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BRAIN COMMUNICATIONS

Longitudinal evaluation of the natural history of amyloid- β in plasma and brain

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Plasma amyloid- β peptide concentration has recently been shown to have high accuracy to predict amyloid- β plaque burden in the brain. These amyloid- β plasma markers will allow wider screening of the population and simplify and reduce screening costs for therapeutic trials in Alzheimer's disease. The aim of this study was to determine how longitudinal changes in blood amyloid- β track with changes in brain amyloid- β . Australian Imaging, Biomarker and Lifestyle study participants with a minimum of two assessments were evaluated (111 cognitively normal, 7 mild cognitively impaired, 15 participants with Alzheimer's disease). Amyloid- β burden in the brain was evaluated through PET and was expressed in Centiloids. Total protein amyloid- β 42/40 plasma ratios were determined using ABtest[®] assays. We applied our method for obtaining natural history trajectories from short term data to measures of total protein amyloid- β 42/40 plasma ratios and PET amyloid- β . The natural history trajectory of total protein amyloid- β 42/40 plasma ratios appears to approximately mirror that of PET amyloid- β , with both spanning decades. Rates of change of 7.9% and 8.8%, were observed for total protein amyloid- β 42/40 plasma ratios and PET amyloid- β , respectively. The trajectory of plasma amyloid- β preceded that of brain amyloid- β by a median value of 6 years (significant at 88% confidence interval). These findings, showing the tight association between changes in plasma and brain amyloid- β , support the use of plasma total protein amyloid- β 42/40 plasma ratios as a surrogate marker of brain amyloid- β . Also, that plasma total protein amyloid- β 42/40 plasma ratios has potential utility in monitoring trial participants, and as an outcome measure.

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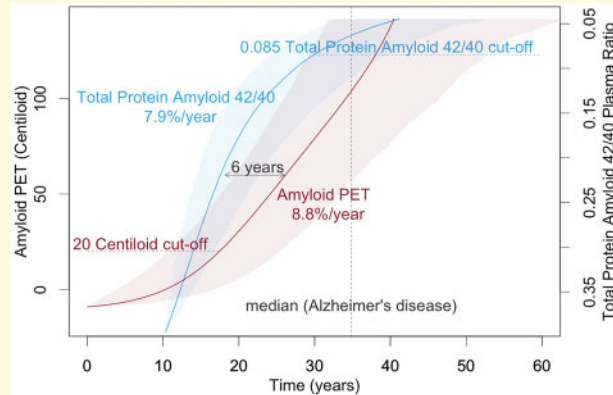
Abbreviations: A β = amyloid- β ; AIBL = The Australian Imaging, Biomarker and Lifestyle; CL = Centiloids; CN = cognitively healthy normal controls; MCI = mild cognitively impaired

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Graphical Abstract



Introduction

Recently proposed frameworks suggest that a triad of biomarkers (Burnham *et al.*, 2019a, b; Jack *et al.*, 2019; van Maurik *et al.*, 2019), namely amyloid- β ($A\beta$; A), tau (T) and neurodegeneration ([N]), are able to biologically classify Alzheimer's disease even at preclinical disease stages (Jack *et al.*, 2018). These biomarkers have predominantly been quantified using imaging techniques (PET, MRI) or CSF levels. PET imaging is relatively expensive and has limited availability; CSF requires lumbar puncture and is considered invasive by many. Therefore, alternative approaches are desirable for widespread population screening.

A number of reports now demonstrate the accuracy with which plasma levels estimate both the insoluble $A\beta$ via PET imaging and the soluble $A\beta$ via CSF measures. Plasma $A\beta$ has reported area under the receiver operating curve values of 90% for discriminating between brain $A\beta$ positives and negatives (Fandos *et al.*, 2017; Ovod *et al.*, 2017; Nakamura *et al.*, 2018). In regard to the $A\beta$ (A), tau (T) and neurodegeneration ([N]) framework (Jack *et al.*, 2018), recent reports show that plasma pTau can discriminate between controls and Alzheimer's disease, achieving area under the receiver operating curve values of 80% (Kovacs *et al.*, 2017; Fossati *et al.*, 2019). Along the same line, neurofilament light has emerged as an accurate plasma measure for Alzheimer's disease progression and has been shown to discriminate between controls and Alzheimer's disease, suggesting that it could be used as a robust marker of neurodegeneration (Kovacs *et al.*, 2017; Lewczuk *et al.*, 2018; Mattsson *et al.*, 2019).

