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Potential Utility of Plasma P-Tau and Neurofilament Light Chain as Surrogate Biomarkers for Preventive Clinical Trials

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Abstract

Objective: To test the utility of longitudinal changes in plasma phosphorylated tau 181 (p-tau181) and neurofilament light chain (NfL) as surrogate markers for clinical trials targeting cognitively unimpaired (CU) populations.

Methods: We estimated the sample size needed to test a 25% drug effect with 80% of power at a 0.05 level on reducing changes in plasma markers in CU participants from ADNI database.

Results: We included 257 CU individuals [45.5% males; mean age = 73 (6) years; 32% amyloid-beta (Aβ) positive]. Changes in plasma NfL were associated with age, while changes in plasma p-tau181 with progression to amnestic mild cognitive impairment. Clinical trials using p-tau181 and NfL would require 85% and 63% smaller sample sizes, respectively, for a 24-month than a 12-month follow-up. A population enrichment strategy using intermediate levels of Aβ positron emission tomography (Centiloid 20-40) further reduced the sample size of 24-month clinical trial using p-tau181 (73%) and NfL (59%) as a surrogate.

Discussion: Plasma p-tau181/NfL can potentially be used to monitor large-scale population interventions in CU individuals. The enrollment of CU with intermediate Aβ levels constitutes the alternative with the largest effect size and most cost-effective for trials testing drug effect on changes in plasma p-tau181 and NfL.

Introduction

Cognitively unimpaired (CU) individuals with underlying amyloid-beta (Aβ) plaques, tau tangles, and neurodegeneration have been a target population in recent clinical trials, based on the assumption that better therapeutic outcomes can be achieved before cognitive deterioration[1, 2]. Although these individuals present an elevated risk for cognitive decline, the vast majority will remain clinically stable during typical clinical trial periods (12- to 24-month)[3]. This limits the use of changes in cognitive measures as a single primary outcome of therapeutical trials in this population.

Blood-based biomarkers have been proposed as a simple and cost-effective alternative to facilitate clinical trials[4-7]. Recent studies investigated the role of plasma markers in selecting individuals for clinical trials that are most likely to progress over time[8]. Tau pathology and neurodegeneration are key features of Alzheimer's disease (AD) and closely related to cognitive decline, suggesting that biomarkers representing these pathologies have the potential to surrogate AD-related progression[9]. Changes in plasma phosphorylated tau (p-tau) represent early brain accumulation of tau[9-11], whereas changes in plasma neurofilament light chain (NfL) have been associated with neurodegeneration in aging[9]. Thus, changes in plasma p-tau and NfL could be an alternative to monitoring drug effects in preventive trials. Here, we tested whether longitudinal changes in plasma p-tau and NfL levels can be used to monitor therapeutic response in clinical trials focusing on CU elderlies.

Materials and methods

We used participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (**eMethods 1**). [^{18}F]florbetapir positron emission tomography (PET) standardized uptake ratio (SUVR) measured Aβ load. Plasma p-tau181 and NfL were measured using the Simoa platform. Effect size was calculated as the ratio between the mean and standard deviation (SD), and sample size was estimated using a well-validated formula[12, 13]. Further details about biomarker analyses can be found on **eMethods 2–5** and **eFigure 1 in the Supplement**.

Results

We included 257 CU individuals [mean age, 72.8 (6.2) years;45.5% males; 32.3% Aβ positive(+)]. Demographics are summarized in **eTable 1** and **eFigure 2 in the Supplement**.

Changes in plasma biomarkers as a function of their baseline levels

We observed a negative correlation between baseline plasma p-tau181 levels and its slope of change over 24 months (r= -0.32, *P*<0.001, **eFigure 3 and eTable 2 in the Supplement**). By contrast, we found a positive association between baseline plasma NfL and its slope of change (r=0.59, *P*<0.001, **eFigure 3**).

Association of longitudinal changes in plasma biomarkers with age and clinical progression

Longitudinal changes in plasma NfL, but not p-tau181, significantly correlated with participants' age at baseline (r=0.49, *P*<0.001, **eFigure 4 in the Supplement**). Longitudinal changes in plasma p-tau181, but not NfL, significantly associated with an increased risk of clinical progression to mild cognitive impairment (MCI) (31/257 progressed over 24 months) [HR=1.57 (CI: 1.03–2.4), **eFigure 5**]. Results were not influenced by sex.

