Original article

Validation of prognostic biomarker scores for predicting progression of dementia in patients with amnestic mild cognitive impairment

Jamie Moreland[a], Timo Urhemaa[b], Mark van Gils[b], Jyrki Lötjönen[c], Jan Wolber[a] and Christopher J. Buckley[a]

Objective The objective of this study was to develop and validate a practical computerized prognostic model that uses baseline psychometric and imaging data, including results of PET imaging of amyloid deposition, to predict the progression to dementia in patients at risk for Alzheimer's disease (AD).

Patients and methods Data from patients in a phase II trial of [^{18}F]flutemetamol for PET imaging of brain amyloid and from the Alzheimer's Disease Neuroimaging Initiative were used to train the prognostic model to yield a disease state index (DSI), a measure of the similarity of an individual patient's data to data from patients in specific diagnostic groups. Inputs to the model included amyloid PET results, MRI measurements of hippocampal volume, and the results of psychometric tests. The model was subsequently validated by using data from a prospective study of an independent cohort of patients with mild cognitive impairment.

Results In total, data from 223 patients of the 233 enroled were suitable for analysis. The DSI predicted by the model and the risk of progression to AD dementia within 3 years were higher for patients with amyloid deposition and

neurodegeneration than for patients with amyloid deposition without neurodegeneration. Rates of non-AD dementia among patients with neurodegeneration at baseline were consistent with the results of other studies. The results were consistent with the Jack model of AD progression.

Conclusion The DSI from the model that included psychometric, MRI, and PET amyloid data provides useful prognostic information in cases of mild cognitive impairment. *Nucl Med Commun* 39:297–303 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

Introduction

To provide a framework for in-vivo staging of Alzheimer's disease (AD), Jack *et al.* [1] developed a model of the trajectories of the major biomarkers of AD and the clinical progression of AD. Evidence of brain amyloid deposition (as revealed by low levels of Aβ$_{42}$ in cerebrospinal fluid or high uptake of amyloid PET tracers in the brain) is present for years before the onset of cognitive deficit. The appearance of biomarkers of amyloid deposition is followed by the appearance of biomarkers of neurodegeneration (elevation of tau in cerebrospinal fluid and increased brain uptake of tau ligands as shown by tau-PET imaging). These changes are then followed by the onset of hypometabolism in the brain (as shown by fluorodeoxyglucose PET imaging) and brain atrophy (as shown by structural MRI). Typically, the

onset of hypometabolism and structural changes coincides with the onset of amnestic mild cognitive impairment (aMCI), as measured by psychometric tests. Over the course of a few years, a case of aMCI may progress to Alzheimer's dementia, with an accompanying increase of most of the imaging and clinical biomarkers.

The prognostic information provided by the AD biomarkers is valuable, both for clinical management of the patient and for the family's adjustment of lifestyle. In addition, early diagnosis of AD may allow the patient to take part in trials of disease-modifying drugs. The European PredictND research project (*http://www.predictnd.eu*) aims to provide computerized tools that analyse AD biomarkers and psychometric test results to ascertain a patient's status within the pathologic cascade of AD. The PredictND clinical decision support system (CDSS) yields a disease state index (DSI), which is a statistic that is derived from various kinds of data about a patient, as compared with a large cohort that had been studied prospectively [2]. In this article, we

describe how the amyloid PET imaging results were incorporated into the PredictND model and how the resulting DSI was validated, as well as explaining how the resulting DSI reflects the patient's status within the pathologic cascade of AD.

Data from GE Healthcare's [3–5] [^{18}F]flutemetamol clinical trials and from the Alzheimer's Disease Neuroimaging Initiative studies [6,7] were used to incorporate amyloid PET status into the PredictND model. GE Healthcare [8] conducted a study of a separate cohort of aMCI patients, who were followed up every 6 months for 3 years. In a post-hoc analysis from that study, each patient's baseline prognosis, as characterized by the DSI from the updated PredictND, was compared with the patient's actual outcome at 3 years, for patients stratified by amyloid status and neurodegeneration status.