Given the reported accuracies of the plasma biomarkers for quantifying $A\beta$, Tau and neurodegeneration as well as the ease and access for utilizing blood for screening, the $A\beta$ (A), tau (T) and neurodegeneration ([N]) framework for biologically classifying Alzheimer's disease now appears achievable using a blood-based screening test.

Whilst threshold and correlation analyses on cross-sectional data look promising for such screening tests, the

dynamic nature of plasma levels and their relationship with imaging and CSF biomarkers need to be further elucidated to fully understand the value such tests may have for monitoring progression as well as potential outcome measures in clinical trials. This contribution aims to evaluate longitudinal data to understand the natural history of $A\beta$ as measured in both plasma and by PET imaging.

Materials and methods

Australian Imaging, Biomarker and Lifestyle cohort

The Australian Imaging, Biomarker and Lifestyle (AIBL) cohort study of ageing combines data from neuroimaging, biomarkers, lifestyle, clinical and neuropsychological assessments. Two study centres in Melbourne, VIC, and Perth, WA, Australia, recruit mild cognitively impaired (MCI) individuals and individuals with Alzheimer's disease from primary care physicians or tertiary Memory Disorders Clinics. Cognitively healthy normal controls (CN) were recruited through advertisement or from spouses of participants in the study. Exclusion criteria were a history of non-Alzheimer's disease dementia, Parkinson's disease, schizophrenia, bipolar disorder, obstructive sleep apnoea, serious head injury, current depression (geriatric depression score >5 out of 15), cancer in the past 2 years (with the exception of basal-cell skin carcinoma), symptomatic stroke, uncontrolled diabetes or current regular alcohol use. Between 3 November 2006 and 30 October 2008, AIBL recruited 1112 eligible volunteers, who were aged 60 years or older and fluent in English. An enrichment cohort of 86 patients with Alzheimer's disease, 124 MCI and 389 CN was recruited by AIBL between 30 March 2011 and 29 June 2015. At baseline, the AIBL study participants were an average of 72 years of age, the study consisted of 58% women, and 36% were apolipoprotein E- $\epsilon 4$ carriers. The institutional

ethics committees of Austin Health, St Vincent's Health, Hollywood Private Hospital and Edith Cowan University approved the AIBL study, and all volunteers gave written informed consent before participating.

A subset of the AIBL cohort, who had undergone at least two evaluations of both A β PET and total protein A β 42/A β 40 plasma ratios using the ABtest[®] assays (Araclon Biotech, Zaragoza, Spain), was utilized in this study. Furthermore, individuals considered to be A β negative [<20 Centiloids (CL)] and non-accumulators (longitudinal rates of change <0.0 CL/year) based on PET evaluations who were not exhibiting pathology of disease were excluded from this study (Villemagne *et al.*, 2013). Thus, data from 133 participants (111 CN, 7 MCI, 15 Alzheimer's disease) who were an average of 72 years of age, consisted of 54% males and 32% apolipoprotein E- ϵ 4 carriers were evaluated.

PET A β evaluation

AIBL A β PET studies consisted of a 20-min acquisition starting 50 min after the injection of 370 MBq of ¹¹C-Pittsburgh compound-B. For the semi-quantitative analysis, PET images were spatially normalized with CapAIBL[®] using an adaptive atlas (Bourgeat *et al.*, 2015). The spatially normalized PET images were then converted into CL (Bourgeat *et al.*, 2018) using the standard CL cortical and whole cerebellum masks (Bourgeat *et al.*, 2018). Images were then corrected to the standard CL SPM8 approach as previously described (Bourgeat *et al.*, 2018). The abnormal threshold for levels of brain A β in AIBL participants was set as >20 CL (equivalent to 1.44 standardized uptake value ratio using the cerebellar cortex as reference region and 1.25 standardized uptake value ratio using the whole cerebellum as a reference region) (Rowe *et al.*, 2018).

