CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

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

Pamela C.L. Ferreira, PhD,* João Pedro Ferrari-Souza,* Cécile Tissot, PhD, Bruna Bellaver, PhD, Douglas T. Leffa, MD, PhD, Firoza Lussier, MSc, Guilherme Povala, PhD, Joseph Therriault, BSc, Andréa L. Benedet, PhD, Nicholas J. Ashton, PhD, Ann D. Cohen, PhD, Oscar L. Lopez, MD, Dana L. Tudorascu, PhD, William E. Klunk, MD, PhD, Jean-Paul Soucy, MD, MSc, Serge Gauthier, MD, Victor Villemagne, MD, Henrik Zetterberg, MD, PhD, Kaj Blennow, MD, PhD, Pedro Rosa-Neto, MD, PhD, Eduardo R. Zimmer, PhD, Thomas K. Karikari, PhD, and Tharick A. Pascoal, MD, PhD, for the Alzheimer's Disease Neuroimaging Initiative

Correspondence
Dr. Pascoal
pascoalt@upmc.edu

Neurology® 2023;101:38-45. doi:10.1212/WNL.0000000000207115

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 Alzheimer's Disease Neuroimaging Initiative database.

Results

We included 257 CU individuals (45.5% males; mean age = 73 [6] years; 32% β-amyloid [Aβ] positive). Changes in plasma NfL were associated with age, whereas 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 PET (Centiloid 20–40) further reduced the sample size of the 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.

*These authors contributed equally to this work.

From the Departments of Psychiatry (P.C.L.F., J.P.F.-S., C.T., B.B., D.T.L., F.L., G.P., A.D.C., D.L.T., W.E.K., V.V., T.K.K., T.A.P.) and Neurology (O.L.L.), School of Medicine, University of Pittsburgh, PA; Graduate Program in Biological Sciences: Biochemistry (J.P.F.-S., B.B., E.R.Z.), Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Translational Neuroimaging Laboratory (C.T., F.L., J.T., J.-P.S., P.R.-N.), McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal, Pointe-Claire; Department of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics (C.T., J.T., S.G., P.R.-N.), McGill University, Montreal, Quebec, Canada; Department of Psychiatry and Neurochemistry (A.L.B., N.J.A., H.Z., K.B., T.K.K.), The Sahlgrenska Academy at the University of Gothenburg, Mölndal; Clinical Neurochemistry Laboratory (A.L.B., N.J.A., H.Z., K.B.), Sahlgrenska University Hospital, Gothenburg; Wallenberg Centre for Molecular and Translational Medicine (N.J.A., H.Z.), University of Gothenburg, Sweden; Department of Old Age Psychiatry (N.J.A.), Institute of Psychiatry, Psychology & Neuroscience, King's College London; Department of Neurodegenerative Disease (H.Z.), UCL Queen Square Institute of Neurology; UK Dementia Research Institute at UCL (H.Z.), London, United Kingdom; Hong Kong Center for Neurodegenerative Diseases (H.Z.), China; and Department of Neurology (T.A.P.), School of Medicine, University of Pittsburgh, PA.

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.

The Article Processing Charge was funded by the NIH.

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 in the coinvestigators list at links.lww.com/WNL/C669.

Cognitively unimpaired (CU) individuals with underlying β-amyloid (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 months).[3] This limits the use of changes in cognitive measures as a single primary outcome of therapeutic 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 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.

Methods

We used participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (eMethods 1, links.lww.com/WNL/C670). [^{18}F]florbetapir PET standardized uptake ratio measured Aβ load. Plasma p-tau181 and NfL were measured using the Simoa platform. The effect size was calculated as the ratio between the mean and SD, and the sample size was estimated using a well-validated formula.[12,13] Further details about biomarker analyses can be found in eMethods 2–5 and eFigure 1.

Results

We included 257 CU individuals (mean age 72.8 [6.2] years; 45.5% males; 32.3% Aβ+). Demographics are summarized in eTable 1 and eFigure 2 (links.lww.com/WNL/C670).

Changes in Plasma Biomarkers as a Function of Their Baseline Levels

We observed that baseline plasma p-tau181 levels correlated with a decrease in its slope of change over 24 months (r =−0.32, p < 0.001, eFigure 3 and eTable 2, links.lww.com/WNL/C670). By contrast, we found that baseline plasma NfL levels correlated with an increase in 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, links.lww.com/WNL/C670). 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) (hazard ratio 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, whereas significant progression and larger effects size were observed at 24 months (Figure 1, A and B and eFigure 6, links.lww.com/WNL/C670).

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, links.lww.com/WNL/C670). 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.