Effect size of longitudinal changes in plasma biomarkers

Longitudinal changes in plasma p-tau181 and NfL were not significantly different from zero at 12 months, while significant progression and larger effects size were observed at 24 months (**Figure 1, A–B, and eFigure 6 in the Supplement**).

Sample size required for clinical trials

Clinical trials performed over 24 months would require 85% (*n*=8,884) and 63% (*n*=3,448) smaller sample sizes than 12-month trials using plasma p-tau181 and NfL, respectively (**eTable 3 in the Supplement**). Using Aβ+ for population enrichment reduced the sample size by 43% for p-tau181 (*n*=5,040) and 16% for NfL (*n*=2,868). Using intermediate levels of Aβ (Centiloid 20-40) for enrichment, the sample size was reduced by 73% for p-tau181 (*n*=2,432) and 59% for NfL (*n*=1,396) over 24 months (**Figure 2A**). **Figure 3** shows a progressive reduction in sample size estimates as a function of progressively higher drug effects.

Cost-effectiveness analysis of plasma biomarkers for clinical trials

Figure 2B demonstrates that the estimated cost of a clinical trial considering only the biomarker costs is lower using plasma than neuroimaging as surrogates. However, due to the larger number of individuals required using plasma markers, the total estimated trial cost when considering surrogate markers plus other related costs is higher using plasma (~2-fold at 24 months) than neuroimaging biomarkers (**Figure 2C**). Interestingly, for a trial including only individuals with intermediate Aβ levels, the total estimated cost was similar using plasma and neuroimaging for surrogacy. The estimated costs of trial using other strategies of population enrichment (CSF Aβ42 for Aβ+, *APOE*ε4 allele) are described in **eFigure 7 in the Supplement**.

Discussion

We showed that longitudinal plasma p-tau181 changes were associated with progression to MCI, while NfL changes were more closely related to aging. Plasma p-tau181 and NfL changes at 24 months, rather than 12 months, showed the potential to be used as surrogate markers in large-scale preventive clinical trials focusing on CU individuals. Cost-effectiveness analysis suggested that studies on CU Aβ+ will have higher total costs using plasma p-tau181 and NfL for surrogacy compared to using PET/MRI biomarkers. We also demonstrated that studies enriched with CU participants with intermediate Aβ levels would be more cost-effective than with CU Aβ+.

Longitudinal changes in plasma p-tau181 and NfL can potentially be used in 24-month preventive clinical trials. Recent anti-Aβ trials targeting symptomatic individuals have used changes in plasma biomarkers to monitor disease modification[5-7]. Our results suggest that plasma biomarkers can potentially be used in clinical trials focusing on asymptomatic individuals. Interestingly, we demonstrated that population enrichment strategies based on Aβ burden will have a larger impact on reducing required sample size for trials using p-tau181 than NfL as surrogates. Clinical trials testing 25% drug effects on marker reduction would require more than 5,000 and 2,800 individuals using p-tau181 and NfL, respectively, suggesting that these markers will be more suitable for monitoring large-scale population interventions than for formal randomized controlled trials. Noteworthy, our analysis supported that this scenario could be different if we consider medications with larger effect sizes on reducing biomarker changes.

Surprisingly, our results suggest that using longitudinal changes in plasma p-tau181 and NfL would not reduce the cost of clinical trials using Aβ+ individuals compared to using changes in PET or MRI as surrogate outcomes. Although both tau-PET and plasma p-tau181 are postulated to reflect tau deposition in the brain[14, 15], longitudinal tau-PET changes reported in previous studies show more robust estimates, with less intra-subject variably and, consequently, translating into considerably smaller required sample sizes[13]. It is known that both plasma NfL and MRI reflect non-specific neuronal damage[15]. However, because structural MRI is a relatively inexpensive exam and has relatively robust longitudinal estimates, it is more cost-effective. While it is indisputable that blood-based markers are more accessible and less expensive than neuroimaging for a single patient, our results demonstrate that plasma markers can be less cost-effective for preventive trials due to their higher longitudinal variability.

Enrolling CU individuals with intermediate Aβ levels led to smaller sample size and costs for clinical trials using either plasma p-tau181 or NfL as surrogates compared to studies using the concept of Aβ+. In our study, individuals with higher Aβ levels (Centiloid>40) showed high variability and low average change in longitudinal plasma estimates, some individuals had elevated longitudinal changes, others plateaued. Thus, their exclusion reduced the standard deviation of biomarker changes and, in turn, increased the effect size, leading to smaller sample size and cost estimations.