Plasma A β evaluation

Plasma samples were obtained using Ethylenediaminetetraacetic acid (EDTA) as anticoagulant and following AIBL procedures (Rembach *et al.*, 2014) and were conserved at -70°C until analysis without undergoing any extra freezing/thaw cycles. Total protein A β 42/A β 40 plasma ratios were determined using ABtest[®] assays, two validated colorimetric assays based in the sandwich enzyme-linked immunosorbent assay technique, as described elsewhere (Pérez-Grijalba *et al.*, 2016). The analyses were always performed in a coded manner to ensure that the knowledge of other participant evaluations was not available to the operator. The abnormal threshold for the ratio of plasma A β in AIBL participants was set as <0.085 . This threshold was based upon receiver operating characteristics using the Youden index for plasma A β against brain A β positives and negatives (Doecke *et al.*, 2020).

Statistical analyses

AIBL participants ($n = 133$) with at least 18 months of follow-up evaluations for A β who were considered to be accumulating A β (rate of deposition >0.0 CL/year; Villemagne *et al.*, 2013) were included in this study. All analyses were performed in the R environment (R Development Core Team, 2017). Note, analyses were replicated in a subset of these participants ($n = 112$) with at least 3 years of follow-up testing, the findings were not altered.

Baseline differences between CN, MCI and Alzheimer's disease were assessed with one-way *t*-tests for continuous data (age, amyloid PET, plasma amyloid, rate of change in amyloid measures), χ^2 testing for categorized data (sex, years of education, disease classification, number of follow-ups) and Kruskal–Wallis testing for non-normally distributed data (length of follow-up).

Natural history of deposition for both plasma and PET A β was evaluated using the four-step procedure described previously (Villemagne *et al.*, 2013; Budgeon *et al.*, 2017). Briefly, the four-step procedure comprises (i) estimating the mean and slope of each individuals' A β using linear models (refer to Fig. 1A and D), (ii) fitting a polynomial to the estimated means and slopes across all individuals (refer to Fig. 1B and E), (iii) integrating the reciprocal of the fitted polynomial (refer to Fig. 1C and F) and (iv) inverting the function to obtain the natural history trajectory (refer to Fig. 2). Confidence intervals for the natural history curves were created using the bootstrapping procedure described previously (Budgeon *et al.*, 2017). Axes were anchored by taking the mean of the values exhibited by individuals at the extremes of each measure. The curves were anchored using the median values exhibited by the mild Alzheimer's disease participants.

Data availability

A subset of the AIBL data including images is shared through the LONI Image and Data Archive (<http://adni.loni.usc.edu>), a secure research data repository. Applications for access to the entirety of the AIBL data can be made via application through the AIBL website (<https://aibl.csiro.au/>).

Results

Demographics

The Alzheimer's disease participants had significantly less education than CN, and MCI and Alzheimer's disease had significantly less follow-up than CN (Table 1).

Baseline amyloid evaluations

MCI and Alzheimer's disease participants had significantly higher levels of brain A β than the CN. No differences were observed for the plasma A β .