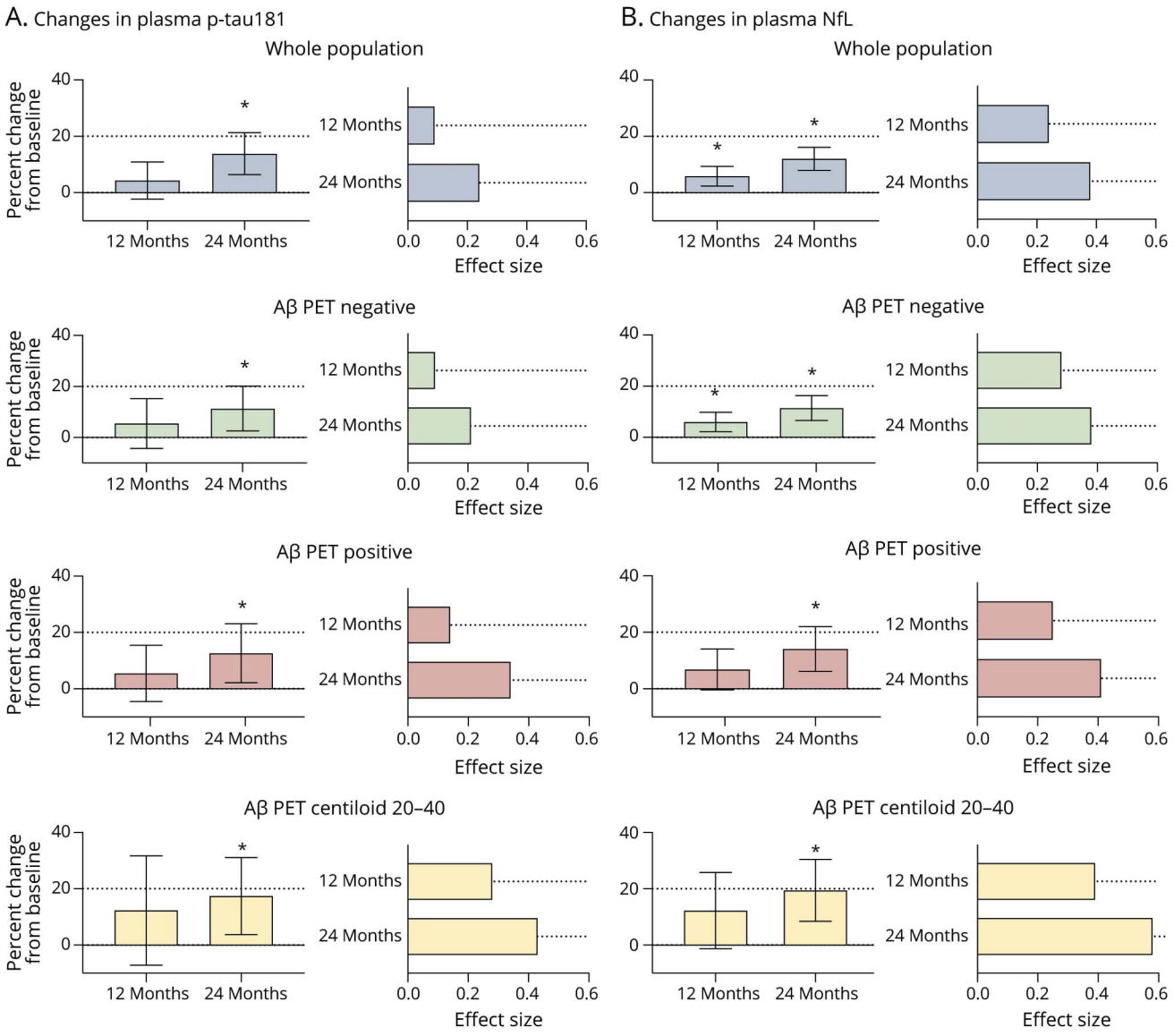
Cost-Effectiveness Analysis of Plasma Biomarkers for Clinical Trials

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 higher sample size required using plasma as surrogate biomarkers, 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). Of interest, 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 trials using other strategies of population enrichment (CSF Aβ42 for Aβ+, *APOE* ε4 allele) are described in eFigure 7 (links.lww.com/WNL/C670).

Discussion

We showed that longitudinal plasma p-tau181 changes were associated with progression to MCI, whereas 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.