ADNI database includes a self-selected population comprised of highly educated mostly white participants, which while generalizable to current clinical trial populations does not represent the more diverse general world population. Modifications in p-tau/NfL markers alone may fail to predict the overall benefit of a treatment. They need to be supported by clinical endpoints and/or a rigorous post-marketing monitoring of clinical benefit.

To conclude, our results suggest that 24-month changes in plasma p-tau181/NfL show large inter-subject variability but can potentially be used to monitor large-scale population interventions in CU elderlies.

http://links.lww.com/WNL/C669

http://links.lww.com/WNL/C670

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Figure 1. Percentage of change and effect size of plasma biomarkers over 12 and 24 months. The bar plots show the percentage of changes with their respective 95% confidence intervals for plasma (**A**) p-tau181 (left side) and (**B**) NfL (right side) concentrations in CU older individuals over 12 and 24 months in relation to the biomarker value at the baseline visit. The 12- and 24-month follow-ups showed a similar annualized rate of progression. The effect size at 24 months was larger due to both a greater mean of progression and a relatively more stable change among participants (smaller standard deviation). The effect size was calculated as the ratio between the mean and standard deviation of the percentage of change overtime points. The higher the effect size, the smaller the measure's variability, which indicates a more precise populational estimate. (*) indicates that the 95% confidence interval did not cross the zero line, therefore, the longitudinal change was significantly different from zero.

