises portions of the bilateral parietal and temporal lobes as well as the posterior cingulate gyri (figure e-2 and supplemental results, data available from Dryad; doi.org/10.5061/dryad.j6q573nc3).

Classification of MCI

CSF and plasma data, analyzed at the ADNI biomarker core laboratories at the University of Pennsylvania or University of Gothenburg according to the published methods,[14] were also downloaded from ADNI (adni.loni.usc.edu).

The p-tau cutoff value was selected from previous reports on ADNI MCI[15,16] and was defined as positive for AD if the concentration exceeded 26.6 pg/mL. Amyloid positivity was defined based on a comparison of calculated mean SUVR in AD-typical regions with the binary amyloid positivity status available at ADNI (UC Berkeley analysis, available only for a subgroup of patients, n = 264/269). This resulted in a SUVR cutoff value of 1.3 and an amyloid-positive rate of 59%. Based on Aβ on PET (A) and p-tau in CSF (T), patients were categorized to the following groups, adopting the NIA-AA research framework nomenclature: A−T− (normal AD biomarkers), A+T− (AD pathologic change), A+T+ (AD), and A−T+ (non-AD pathologic change).

Statistics

Subject score of ADCRP, t-tau in CSF, and NfL in plasma were statistically compared between the aforementioned groups by analysis of variance (ANOVA), followed by pairwise *t* test using false discovery rate adjustment for multiple comparisons.[17] The effect size for ANOVA was computed by Cohen *f*, and Cohen *d* was calculated for pairwise comparisons.

The large majority (56/66 [85%]) of MCI-c stems from the A+T+ group, which is in line with the assumption that A− or T− patients do not have MCI caused by AD. Thus, further investigations on the predictive power of the given biomarkers were restricted to the A+T+ group, representing the clinical target group. Furthermore, the small number of MCI-c in the other groups precluded meaningful statistical analyses. The independent predictive values of (N) biomarkers for conversion to AD dementia were assessed within the A+T+ group by Cox proportional hazards regression with each biomarker alone (i.e., subject score of ADCRP, t-tau, and NfL) adjusted for age at baseline (years) and sex. Multivariate model including all biomarkers of neurodegeneration was constructed employing the ridge regression option to account for multicollinearity among variables. The resulting hazard ratio (HR) reflects risk changes per SD increase. In addition, the predictive power of (N) biomarkers was estimated by ROC analyses at a time point of 3 years from baseline evaluation with optimal cutoffs defined by the maximum of the Youden index.

Subject score of ADCRP, t-tau, and NfL were also tested for significant stratification of patients into risk groups: for each of the 3 biomarkers, patients within the A+T+ group were sorted to 1 of 3 equally sized groups (low, medium, or high range of the biomarker values), and significance of stratification was assessed by Kaplan-Meier survival analyses.

We also constructed Cox proportional hazards regression models using continuous A, T, and (N) biomarkers employing the "survival" package[18] in R (R-project.org) and the ridge regression option to account for multicollinearity.

Three models were constructed including the following sets of variables: (1) subject score of ADCRP, Aβ PET, and p-tau; (2) subject score of ADCRP, CSF $A\beta_{42/40}$, and p-tau; and (3) subject score of ADCRP, Aβ PET, p-tau, MMSE, age, and the following interactions: p-tau×MMSE, p-tau×Aβ PET, Aβ PET×age (in analogy to van Maurik et al.[2]). All continuous covariates were z transformed such that the HR reflects risk changes per SD increase. The prediction accuracy of each model was assessed by Harrell concordance C. Analysis of deviance was conducted for pairwise comparison between models.

Data Availability

All ADNI data are shared without embargo through the LONI Image and Data Archive (IDA; ida.loni.usc.edu). Access to ADNI imaging, clinical, and biomarker data for the purpose of scientific investigation or planning clinical research studies can be granted after application process including acceptance of the data use agreement and submission of an application form.

Results

(N) Biomarker Findings Across AT Groups

A total of 136 patients were categorized as A+T+ (41% of whom converted to AD dementia), 22 as A+T−, 44 as A−T+, and 67 as A−T− (table 1). Only 10 patients diagnosed as MCI-c did not fall into the biologically defined AD group, with 4 patients being classified as A−T−, 3 as A−T+, and 3 as A+T−. Age and sex did not significantly differ among groups (ANOVA, both $p > 0.1$). FAQ and MMSE both showed significant group effects (both $p < 0.001$, ANOVA and Kruskal-Wallis test, respectively), with the A+T+ group having the highest FAQ and the lowest MMSE mean values. The frequency of MCI-c and *APOE* ε4 positive cases (at least 1 ε4 allele present) was significantly higher (χ^2 test, both $p < 0.001$) in the A+T+ group. As expected, Cox regression analyses revealed a significantly increased risk of progression to AD dementia (as labeled by ADNI) in patients of the A+T+ group, whereas patients of the other groups did not show a significantly increased risk (A−T− as reference group; A−T+: HR [95% confidence interval], 1.23 [0.27, 5.50], $p = 0.78$; A+T−: HR, 2.18 [0.48, 9.77], $p = 0.30$; A+T+: HR, 9.17 [3.32, 25.34], $p = 1.8 \times 10^{-5}$).