Patients and methods
Model construction
Model development cohort
The data that were used to train the PredictND CDSS model were derived from two main sources. The data on amyloid PET imaging results for patients with AD as compared with elderly healthy volunteers were drawn from GE Healthcare's phase II studies (ALZ201 [4,5] and GE067-017 [3]). The data on structural MRI findings were drawn from the Alzheimer's Disease Neuroimaging Initiative studies of AD patients [mean Mini-Mental State Examination (MMSE) score of 23.3] and patients who were cognitively normal (clinical dementia rating of 0 and a mean MMSE of 29.13) but who expressed a significant memory concern and were exhibiting slight symptoms of forgetfulness [6,7]. The demographics of these patients are shown in Table 1.

Table 1   Demographics of the cohort used for training PredictND clinical decision support system

	ALZ201[a]		GE067-017[a]		ADNI[b]	
	EHV	AD	EHV	AD	CN	AD
Patients	14	23	15	30	215	188
Sex						
Male	8	10	8	11	111	98
Female	6	13	7	19	104	90
Age						
Mean	68.57	68.39	62.47	74.6	76.03	75.48
SD	7.89	6.81	5.64	5.57	5.04	7.38
Years of education						
Mean	12.93	14.3	13.27	11.3	16.01	14.6
SD	3.15	4.31	1.58	2.65	2.87	3.15
MMSE						
Mean	28.71	23.43	29.87	21.08	29.13	23.30
SD	0.99	2.25	0.35	3.07	0.99	2.04

AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CN, cognitively normal; EHV, elderly healthy volunteer; MMSE, Mini-Mental State Examination.
[a]Baseline data from patients enrolled in phase II studies of [^{18}F]flutemetamol [3–5].
[b]Screening data from patients enrolled in Alzheimer's Disease Neuroimaging Initiative [6,7].

Variables
The variables in PredictND CDSS included the standardized uptake value ratio (SUVr) of the amyloid PET agent [^{18}F]flutemetamol in several brain regions where amyloid may build up, structural information derived from MRI, and the results of psychometric testing.

SUVr measurements were performed by the CortexID package [9]. The cortical scores from the package included SUVrs from the parietal, occipital, anterior cingulate, prefrontal, temporal lateral, and precuneus/posterior cingulate regions, as well as a composite score that CortexID provides. The reference region was whole cerebellum.

In addition to the volumetry of the hippocampus, amygdala, and ventricles, MRI images were quantified by using tensor-based morphometry and voxel-based morphometry [10].

Disease state index
The DSI is a metric for estimating the similarity of the data from an individual patient to data from previously diagnosed cases, such as cognitively normal patients, AD patients, and patients with stable or progressive mild cognitive impairment (MCI). The DSI has two key components: fitness and relevance. The similarity is measured through the fitness function defined as follows:

$$\text{Fitness}(x) = \frac{\text{FN}(x)}{\text{FN}(x) + \text{FP}(x)},$$

where $\text{FN}(x)$ and $\text{FP}(x)$ are false-negative and false-positive rates, respectively, if the feature value x is used to classify the feature. The fitness function maps a feature value to a comparable value space between 0 and 1. A value of 0 indicates strong similarity to the negative group (e.g. cognitively normal patients or patients with stable MCI), whereas a value of 1 indicates strong similarity to the positive group (e.g. AD patients or patients with progressive MCI). Relevance, which defines the performance of the feature in separating the two diagnostic classes in question, is defined as follows:

$$\text{Relevance} = \max\left(\text{sensitivity} + \text{specificity} - 1, 0\right).$$

In other words, relevance is related to the classification accuracy of the feature. Finally, the total DSI is computed over all N available features as follows:

$$\text{DSI}(x) = \frac{\sum_{i=1}^{N} \text{relevance}_i \times \text{fitness}_i(x)}{\sum_{i=1}^{N} \text{relevance}_i}.$$

The DSI values can also be defined hierarchically, which means that DSI can be computed for PET, MRI, and psychometric data separately, providing a composite similarity measure for each data source. Finally, these composite scores can be combined for creating the total DSI.