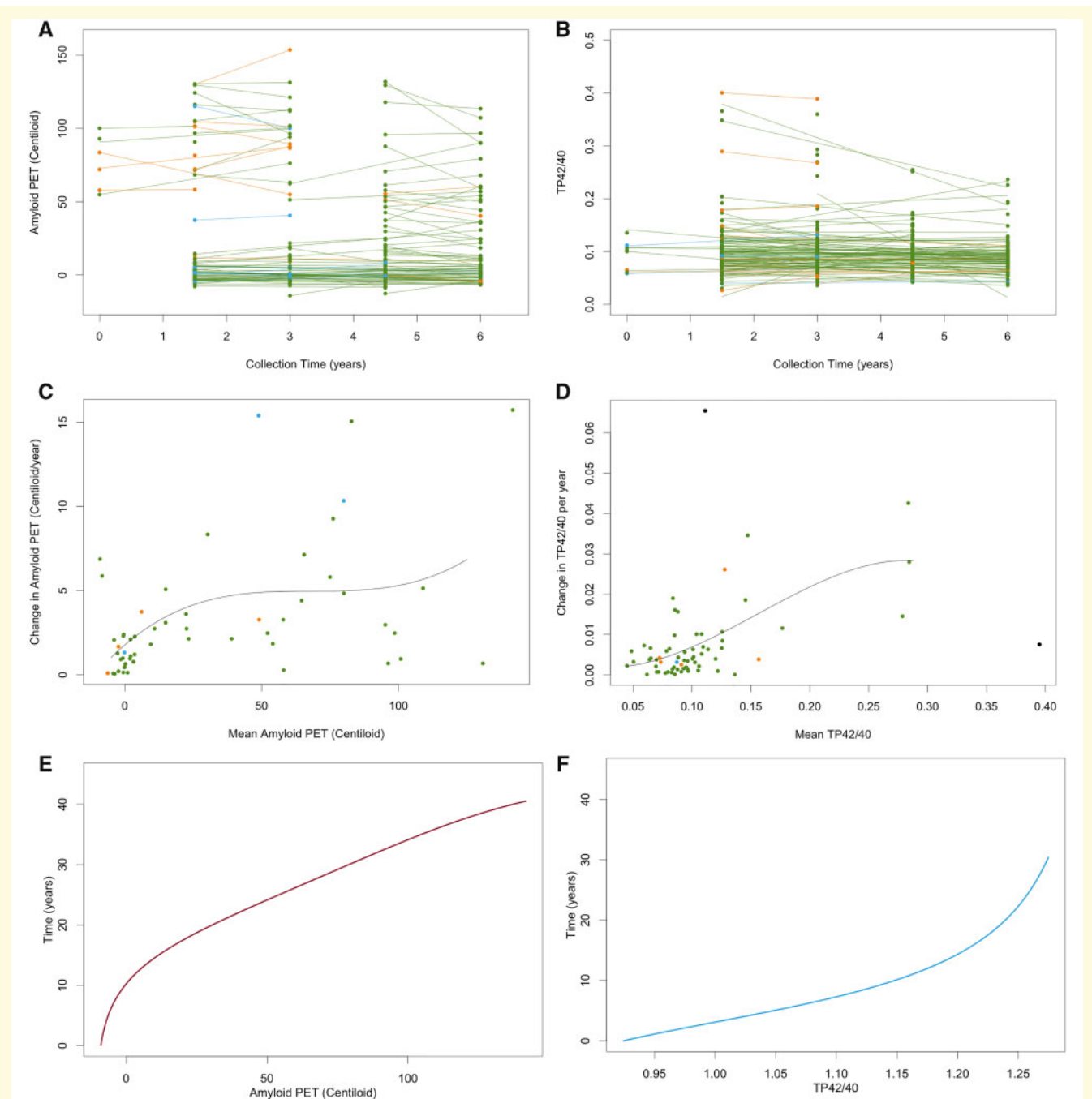


Figure 1 Graphical representations of the first three steps of the data analysis method for Ab PET (A, C, E) and plasma AbTP42/40 ratio (B, D, F). Step 1 (A and B) represents the raw data and fitted linear models for each individual; Step 2 (C and D) represents plots of the individuals' slopes versus their mean observed values and the fitted cubic polynomial to this data; and Step 3 (E and F) represents the integral of the fitted cubic polynomial. Green points are CN, blue points are MCI, orange points are Alzheimer's disease and black points are outliers. TP42/40 = total protein amyloid- β 42/40 plasma ratios.