The mean subject score of ADCRP was significantly different among the AT groups (ANOVA $p = 5.0 \times 10^{-5}$, f = 0.30 [0.16, 0.41]), showing higher values in the A+T+ group compared to all other groups (A+T+ vs A−T−, $p = 6.4 \times 10^{-4}$, d = 0.57 [0.27, 0.87]; A+T+ vs A−T+, $p = 0.002$, d = 0.55 [0.20, 0.89]; A+T+ vs A+T−, $p = 0.02$, d = 0.54 [0.08, 0.99]; figure 1). A 2-way ANOVA analysis indicated a significant interaction of group and conversion state on subject score of ADCRP ($p = 4.2 \times 10^{-15}$). In line with this, the aforementioned difference was driven by A+T+ MCI-c (vs other groups, all $p < 0.001$), while A+T+ MCI-nc were not different from the other groups (all $p > 0.1$). Within the A+T+ group, MCI-c had higher subject scores than MCI-nc ($p = 8.1 \times 10^{-6}$, d = 0.85 [0.48, 1.20]). Although a subgroup of patients (121 of 269) included in this study was part of larger group of patients (n = 272)[4] used to construct the ADCRP, the exclusion of these patients did not relevantly change the results (figure e-1, data available from Dryad; doi.org/10.5061/dryad.j6q573nc3).

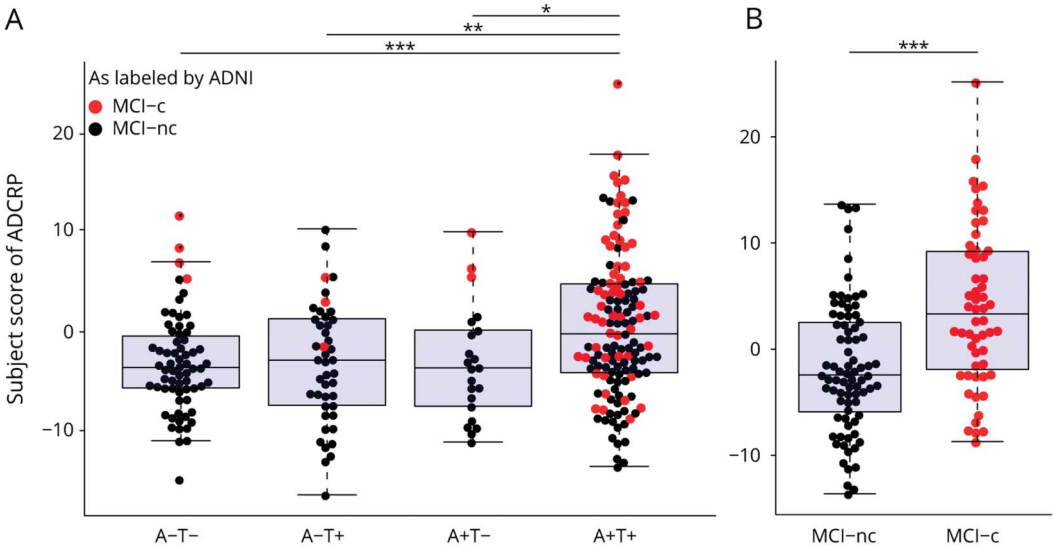
t-Tau was significantly different among the biomarker profile groups (ANOVA $p = 2.0 \times 10^{-16}$, f = 0.70 [0.58, 0.81]), and showed significant differences in all pairwise contrasts except A−T− vs A+T− groups (A−T+ vs A−T−, $p = 5.3 \times 10^{-4}$, d = 1.08 [0.66, 1.49]; A−T+ vs A+T−, $p = 0.04$, d = 0.67 [0.13, 1.20]; A+T+ vs A+T−, $p = 7.9 \times 10^{-9}$, d = 1.20 [0.72, 1.67]; A+T+ vs A−T+, $p = 1.6 \times 10^{-6}$, d = 0.74 [0.39, 1.09]; A+T+ vs A−T−, $p = 2.0 \times 10^{-16}$, d = 1.50 [1.16, 1.82]; figure 2). A 2-way ANOVA indicated a significant interaction of group and conversion state on t-tau ($p = 1.1 \times 10^{-10}$). In contrast to the subject score of ADCRP, this effect was not only driven by A+T+ MCI-c, but by T status and conversion status. Still,