Fig. 1
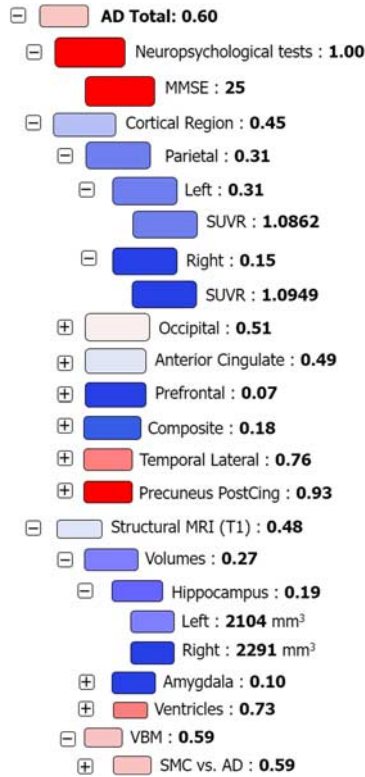
A visualization of the disease state fingerprint in the PredictND tool. The individual's value for the amyloid burden in the parietal region can be seen to be highly relevant and close to MCI pathology because of the size and colour of the box. Different nodes may have different colours, indicating that some features may align more than others to AD pathology. The 'Neuropsychological tests' seem to indicate AD, whereas 'Structural MRI (T1)' does not. AD, Alzheimer's disease; DSI, disease state index; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SMC, subjective memory complaints; SUVr, standardized uptake value ratio; VBM, voxel-based morphometry.

Fig. 2

A visualization of the disease state index in the PredictND tool. The graph shows the DSI for a hypothetical patient (depicted by the thick black line) in comparison with the distribution of DSIs for the AD population (in red) and the non-AD population (in blue). In this case, the score was calculated by using neuropsychological tests, cortical regions (amyloid PET standardized uptake value ratio), and data from the MRI. AD, Alzheimer's disease; SMC, subjective memory complaints.
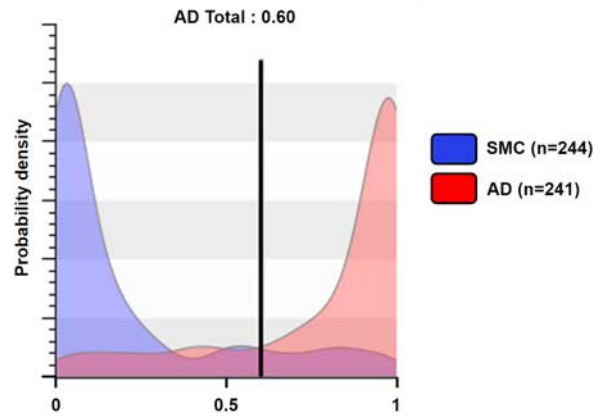
Disease state fingerprint

All of these values can be presented graphically and interactively in the disease state fingerprint (Fig. 1), which is a graphical counterpart of DSI (Fig. 2). In the disease state fingerprint, the size of the box indicates the relevance of the feature and the colour of the box indicates the fitness of the feature.

Model validation
Model validation cohort

GE Healthcare conducted a study (GE067-005 [8]) that enroled an independent cohort, which was used to validate the PredictND CDSS. To be eligible for enrolment, a patient had to be at least 55 years old and meet the Peterson criteria [11] for aMCI [a memory complaint; a delayed paragraph recall of less than or equal to 11 for patients with 16 or more years of education (YoE), less than or equal to 9 for patients with 8–15 YoE, and less than or equal to 6 for patients with 0–7 YoE; a Clinical

Dementia Rating scale score of 0.5; activities of daily living performance such that probable AD could not be diagnosed; a score of less than or equal to 4 on the Modified Hachinski Ischaemia Scale; and an MMSE score of 24–30]. The patients had undergone non-contrast three-dimensional T1-weighted MRI within 6 months of enrolment to exclude structural or vascular causes. The patient had to have a score of less than or equal to 12 on the 17-item Hamilton Depression Scale. Data from GE067-005 was used here in a post-hoc analysis to perform validation of the model.