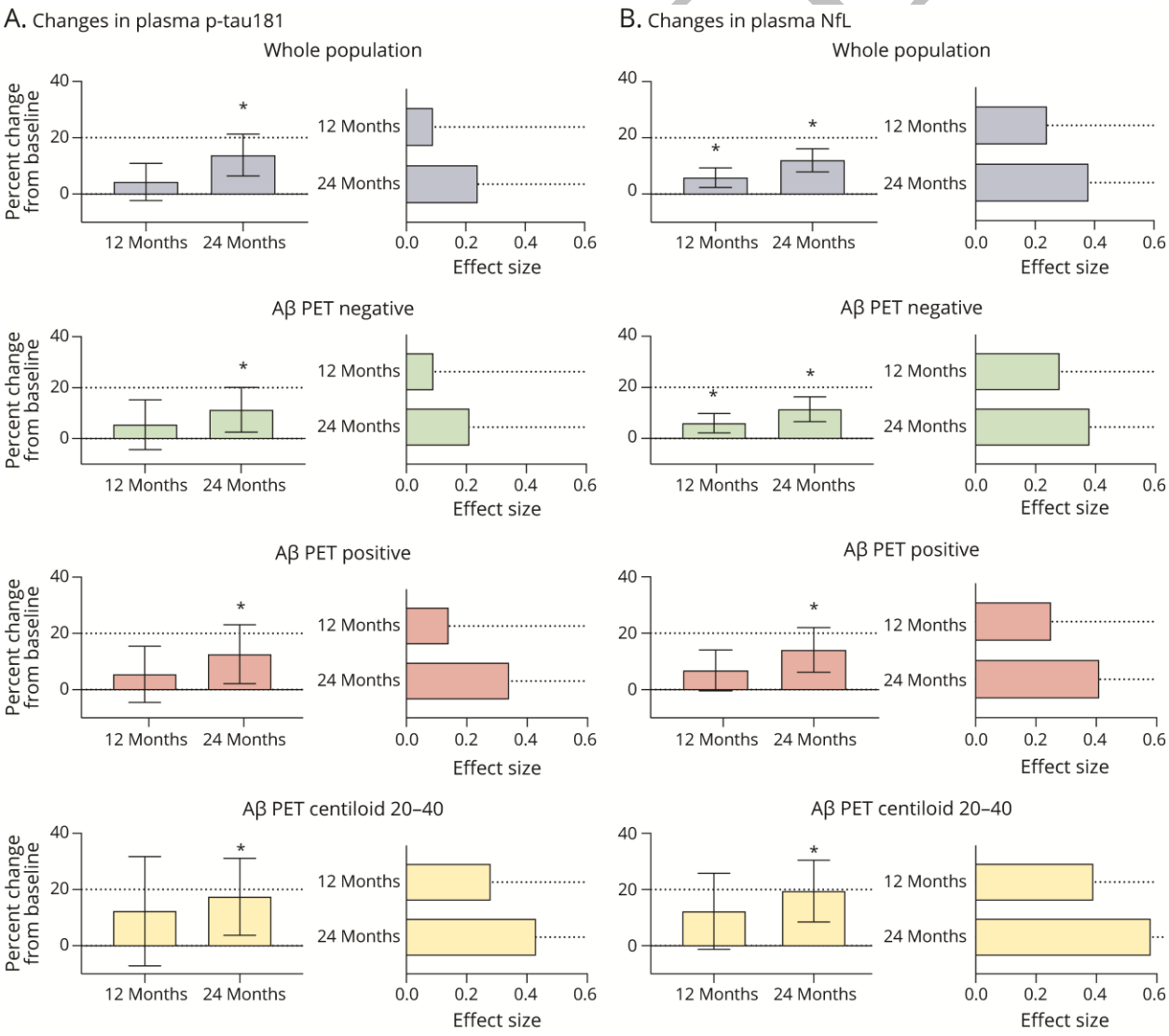


Figure 2. Cost-effectiveness of plasma biomarkers as surrogate for preventive clinical trials in CU individuals. (A) Sample sizes required for hypothetical clinical trials powered to use plasma biomarkers to monitor drug effects in CU older individuals. **(B)** Estimated cost with surrogate neuroimaging (Jack *et al.*[13]) and plasma biomarkers only for clinical trials powered to use changes in these biomarkers to monitor drug effects. **(C)** Estimated cost of biomarkers plus the costs with some of the other necessary tests that are influenced by total sample sizes, such as costs with the definition of Aβ positivity (using PET) for population enrichment and a standard clinical evaluation for each participant. The costs of clinical trials using changes in tau-PET (^{18}F-flortaucipir uptake in the temporal lobe) or structural MRI (tensor-based morphology cortical volume) as surrogate were estimated based on the mean and SD of a 12-month change in these biomarkers reported previously by Jack and colleagues[13]. For the calculations presented in the figure, we used the following hypothesized costs: MRI = $500; PET = $3,000; plasma marker = $200; Recruitment/consenting/clinical assessment = $1,000. Assessments (except for biomarker of enrichment) were calculated to 2-time points (baseline and follow-up). Biomarker and procedure costs were estimations based on research assessments in the US. These costs are simplified estimations for the sake of analysis and can vary highly depending on several factors. We estimated an attrition rate of 10% in the calculations. Δ = longitudinal change. Reduction in the sample size was calculated in relation to the whole population.