Table 1 Characteristics of the Biomarker Profile Groups

AT profile	Biomarker category	N	MCI-c	Age, y	M/F	FAQ	Follow-up time, mo	*APOE* ε4 positive	MMSE
A−T−	Normal	67	4 (6)	72.0 ± 8	38/29	1.5 ± 2.6	47 (36; 51)	17 (25)	28.7 ± 1.2
A−T+	Non-AD pathologic change	44	3 (6)	71.8 ± 8	18/26	1.2 ± 3.1	47 (35; 48)	15 (34)	28.0 ± 1.6
A+T−	Alzheimer pathologic change	22	3 (12)	74.4 ± 6	16/6	1.9 ± 2.3	48 (36; 59)	10 (45)	28.4 ± 1.1
A+T+	AD	136	56 (41)[a]	72.4 ± 7	79/57	3.2 ± 4.2[a]	48 (36; 51)	97 (71)[a]	27.6 ± 1.9[a]

Abbreviations: AD = Alzheimer disease; FAQ = Functional Activities Questionnaire; MCI-c = patients with mild cognitive impairment who converted to Alzheimer disease; MMSE = Mini-Mental State Examination.
Values are n (%), mean ± SD, or median (interquartile range).
[a] Significantly different from all other groups ($p < 0.05$).

Figure 1 Distribution of the Subject Score of the Alzheimer Disease Dementia Conversion-Related Pattern (ADCRP)



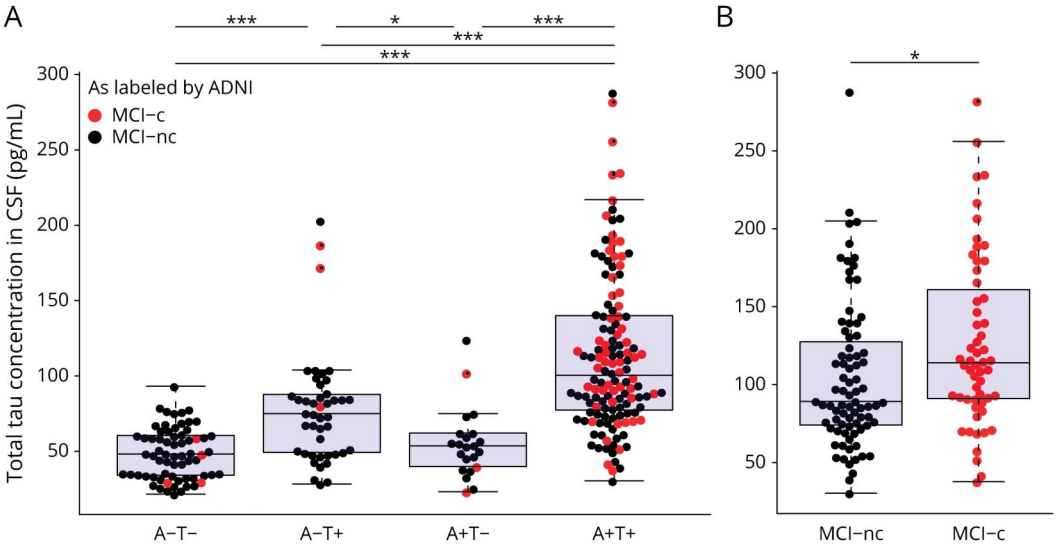
(A) Subject score of ADCRP across biomarker profile groups. (B) Subject score of ADCRP within the A+T+ group and comparison between patients with mild cognitive impairment who converted (MCI-c) and who did not convert (MCI-nc) to Alzheimer disease dementia. *$p < 0.05$; **$p < 0.005$; ***$p < 0.001$. ADNI = Alzheimer's Disease Neuroimaging Initiative.

within the A+T+ group t-tau concentration was significantly higher in MCI-c than in MCI-nc (p = 0.02, d = 0.44 [0.08, 0.78]).

Plasma NfL also differed significantly between AT groups (ANOVA p = 0.01, f = 0.21 [0.07, 0.29]), but it was increased only in the A+T− group (A+T− vs A−T+, p = 0.005, d = 0.67 [0.13, 1.20]; A+T− vs A+T+, p = 0.03, d = 0.54 [0.07, 0.99]; A+T− vs A−T−, p = 0.03, d = 0.43 [0.06, 0.91]; figure 3). A 2-way ANOVA indicated no significant interaction of group and conversion state on NfL in plasma (p = 0.07).Within the A+T+ group, no significant separation between MCI-c and MCI-nc was observed (p = 0.19, d = 0.22 [−0.12, 0.56]).