Natural history of brain A β

Analyses of the present cohort indicated that brain A β followed a trajectory of exponential growth spanning 40 years. The abnormal threshold of 20 CL was reached 17 years prior to typical levels seen in mild Alzheimer's disease, and the fast, dynamic part of

trajectory was associated with an 8.8% change per year (Fig. 2).

Natural history of plasma A β

Analyses indicated that plasma A β followed a trajectory of logarithmic growth spanning 34 years. The abnormal

threshold of total protein amyloid- β 42/40 plasma ratios 0.085 was reached 5 years prior to typical levels seen in mild Alzheimer's disease, and the fast, dynamic part of trajectory was associated with an 7.9% change per year (Fig. 2).

Comparison of natural history curves

Inverting the trajectory for the plasma A β and overlaying on the brain A β trajectory, anchored at the median levels observed in the mild Alzheimer's disease participants, indicated that the trajectory for plasma amyloid preceded that of brain amyloid by a median value of 6 years; however, this was not statistically significant with 95% confidence (Fig. 2). It should be noted that 88% confidence was observed in this temporal difference.

Discussion

Our findings indicate that the natural history of plasma A β changes preceded that of brain A β deposition by 6 years. This temporal difference in the longitudinal trajectories of brain and plasma A β was observed with 88%

confidence. However, it should be noted that we were under-powered to observe a statistical difference with 95% confidence. The figure also suggests that we were not able to observe an early inflection point, representing a change from steady state to a dynamic change, in plasma A β with the observed trajectory starting at a very fast dynamic rate of (7.9%/year). Conversely, for brain A β , we were able to observe an initial inflection point but not a second inflection point indicating a plateauing of the deposition. These observations also lend to the hypothesis that changes in plasma A β precede changes in brain A β . Increasing both the sample size and the sample range, to capture higher levels of brain A β (more abnormal) and higher ratios of plasma A β (more normal), in future studies would further our knowledge, understanding and confidence in these findings.

The differences observed in the shape and timing of the different trajectories seen between brain and plasma A β , as previously reported between imaging and CSF (Villemagne, 2013; Toledo 2013), are indicative of the different pools of A β , a more soluble easily diffusible pool captured in biofluid assays and a larger, insoluble pool of A β captured by imaging (Roberts *et al.*, 2017). This explains the non-linear relationship between A β measured in biofluids and by imaging. The changes in these pools likely reflect the same process of A β aggregation and accumulation, translating into a decrease in A β in biofluids and an increase in the imaging signal.

Given the correlation between brain and plasma A β , ethical concerns should also be considered in obtaining and revealing blood-based levels of A β . It is likely that some of the same considerations regarding the appropriate use of A β imaging (Johnson *et al.*, 2013) would also be applicable here.

It is noted that, whilst the longitudinal comparisons of the trajectories indicate that plasma A β precedes that of brain A β , this is contradicted when they are considered as dichotomous diagnostic biomarkers, with brain A β reaching abnormal levels 12 years before that of plasma A β . The utility of brain and plasma A β for screening is currently based upon thresholds of 20 CL and a ratio of 0.085, respectively. If the ratios were to change to

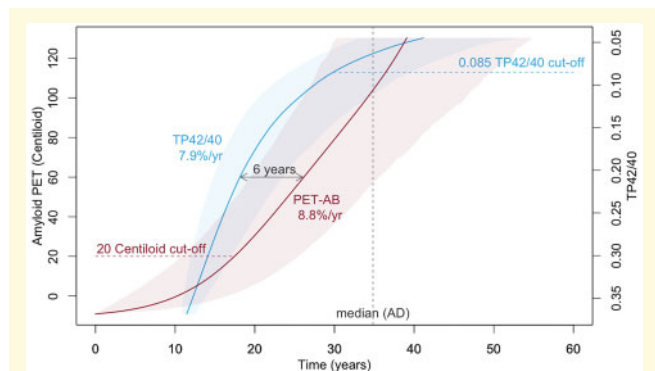


Figure 2 The natural history of brain A β deposition and inverted plasma A β changes anchored by median levels observed in mild Alzheimer's disease participants.