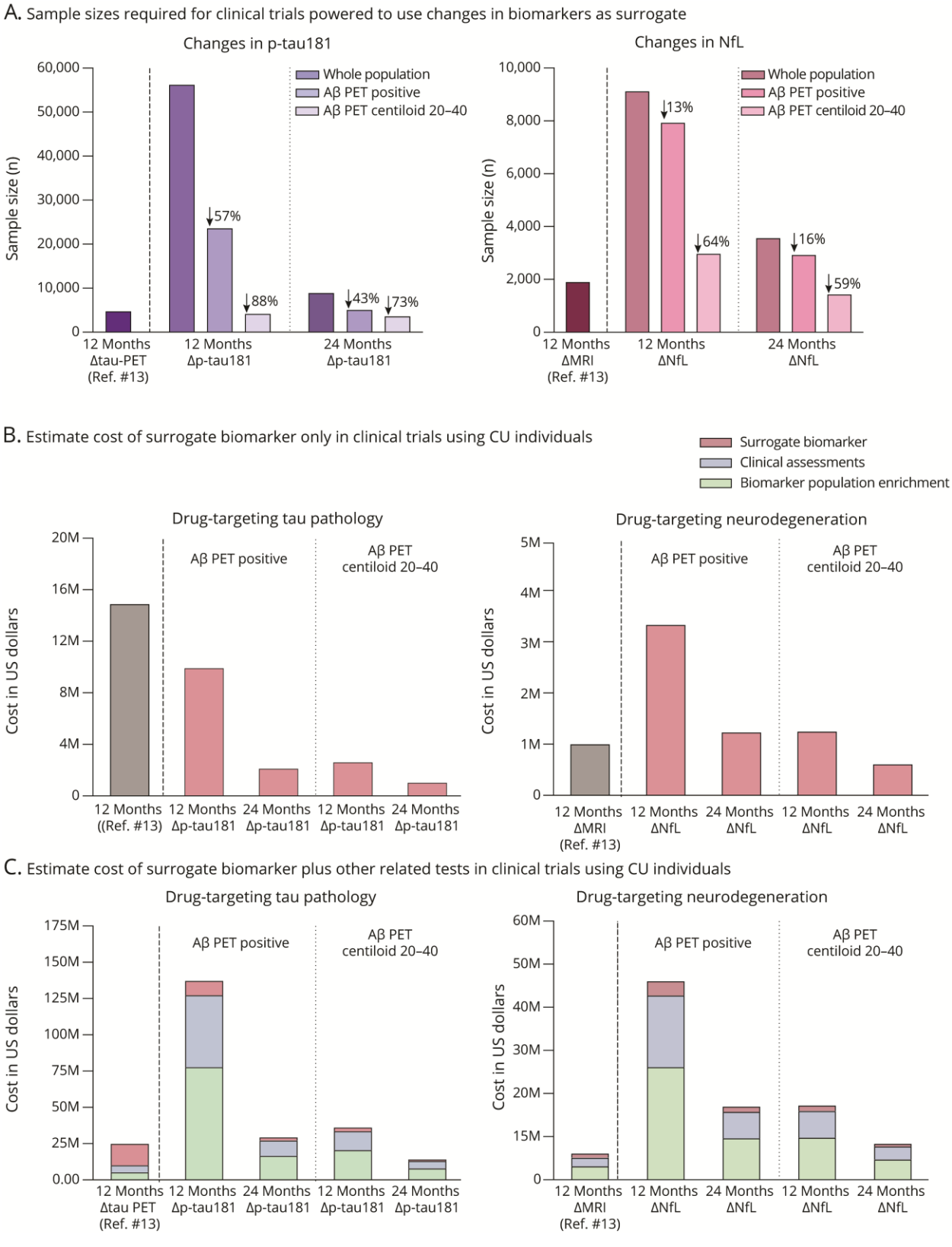
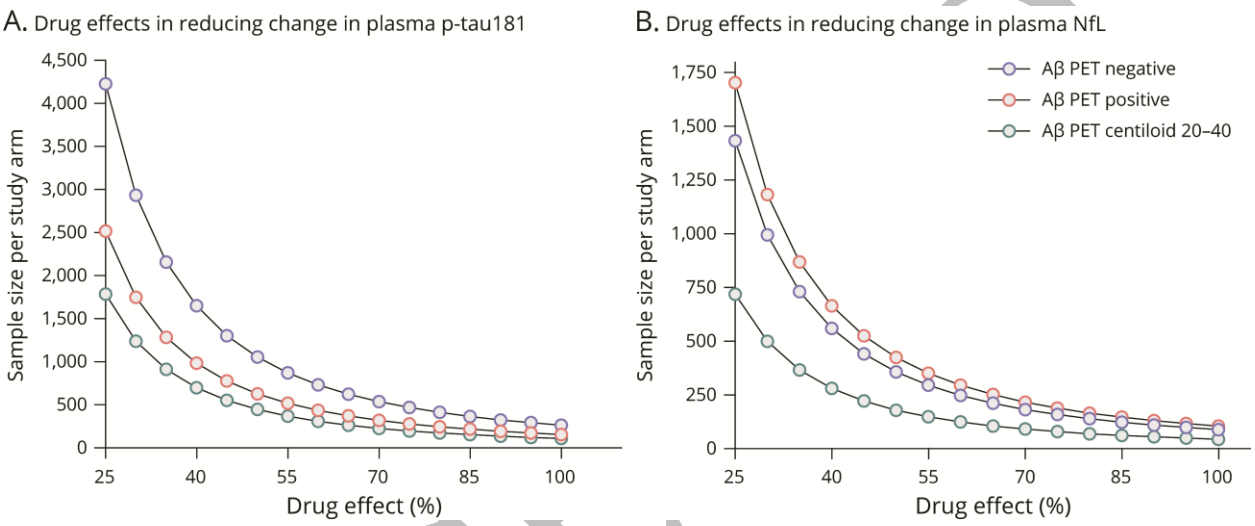


Figure 3. Sample sizes of clinical trials as a function of multiple estimated drug effects. The dots in the curves represent the sample size per study arm as a function of multiple hypothesized drug effects (greater than the tested 25% in reducing the rate of biomarker progression). (**A**) For plasma p-tau181, a drug effect large than 60% would represent the need for a sample size of less than 500 CU Aβ PET positive or Aβ PET Centiloid 20-40 per study arm. (**B**) For plasma NfL, a drug effect large than 45% would represent the need for a sample size of less than 500 CU Aβ PET positive or Aβ PET Centiloid 20-40 per study arm.



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