Imaging procedures

At baseline, each patient underwent three-dimensional T1-weighted MRI (if not already available), followed by an amyloid PET scan with [18F]flutemetamol. Patients received ~ 185 MBq [18F]flutemetamol and underwent a 30 min [collected in six 5-min frames] brain scan at ~ 90 min postinjection. The first two frames were summed for image reading. As part of the study, the amyloid images were read by five independent readers who were blinded to study details. The readers rated the images as either positive or negative for amyloid. Classification by majority read was used for dichotomous analysis.

Psychometric testing

The baseline assessment included a battery of psychometric tests. The psychometric assessments were repeated every 6 months for up to 3 years. These psychometric assessments were reviewed periodically by an independent clinical adjudication committee, which decided whether the patient had progressed from aMCI and qualified for a diagnosis of

Table 2 Stratification of patients, according to baseline characteristics

Amyloid status[a]	Hippocampal volume status[b]
Amyloid-negative (A−)	Neuronal injury negative (N−)
Amyloid-negative (A−)	Neuronal injury positive (N+)
Amyloid-positive (A+)	Neuronal injury negative (N−)
Amyloid-positive (A+)	Neuronal injury positive (N+)

[a]In the amyloid PET scan, amyloid status was determined in a blinded visual read.
[b]In the MRI, a hippocampal volume of less than 4.5 cm^3 was considered to be evidence of neuronal injury.

Table 3 Baseline demographics of validation cohort

Variables	Value
Age [mean (SD)] (years)	71.1 (8.62)
Sex [n (%)]	
Female	118 (51)
Male	114 (49)
Race [n (%)]	
Asian	1 (<0.5)
Black	5 (2)
White	225 (97)
Other	1 (<0.5)
Ethnicity [n (%)]	
Not Hispanic or Latino	191 (82)
Hispanic or Latino	41 (18)
Height [mean (SD)] (cm)	167 (10.7)
Weight [mean (SD)] (kg)	74.6 (15.28)
BMI [mean (SD)] (kg/m^2)	27 (4.3)

Table 4 Results of baseline neurologic testing, validation cohort

Test	Results [mean (SD)]	Normal value or range
Mini-Mental State Examination	27.1 (2.15)	30
17-item Hamilton Depression Scale	2.0 (2.23)	0–7
Activities of Daily Living	73.8 (4.15)	72–78
Logical Memory II, immediately after story	9.0 (3.55)	Varies with age and years of education
Logical Memory II, 30 min after story	5.8 (3.30)	Varies with age and years of education
Clinical Dementia Rating	0.50 (0)	0
Modified Hachinski Ischaemic Scale	0.6 (0.74)	0–2

Table 5 Kaplan–Meier survival estimate (no dementia) and disease severity index for patients stratified by amyloid status and neuronal injury

Study status	Number of patients	Survival estimate [% (95% CI)] after 36 months	Mean DSI	Median DSI	DSI > 0.5 (%)
A−N−	83	86 (75.1–92.4)	0.27	0.16	20.5
A−N+	42	53.3 (35.8–68.1)	0.45	0.43	45.2
A+N−	40	45.7 (28.0–61.8)	0.58	0.50	52.5
A+N+	57	12.9 (1.3–38.5)	0.77	0.91	86.0

Amyloid status was rated as abnormal (A+) or normal (A−) according to the majority read of a [^{18}F]flutemetamol amyloid PET scan. Neuronal injury was classified as present (N+) or absent (N−) according to the hippocampal volume (≤4.5 or >4.5 cm^3, respectively).
CI, confidence interval; DSI, disease severity index.

Alzheimer's-type dementia. Once the patient received a diagnosis of AD, no further assessments were made.