Figure 1 Percentage of Change and Effect Size of Plasma Biomarkers Over 12 and 24 Months

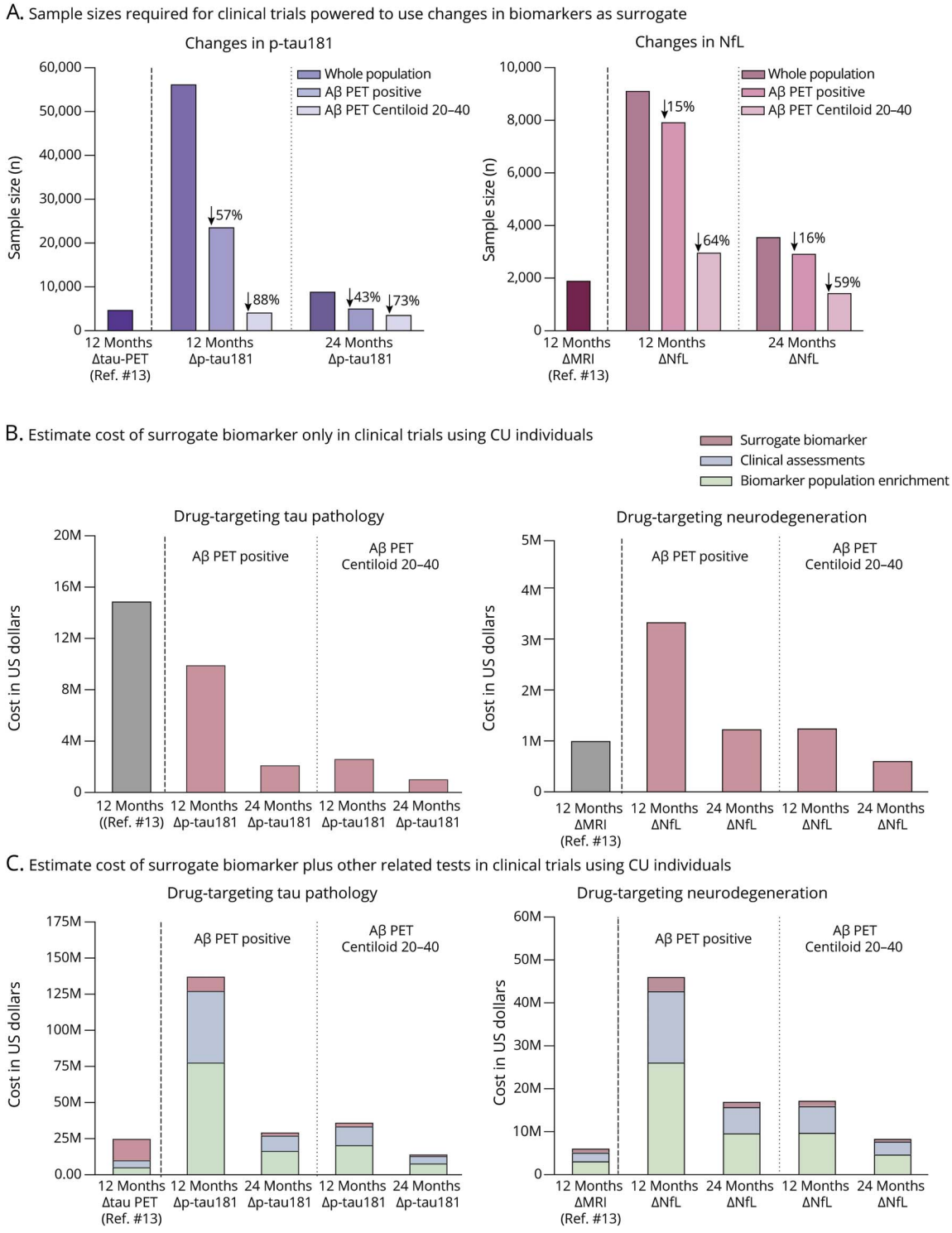


The bar plots show the percentage of changes with their respective 95% CIs for plasma (A) p-tau181 (left side) and (B) NfL (right side) concentrations in CU older individuals over 12 and 24 months in relation to the biomarker value at the baseline visit. The 12- and 24-month follow-ups showed a similar 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 SD). The effect size was calculated as the ratio between the mean and SD of the percentage of change over time points. The higher the effect size, the smaller the measure's variability, which indicates a more precise populational estimate. (*) indicates that the 95% CI did not cross the zero line; therefore, the longitudinal change was significantly different from zero. Aβ = β-amyloid; CU = cognitively unimpaired; NfL = neurofilament light chain; p-tau181 = phosphorylated tau 181.

Cost-effectiveness analysis suggested that studies on CU Aβ+ will have higher total costs using plasma p-tau181 and NfL for surrogacy compared with 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+.