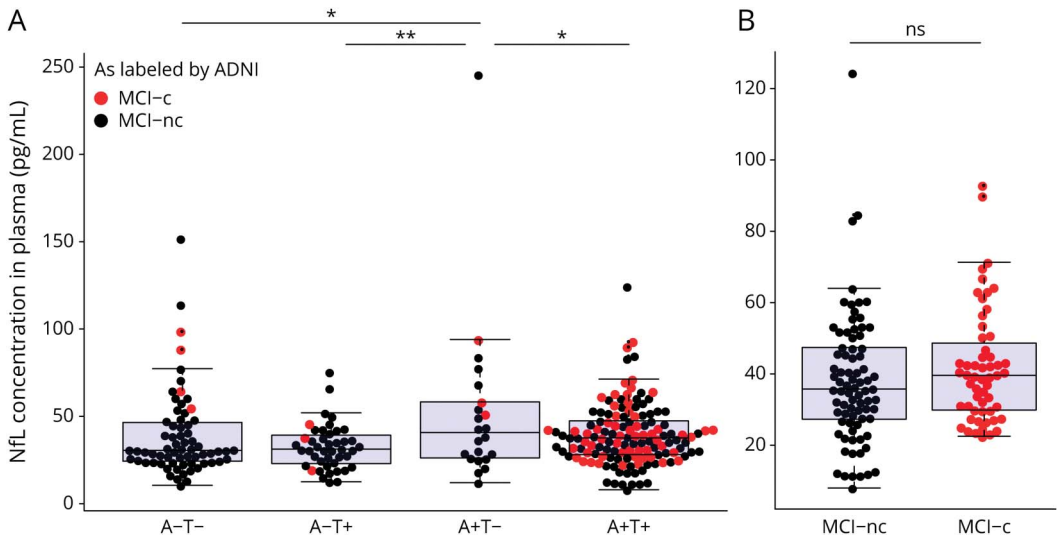
The 3 (N) biomarkers were significantly associated with each other in the present cohort. Subject score of ADCRP was

Figure 2 Distribution of Total Tau Concentration in CSF



(A) Total tau in CSF across biomarker profile groups. (B) Total tau within the A+T+ group and comparison between patients with mild cognitive impairment who converted (MCI-c) and who did not convert (MCI-nc) to Alzheimer disease dementia. *$p < 0.05$; ***$p < 0.001$. ADNI = Alzheimer's Disease Neuroimaging Initiative.

Figure 3 Distribution of Axonal Protein Neurofilament Light Chain (NfL) in Plasma



(A) Distribution of the NfL in plasma across biomarker profile groups. (B) Plasma NfL within the A+T+ group and comparison between patients with mild cognitive impairment who converted (MCI-c) and who did not convert (MCI-nc) to Alzheimer disease dementia. *$p < 0.05$; **$p < 0.005$. ADNI = Alzheimer's Disease Neuroimaging Initiative; ns = not significant.

significantly associated with t-tau (Pearson correlation: $r = 0.22$, $p = 1.0 \times 10^{-4}$) and NfL in plasma (Pearson correlation $r = 0.18$, $p = 0.001$), with both biofluid markers being associated at trend level (Pearson correlation $r = 0.09$, $p = 0.09$).

Prediction of Development of AD Dementia

In the A+T+ group (i.e., biologically defined AD), Cox proportional hazards regression analyses identified the subject score of ADCRP as a significant independent predictor of conversion to AD dementia (HR, 2.02 [1.58, 2.58] per z score increase [SD 7.20], $p = 1.6 \times 10^{-8}$), with higher predictive value than t-tau (HR, 1.42 [1.13, 1.78] per z score increase [SD 51.54], $p = 0.002$) and NfL (HR, 1.60 [1.08, 2.38] per z score increase [SD 17.57], $p = 0.017$). In a multivariate model, subject score of ADCRP showed higher significance in predicting conversion from MCI to AD (HR, 1.91 [1.51, 2.43] per z score increase, $p = 1.2 \times 10^{-7}$) compared to t-tau (HR, 1.28 [1.02, 1.59] per z score increase, $p = 0.030$) and NfL (HR, 1.25 [0.85, 1.84] per z score increase, $p = 0.25$).

For additional assessment of the prognostic value (e.g., for patient counseling and planning of clinical trials), we estimated the performance of (N) biomarkers at a time point of 3 years from baseline evaluation (typical follow-up time of clinical trials). A total of 101 patients reached this time point (35 censored), of whom 45 converted to AD dementia and 56 did not convert. In these 101 patients, the subject score of ADCRP (area under the curve [AUC] 0.796) outperformed NfL (AUC 0.631), and t-tau (AUC 0.702) in correctly predicting conversion from MCI to AD dementia (table 2). The relatively low specificity and PPV (cutoffs defined based on Youden index: subject score of ADCRP = −0.24, t-tau = 90.9 pg/mL, and NfL = 22.5 pg/mL) of all measures are expected due to their inherent strong dependence on follow-up time.

Risk Stratification

Stratification of A+T+ patients by the subject score of ADCRP into 3 equally sized risk groups yielded well-separated (all $p < 0.05$, pairwise log-rank test) groups of high, medium, and low conversion risks with median conversion times of 25, 47, and >120 months (median not reached), respectively (figure 4). By contrast, t-tau concentration in CSF allowed for a significant stratification of A+T+ patients only into high- vs low-risk groups, whereas NfL in plasma provided no significant risk stratification (figure 5; table e-1, data available from Dryad; doi.org/10.5061/dryad.j6q573nc3).