Statistical analysis

The results of the amyloid PET imaging were used to stratify the patients as amyloid-positive (A+) or amyloid-negative (A−). In a post-hoc analysis, the results of the three-dimensional T1-weighted MRI were used to classify the patients according to the presence or absence of neurodegeneration (N+ or N−), as indicated by hippocampal volume. The hippocampus was segmented by using a local, patch-based label fusion approach [12]. Mean volumes were adjusted for intracranial volume by multiplying native space volume by a scaling factor estimated from the affine matrix needed to coregister the individual skull to a standard MNI152 reference (e.g. the SIENAX approach) [13]. Scaled hippocampal volumes less than 4.5 cm^3 were considered abnormal.

The initial goal of the study was to measure the rate of conversion to AD for A+ versus A− patients. However, the patients were ultimately stratified into four groups (A+N+, A+N−, A−N+, and A−N−; see Table 2) because hippocampal volume is associated with prediction of AD in patients with MCI [14].

The mean and median DSI, as well as the percentage of patients with DSI more than 0.5, were calculated for each stratum. The Kaplan–Meier method was used to analyse conversion from aMCI to AD, according to the diagnosis made by the clinical adjudication panel, for each stratum. The percentage of patients whose conversion status was accurately predicted by their DSI was calculated for a DSI cutoff of 0.5 and for the upper and lower quartiles of DSI.

Results

In total, 232 patients were enroled in the validation study; 10 of these patients were excluded from this validation analysis because of missing information (psychometric status, MRI structural information, or amyloid PET scan results). The baseline demographic characteristics are shown in Table 3. The results of baseline neurologic testing are shown in Table 4.

The mean DSI was 0.69 for patients who converted from MCI to AD and 0.38 for those who did not convert. When a DSI cutoff of 0.5 was used, the DSI score accurately predicted the conversion status for 71% of the patients. In comparison, the accuracy increased to 81% when the prediction for patients in the highest and lowest DSI quartiles was compared with the clinical outcome.

Table 5 shows the DSIs and 3-year survival estimates (i.e. estimates of the percentage of patients who did not convert from an MCI to AD diagnosis) for patients stratified as shown in Table 2. Figure 3 shows the DSI scores for these four strata. Table 6 shows the survival estimates at 6-month intervals for the four strata. When final survival rates for the groups were compared with their

Fig. 3
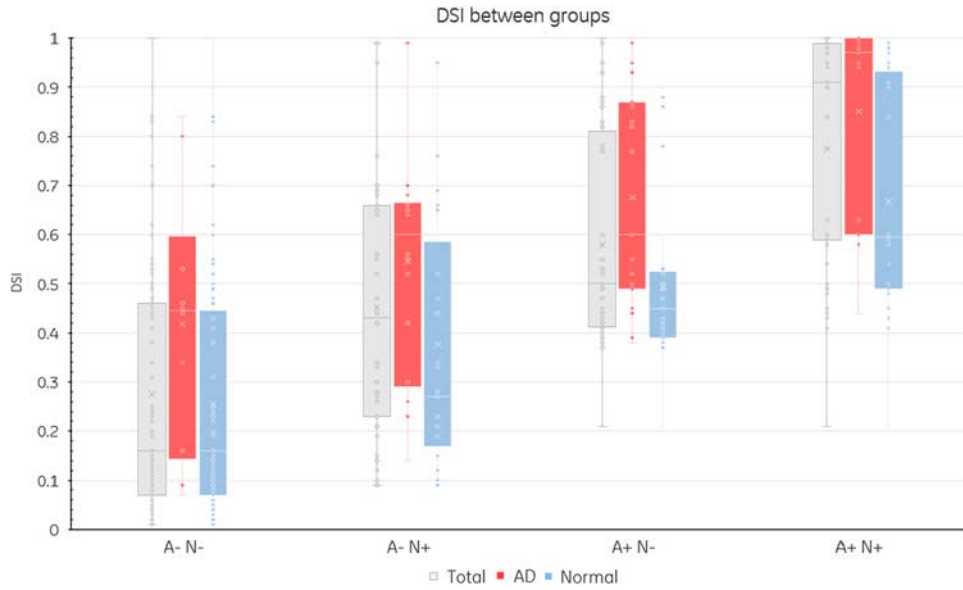
A box plot showing the DSI scores for the groups A−N−, A−N+, A+N− and A+N+. For each group, the DSIs for all patients are shown in grey for each patient, the DSIs for just those who converted to AD are shown in red, and the DSIs for those who did not convert are shown in blue. AD, Alzheimer's disease; DSI, disease state index.