Table 1 Demographics

Participant demographics summary	CN	MCI	Alzheimer's disease	Total
Number of participants, N	111	7	15	133
Male gender, N (%)	63 (65.8)	4 (57.1)	5 (33.3)	72 (54.1)
Age (years), mean (SD)	71.8 (6.3)	75.6 (7.9)	74.9 (9.1)	72.3 (6.8)
Years of education, mean (SD)	13.4 (2.7)	11.9 (2.8)	12.5 (3.0)	13.2 (2.8)
APOE ϵ 4 carriers, N (%)	30 (27.0)	3 (42.9)	9 (60.0)	42 (31.6)
Years of follow-up, mean (SD)	4.1 (0.8)	2.1 (1.2)	2.6 (1.4)	3.9 (1.1)
Number of data collections, median (range)	4 (2–4)	2 (2–3)	2 (2–4)	4 (2–4)
Centiloid scores at baseline, mean (SD)	17.9 (31.0)	62.6 (55.8)	87.3 (39.5)	28.2 (40.8)
TP42/40 at baseline, mean (SD)	0.10 (0.05)	0.09 (0.03)	0.10 (0.10)	0.10 (0.06)
Rate of change in TP42/40 per year, mean (SD)	0.007 (0.01)	0.003 (0.01)	0.008 (0.01)	–0.01 (0.01)

Bold fonts indicate statistically significant differences from the cognitively normal subgroup.

APOE = apolipoprotein E; TP42/40 = total protein amyloid- β 42/40 plasma ratios.

increase sensitivity or specificity, then the difference in timing, reported as 12 years here, would also change. The results presented here suggest that, if the sensitivity of the plasma biomarkers is sufficient, then a higher ratio capturing earlier changes in the plasma $A\beta$ signal may better serve the screening process.

There are some limitations in the present study. First, the number of participants included in the assessments is somewhat small, especially in the Alzheimer's disease group, warranting validation in a larger independent cohort. Second, the participants were volunteers who were not randomly selected from the community and were generally well educated and had high scores on cognitive tests; thus, these findings might only be valid in similar cohorts and this limitation precludes the generalization of the findings to the general population. Third, AIBL's astringent selection criteria, which excluded individuals with other neurodegenerative conditions (such as dementia with Lewy bodies or frontotemporal lobar degeneration) as well as other metabolic co-morbidities, might have influenced the trajectories of $A\beta$ in blood and brain reported. Finally, the 20 CL (1.25 standardized uptake value ratio using the whole cerebellum as a reference region) threshold used is equivalent to a ^{11}C -Pittsburgh compound-B 1.44 standardized uptake value ratio using the cerebellar cortex as reference region. This is slightly higher than the threshold of 1.40 standardized uptake value ratio using the cerebellar cortex as reference region which is usually applied. This, along with the use of only two points to establish the rates of $A\beta$ accumulation, and the small number of Alzheimer's disease patients, may explain the shorter time to reach mild Alzheimer's disease levels and the lack of a plateau.

Findings indicate that longitudinal changes in plasma $A\beta$ match and potentially precede changes in brain $A\beta$. Therefore, plasma $A\beta$ may be a suitable screening tool for recruitment to clinical trials and may be able to identify individuals at risk to develop Alzheimer's disease even earlier than with PET. The use of plasma as a screening tool could significantly reduce the cost of trial recruitment, allowing for larger clinical trials in the attempt to find disease-modifying therapies. Furthermore, the results presented here provide strong evidence that plasma $A\beta$ has a strong dynamic range that is likely useful for monitoring, and even as an outcome measure in prodromal and preclinical trials.

The ABtest[®] assay was able to effectively map and track brain $A\beta$ accumulation. The results presented here add to the body of information that blood-based biomarkers hold utility for diagnosis, prognosis, monitoring and, thus, treatment in the field of Alzheimer's.

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Competing interests

N.F., V.P.-G., M.S. and P.P. are full-time employees of Araclon Biotech. No other authors report any relevant conflicts of interest.

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