Continuous AT(N) Cox Models

The subject score of ADCRP was identified as the strongest predictor among the biomarkers of neurodegeneration and therefore chosen as (N) biomarker for continuous AT(N) Cox proportional hazard regression models. The first model with the subject score of ADCRP, Aβ PET, and p-tau identified all the included biomarkers as significant predictors of conversion from MCI to AD dementia (all $p < 0.001$). Subject score of ADCRP showed higher HR (1.56 [1.31, 1.85]) compared to Aβ PET (HR. 1.37 [1.15, 1.63]) and p-tau (HR, 1.30 [1.11, 1.54]). In the second model, Aβ PET was substituted by CSF $A\beta_{42/40}$ (available for a subset of 260 patients) and yielded similar HRs of the predictors: subject score of ADCRP HR, 1.59 (1.33, 1.89), $A\beta_{42/40}$ HR, 1.40 (1.15, 1.70), p-tau HR, 1.33 (1.11, 1.55); all $p < 0.001$.

In analogy to van Maurik et al.,[2] we added MMSE, age, and interaction terms between the variables to the first model. Only the aforementioned biomarkers reached a level of significance (ADCRP: HR, 1.52 [1.28, 1.80], $p = 1.2 \times 10^{-6}$; Aβ

Table 2 Receiver Operating Characteristic Curve Analysis of the A+T+ Group With Follow-Up Time Limited to 3 Years

	Sensitivity, %	Specificity, %	NPV, %	PPV, %	AUC
Subject score of ADCRP	76.7	69.6	82.5	61.5	0.796
NfL in plasma	98.1	16.1	92.7	43.3	0.631
Total tau in CSF	80.8	54.6	81.0	54.3	0.702

Abbreviations: ADCRP = Alzheimer disease dementia conversion-related pattern; AUC = area under the curve; NfL = neurofilament light chain; NPV = negative predictive value; PPV = positive predictive value.

PET: HR, 1.34 [1.11, 1.61], $p = 0.002$; p-tau: HR, 1.29 [1.09, 1.53], $p = 0.003$); the other variables were not statistically significant (MMSE: HR, 1.18 [1.01, 1.40], $p = 0.06$; age: HR, 1.01 [0.85, 1.21], $p = 0.85$; p-tau×MMSE: HR, 1.01 [0.86, 1.18], $p = 0.88$; p-tau×Aβ PET: HR, 1.02 [0.85, 1.22], $p = 0.81$; Aβ PET×age: HR, 1.07 [0.90, 1.26], $p = 0.42$).

Comparisons between models indicated no significant improvement when MMSE, age, and interaction terms were included (C = 0.841; compared to C = 0.843 for the first model; $p > 0.5$). The model with CSF $A\beta_{42/40}$ (second model) provided comparable goodness of fit (C = 0.845).

Conventional ROI-Based [^{18}F]FDG PET Analysis as a Biomarker of Neurodegeneration

Mean normalized [^{18}F]FDG uptake in the composite ROI by Landau et al.[13] showed overall comparable group differences and performance in predicting conversion from MCI to AD dementia in A+T+ patients compared to the subject score of ADCRP (normalized [^{18}F]FDG uptake: HR, 2.29 [1.72, 3.05] per z score decrease; for patient's score of ADCRP, see above, HR, 2.02 [1.58, 2.58] per z score increase). Details on these analyses are available in the supplemental material (supplemental results, figures e-2–e-4, data available from Dryad; doi.org/10.5061/dryad.j6q573nc3).

Discussion

In patients with MCI, the subject score of ADCRP was significantly increased only in those with underlying AD as biologically defined by the AT(N) scheme. Moreover, the subject score of ADCRP was a significant predictor of progression to dementia in these patients, and it was a better predictor than the biofluid biomarkers of neurodegeneration tested here (t-tau in CSF and NfL in plasma).

The great majority (84%) of the patients with MCI who developed AD dementia as labeled by ADNI (based on clinical examination) exhibited amyloid and tau pathology and were assigned to the A+T+ group. Conversely, only 10 of 133 patients of the A+T−, A−T+, and A−T− groups (i.e., 7.5% of patients without biologically defined AD) developed AD dementia as labeled by ADNI. Within the ADNI project, no dementia diagnosis other than AD dementia was used. This might be unexpected, given that the postmortem outcome of MCI can be diverse.[19–21] At this stage and without histopathologic data it cannot be differentiated whether the small fraction of incongruent cases results from clinical misdiagnosis or false-negative A or T assessments. Still, the aforementioned results support the general appropriateness of the diagnoses of AD dementia as labeled by ADNI. The present study strictly follows the AT(N) research framework by shifting from a clinical to a biological definition of AD and proposes to use a 2-step process: after the presence of AD was defined by A and T biomarkers (first step), an (N) biomarker (subject score of ADCRP) is used for risk stratification (second step).