Table 6   Kaplan–Meier analysis of survival (i.e. lack of dementia diagnosis) among 222 patients from GE067-005 [^{18}F]flutemetamol imaging for progression from amnestic mild cognitive impairment to Alzheimer's disease

Timepoint	Survival estimate [% (95% confidence interval)] at each timepoint			
	A + N + (N=57)	A + N − (N=40)	A − N + (N=42)	A − N − (N=83)
6 months	96.5 (86.6–99.1)	92.5 (78.5–97.5)	97.5 (83.5–99.6)	98.8 (91.8–99.8)
12 months	80.3 (67.3–88.6)	77.5 (61.2–87.6)	87.2 (71.8–94.4)	97.6 (90.7–99.4)
18 months	71.0 (57.0–81.1)	72.0 (55.0–83.4)	70.9 (53.5–82.7)	93.8 (85.9–97.4)
24 months	67.0 (52.8–77.8)	66.2 (48.9–78.9)	62.7 (45.2–76.0)	92.5 (84.2–96.6)
30 months	48.8 (34.1–62.0)	63.2 (45.7–76.4)	60.0 (42.6–73.6)	89.8 (80.5–94.8)
36 months	12.9 (1.3–38.5)	45.7 (28.0–61.8)	53.3 (35.8–68.1)	86.0 (75.1–92.4)

Amyloid status was rated as abnormal (A+) or normal (A−) according to the majority read of a [^{18}F]flutemetamol amyloid PET scan. Neuronal injury was classified as present (N+) or absent (N−) according to the hippocampal volume (≤4.5 or >4.5 cm^3, respectively).

respective mean DSI scores (Fig. 4), it was found that the A − N − stratum, which had a survival rate of 86%, had a mean DSI mean of 0.27. In contrast, the A + N + stratum, which had a survival rate of 12.9%, had a mean DSI of 0.77. The two other groups (which were positive only for neurodegeneration or only for amyloid) had a mean DSI of 0.45 and 0.58, respectively.

Some skew was observed. The A − N − stratum had a skewness of 0.86, indicating a strong positive skew. Conversely, the A + N + stratum had a negative skew (− 0.56). To reduce the impact of patients with unusually high or low DSI values (producing skew), the analysis was run for median rather than mean DSI values. In that analysis, the A − N − and A + N + strata had the largest difference (a DSI of 0.16 for A − N − and a DSI of 0.91 for A + N +).

Discussion

The PredictND CDSS is a tool aimed at early-phase detection and diagnosis of neurodegenerative diseases, to provide prognostic information and potentially allow for interventions to modify disease progression. This tool provides statistical calculations to rank individual patients in relation to the model cohort, as well as providing several visual aids to help users interpret the results.

The results of this study are consistent with the Jack model of the progression of AD [1]. The Jack model posits that amyloid positivity precedes neuronal injury. For this reason, the analysis of amyloid build-up (SUVr scores in various regions of the brain) is an important factor in early detection of AD. In the intermediate stage of the disease, the brain starts suffering neuronal injury, which can be observed as cortical atrophy in structural MRI. In the late