The subject score of ADCRP was significantly increased only in A+T+, whereas it was comparably low in A+T−, A−T+, and A−T− groups. However, this was not the case for t-tau in CSF, which showed, in addition to the increase in A+T+, higher CSF concentrations in A−T+ compared to the 2 T− groups. Levels of t-tau and p-tau in CSF showed moderate correlation within our cohort (Pearson correlation $r = 0.67$, $p < 0.001$), similarly to other studies,[22] explaining the increase of t-tau in all T+ groups. Higher specificity of the subject score of ADCRP than t-tau might be due to the fact that the ADCRP has intentionally been constructed by PCA to reflect AD neurodegeneration and to be associated with conversion from MCI to AD dementia. By contrast, t-tau is a nonspecific indicator of neurodegeneration, being increased in conditions other than AD.[23] Moreover, although both [^{18}F]FDG PET and t-tau in CSF reflect neurodegeneration, t-tau in CSF likely indicates the intensity of neuronal injury at a given time point,[24] while hypometabolism on [^{18}F]FDG PET likely indicates both cumulative loss of neuropil and functional impairment of neurons. These differences may result in discordance between neurodegeneration biomarkers[25] and explain the observed low correlations between the (N) biomarkers ($r = 0.18$ to 0.22).

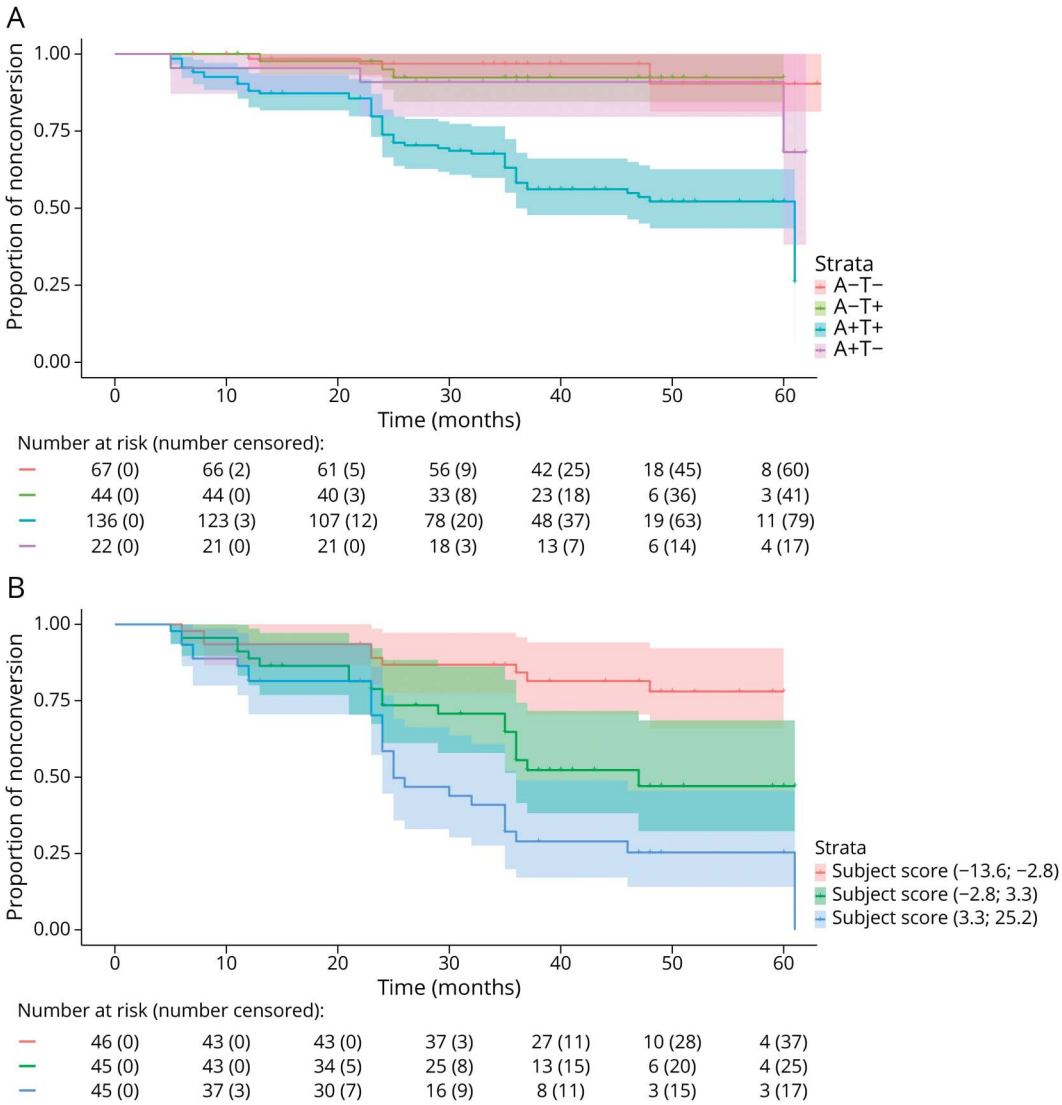
Although NfL concentrations in plasma and CSF were proposed as biomarkers for neurodegeneration in AD,[26] plasma NfL did not show promising results in the current study (e.g., no difference between A+T+ and A−T−). Plasma NfL levels were similar between the MCI-c and MCI-nc, and NfL was

not a significant predictor of conversion within the A+T+ group. This is in accordance with results published by Lin et al.[27]