Fig. 4
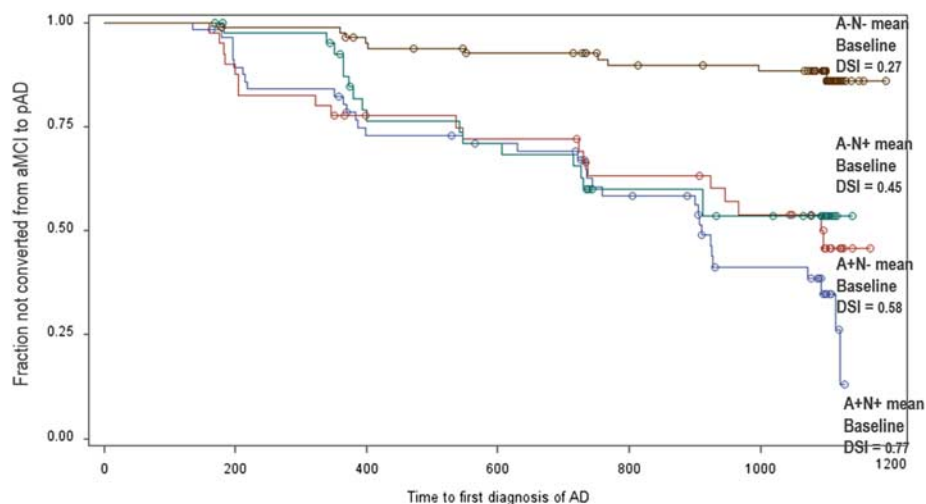
Kaplan–Meier style survival plot. Here, survival means nonconversion to AD from aMCI. Baseline disease state indices are added for the four groupings: A−N−, A−N+, A+N−, and A+N+. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; DSI, disease state index; pAD, probable Alzheimer's disease.

stage of the disease, cognitive decline is readily assessed by psychometric tests, such as the MMSE.

According to the Jack [1] model, A+N− patients are presumed to be at an earlier stage of the development of AD than are A+N+ patients. In this study, the PredictND CDSS tool yielded a median DSI of 0.5 for the A+N− patients and 0.91 for the A+N+ patients. The Kaplan–Meier survival analysis (in which survival meant that the patient had not yet progressed to clinical dementia) provided 3-year survival values of ~0.5 for A+N− patients and 0.1 for A+N+ patients (Fig. 4). Thus, when used with baseline biomarkers, the PredictND CDSS tool accurately predicted that most of the A+N+ group would develop AD dementia. In contrast, the tool gave a mid-range DSI value to the A+N− group, which had a survival estimate of ~0.5 after 3 years.

A subgroup of the patients who were classified as amyloid negative (A−) on the basis of the independent visual read had neuronal injury (N+) as indicated by MRI. Clearly, these A−N+ patients were not following the expected disease path for Alzheimer's. As they did not have appreciable levels of amyloid, they cannot be classified as having AD – even in cases where the clinical adjudication committee (which reviewed the psychometric data at baseline and during follow-up) judged the patients to have converted from aMCI to probable AD. Amyloid-negative patients with evidence of neuronal injury are often described as having suspected non-Alzheimer's disease pathophysiology (SNAP). Non-AD pathologies including cerebrovascular disease, α-synucleinopathy, argyrophilic grain disease, TDP-43 proteinopathy, hippocampal sclerosis, and primary age-related tauopathies are common with advancing age. The accompanying neurodegeneration

is a result of synapse loss [15]. Just under half of individuals with MCI and SNAP progress to non-AD dementia (e.g. Prestia et al. [16]).

Roughly 19% of the patients in the current study had SNAP. In other studies, SNAP accounted for ~25% of cases of MCI [17]. In the study reported here, 45% of the patients with MCI and SNAP developed dementia by the end of the 3-year follow-up. For these patients, the DSI provided by the PredictND tool was 0.5, which is highly consistent with this rate of decline.

At the end of the 3-year follow-up, only 12% of the 83 patients who were A−N− at baseline received a diagnosis of dementia from the clinical adjudication committee. The median DSI for these patients was 0.16. It is unlikely that significant levels of amyloid pathology could have developed within this timeframe. Thus, these dementia cases were probably non-AD dementia. Note that the clinical adjudication committee was set up to review the psychometric scores recorded at baseline and during follow-up. Thus, it could detect whether a patient had progressed to dementia but it would not have been able to differentiate AD dementia from non-AD dementia as the committee was blind to amyloid status. Note that Vos et al. [18] reported that 10% of A−N− patients with MCI converted to a non-AD dementia. That finding is consistent with the rates in this validation study; thus, the DSI level for the A−N− group in this study was appropriate.