We selected amyloid PET among the other biomarkers to define amyloid positivity due to its great specificity[28] and high (>90%) accuracy as shown in postmortem studies.[29–31] The cutoff for amyloid positivity was defined by comparing continuous SUVR values in typical AD regions with available amyloid positivity status provided by ADNI. This resulted in a cutoff of 1.3, which is in good accordance with other studies (e.g., the cutoff of 1.28 proposed by Joshi et al.[32]). We compared amyloid positivity defined by [^{18}F]AV-45 PET to the one defined using CSF measures of the 42 amino acid variant of β-amyloid ($A\beta_{42}$) and ratios of $A\beta_{42/40}$ or $A\beta_{42/38}$. In the present study, the PET Aβ status exhibited a discrepancy of 24% (n = 64/260) to $A\beta_{42}$, 16% (n = 42/260) to the $A\beta_{42/40}$ ratio, and 17% (n = 46/260) to the $A\beta_{42/38}$ ratio. The use of CSF Aβ ratios was shown to be superior to $A\beta_{42}$ alone.[33] The overall concordance of approximately 85% between CSF (based on $A\beta_{42/40}$ and $A\beta_{42/38}$) and PET amyloid status is similar to other studies,[34] which also suggests that the present cutoff selection is appropriate.

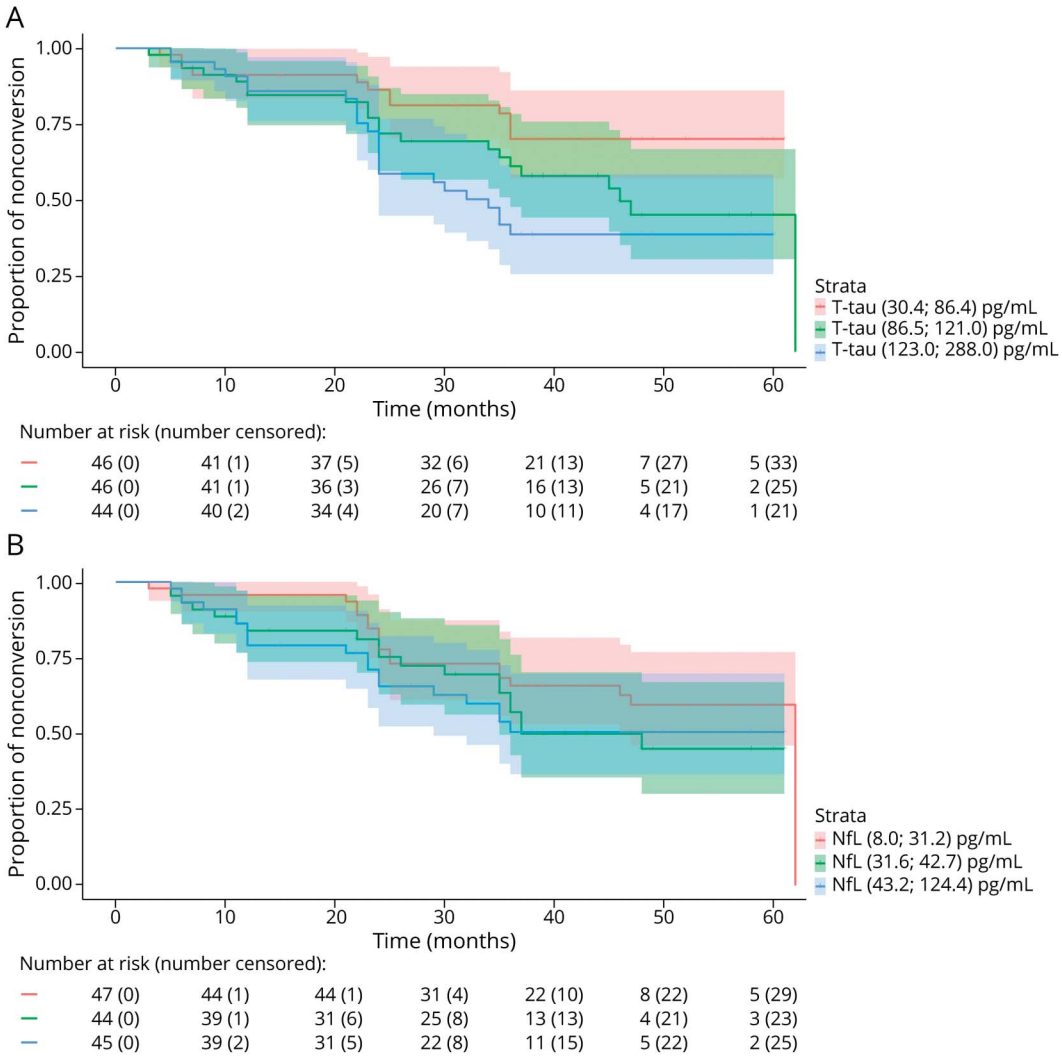
A recently published study by van Maurik et al.[2] combined continuous A, T, and (N) biomarkers into one model to assess their combined predictive value for conversion from MCI to AD dementia (using different clinical definitions) in large cohort of patients, which yielded a high prognostic performance (Harrell C = 0.79). We constructed an analogous model to van Maurik et al.[2] using the present A, T, and (N) biomarker dataset, which provided a higher predictive

Figure 4 Kaplan-Meier Curves



(A) Risk stratification based on biomarker profile groups. (B) Risk stratification based on the subject score of Alzheimer disease dementia conversion-related pattern for the A+T+ group. Ranges of biomarker values for each of the strata are reported in brackets.

Figure 5 Kaplan-Meier Curves



Risk stratification based on total tau (t-tau) in CSF (A) and axonal protein neurofilament light chain (NfL) in plasma (B) within the A+T+ biomarker profile group. Ranges of biomarker values for each of the strata are reported in brackets.

value (C = 0.84) although based on a smaller, but partially overlapping cohort. The study by van Maurik et al.[2] employed hippocampal MRI volumetry instead of the subject score of ADCRP as (N) biomarker and CSF Aβ instead of Aβ PET as A biomarker. For consistency, we also replaced Aβ PET by CSF $A\beta_{42/40}$ in our model, which, however, had little effect (C = 0.84). Likewise, the inclusion of MMSE and age or interaction terms (p-tau × MMSE; p-tau × Aβ PET; Aβ PET × age) into the model (in analogy to van Maurik et al.[2]) did not change the results as MMSE and interaction terms are not significant independent predictors of conversion (all $p > 0.05$). Earlier observations showed that the subject score of ADCRP provided by PCA outperformed nonimaging biomarkers (*APOE* ε4, MMSE, FAQ) and conventional [^{18}F]FDG PET analyses,[4] which in turn performed comparable to slightly better in predicting MCI conversion than structural MRI.[35] Thus, further studies are warranted to explore if the difference in the prediction models is explained by the choice of (N) biomarkers. These should also revisit different methods of PET data analyses, since somewhat surprisingly and opposed to our previous study,[4] results gained from PCA (patient ADCRP score) and conventional analyses (composite ROI proposed by Landau et al.[13]) yielded fairly comparable results in the present study. Finally, the present 2-step approach of applying the subject score of ADCRP only to A+T+ patients instead of using a combined continuous AT(N) model (necessarily relying on all 3 biomarker classes in all patients) may be more cost-effective and easier to implement. As an interesting, cost-effective, and convenient alternative to [^{18}F]FDG PET, one may also consider using an early time frame image of an amyloid scan as a surrogate of a cerebral blood flow image, previously validated to closely correlate with regional glucose metabolism and neuronal function.[36–38] These aspects may be addressed by future studies.

Biological and behavioral heterogeneity of clinical phenotype of amnestic MCI in an ADNI cohort[39] supports the generalization of ADNI MCI participants to a typical population at

risk of AD dementia. The subject score of ADCRP may aid the practical implementation of the AT(N) research framework. In particular, it may be employed as a tool of precision medicine in AD to further stratify patients with MCI with underlying AD (A+T+) according to their conversion risk and time to conversion, which is of great importance for clinical routine and patient selection in clinical trials. Targeted recruitment of biomarker-defined at-risk populations in clinical trials will improve the efficiency of the trial while reducing the study sample size and the risk of exposing to treatment side effects those patients who would not benefit from treatment.[40] Moreover, disease-modifying clinical interventions applied in the preclinical phase of AD might have a better chance of changing disease progression before the onset of severe neurodegeneration.[41] Therefore, it is crucial to define the biomarker profile that will identify individuals most likely to benefit from early intervention.

Our results suggest that the subject score of ADCRP is a promising biomarker of neurodegeneration in patients with MCI and biologically defined AD. It shows great potential for stratifying the risk and estimating the time to conversion to dementia in patients with MCI and biologically defined AD, which is of great interest for clinical practice and future trials.

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Appendix 1 Authors

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Ganna Blazhenets, MSc	University of Freiburg, Germany	Study design, data analysis, drafted the initial version of the manuscript and figures
Lars Frings, PhD	University of Freiburg, Germany	Study design, interpretation of the results, revision of the manuscript
Yilong Ma, PhD	The Feinstein Institutes for Medical Research, Manhasset, NY	Study design, interpretation of the results, revision of the manuscript
Arnd Sörensen, PhD	University of Freiburg, Germany	Interpretation of the results, revision of the manuscript
David Eidelberg, MD	The Feinstein Institutes for Medical Research, Manhasset, NY	Interpretation of the results, revision of the manuscript
Jens Wiltfang, MD	Georg-August-University, Göttingen, Germany	Interpretation of the results, revision of the manuscript
Philipp T. Meyer, MD, PhD	University of Freiburg, Germany	Study design, interpretation of the results, revision of the manuscript

Appendix 2 Coinvestigators

Coinvestigators are listed at http://links.lww.com/WNL/B307

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