Conclusion
In this study, the use of the PredictND tool, which incorporates T1 MRI results, SUVrs from amyloid PET

imaging, and psychometric data, provided DSI values that accurately predicted clinical status 3 years later. This study demonstrates that the tool provides useful prognostic information for patients at risk of AD dementia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1   Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, *et al.* Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013; **12**:207–216.

2   Muñoz-Ruiz MA, Hartikainen P, Hall A, Mattila J, Koikkalainen J, Herukka SK, *et al.* Disease state fingerprint in frontotemporal degeneration with reference to Alzheimer's disease and mild cognitive impairment. *J Alzheimers Dis* 2013; **35**:727–739.

3   GE Healthcare. Brain uptake and safety with probable Alzheimer's disease, amnestic mild cognitive impairment and healthy volunteers (ALZ201): NCT00785759; 2009. Available at: *https://clinicaltrials.gov/ct2/show/NCT00785759*. [Accessed 23 August 2017].

4   Vandenberghe R, van Laere K, Ivanoiu A, Salmon E, Bastin C, Triau E, *et al.* ^{18}F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Ann Neurol* 2010; **68**:319–329.

5   GE Healthcare. Comparison of PET amyloid imaging in Japanese and Western subjects: NCT02813070; 2017. Available at: *https://clinicaltrials.gov/ct2/show/NCT02813070*. [Accessed 23 August 2017].

6   Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, *et al.* The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clin N Am* 2005; **15**:869–877.

7   Carrillo MC, Bain LJ, Frisoni GB, Weiner MW. Worldwide Alzheimer's disease neuroimaging initiative. *Alzheimers Dement* 2012; **8**:337–342.

8   GE Healthcare. Assess the prognostic usefulness of flutemetamol (^{18}F) injection for identifying subjects with amnestic mild cognitive impairment who will convert to clinically probable Alzheimer's disease: NCT01028053; 2014. Available at: *https://clinicaltrials.gov/ct2/show/NCT01028053*. [Accessed 23 August 2017].

9   GE Healthcare. CortexID Suite; 2017. Available at: *http://www3.gehealthcare.com/en/Products/Categories/Advanced_Visualization/Applications/CortexID*. [Accessed 23 August 2017].

10 Koikkalainen J, Rhodius-Meester H, Tolonen A, Barkhof F, Tijms B, Lemstra AW, *et al.* Differential diagnosis of neurodegenerative diseases using structural MRI data. *Neuroimage Clin* 2016; **11**:435–449.

11 Petersen RC, Aisen P, Boeve BF, Geda YE, Ivnik RJ, Knopman DS, *et al.* Mild cognitive impairment due to Alzheimer disease in the community. *Ann Neurol* 2013; **74**:199–208.

12 Coupe P, Manjon JV, Fonov V, Pruessner J, Robles M, Collins DL. Patch-based segmentation using expert priors: application to hippocampus and ventricle segmentation. *Neuroimage* 2011; **54**:940–954.

13 SIENA. Research overview. Available at: *https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/siena*. [Accessed 23 August 2017].

14 Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, *et al.* Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999; **52**:1397–1403.

15 Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, *et al.* Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol* 2006; **63**:674–681.

16 Prestia A, Caroli A, van der Flier WM, Ossenkoppele R, van Berckel B, Barkhof F, *et al.* Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology* 2013; **80**:1048–1056.

17 Jack CR Jr, Knopman DS, Chetelat G, Dickson D, Fagan AM, Frisoni GB, *et al.* Suspected non-Alzheimer disease pathophysiology – concept and controversy. *Nat Rev Neurol* 2016; **12**:117–124.

18 Vos SJ, Verhey F, Frolich L, Kornhuber J, Wiltfang J, Maier W, *et al.* Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain* 2015; **138** (**Pt 5**):1327–1338.