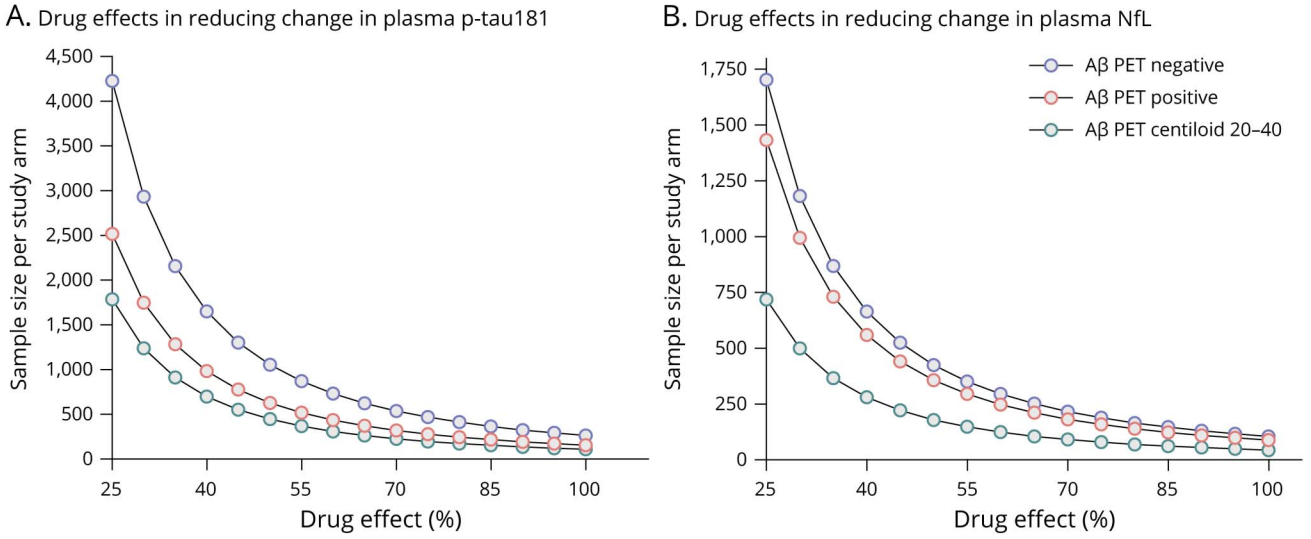
Longitudinal changes in plasma p-tau181 and NfL can potentially be used in 24-month preventive clinical trials. Recent anti-Aβ trials targeting symptomatic individuals have used changes in plasma biomarkers to monitor disease modification.[5-7] Our results suggest that plasma biomarkers can potentially be used in clinical trials focusing on asymptomatic individuals. Of interest, we demonstrated that population enrichment strategies based on Aβ burden will have a larger effect on reducing the 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.

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[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 previously reported.[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 United States. 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. Aβ = β-amyloid; CU = cognitively unimpaired; NfL = neurofilament light chain; p-tau181 = phosphorylated tau 181.

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. Aβ = β-amyloid; CU = cognitively unimpaired; NfL = neurofilament light chain; p-tau181 = phosphorylated tau 181.

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 with 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 intrasubject variably and, consequently, translating into considerably smaller required sample sizes.[13] It is known that both plasma NfL and MRI reflect nonspecific neuronal damage.[15] However, because structural MRI is a relatively inexpensive examination and has relatively robust longitudinal estimates, it is more cost-effective. Although 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.

The enrollment of CU individuals with intermediate Aβ levels (Centiloid 20 -40) can lead to a smaller sample size and cost for clinical trials using either plasma p-tau181 or NfL as a surrogate compared with trials enrolling CU Aβ+. In our study, individuals with higher Aβ levels showed high variability and low average change in longitudinal plasma estimates, some individuals had elevated longitudinal changes, and others plateaued. Thus, their exclusion reduced the SD of biomarker changes and, in turn, increased the effect size, leading to smaller sample size and cost estimations.

The ADNI database includes a self-selected population comprising 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 end points and/or rigorous postmarketing monitoring of clinical benefit. To conclude, our results suggest that 24-month changes in plasma p-tau181/NfL show large intersubject variability but can potentially be used to monitor large-scale population interventions in CU elderlies.

Acknowledgment

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; NIH Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). The ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Araclon Biotech, BioClinica, Biogen, Bristol-Myers Squibb Company, CereSpir, Eisai Inc., Elan Pharmaceuticals, Eli Lilly and Company, Euroimmun, F. Hoffmann-La Roche and its affiliated company Genentech, Fujirebio, GE Healthcare, IXICO, Janssen Alzheimer Immunotherapy Research & Development, Johnson & Johnson Pharmaceutical Research & Development, Lumosity, Lundbeck, Merck, Meso Scale Diagnostics, NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer, Piramal Imaging, Servier, Takeda Pharmaceutical Company, and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the NIH (fnih.org). The grantee organization

is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuroimaging at the University of Southern California.

Study Funding

P.C.L. Ferreira is supported by Alzheimer's Association (AARFD-22-923814). J.P. Ferrari-Souza receives financial support from CNPq (200691/2021-0). H. Zetterberg is a Wallenberg Scholar supported by grants from the Swedish Research Council (2018-02532), the European Research Council (681712 and 101053962), Swedish State Support for Clinical Research (ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (201809-2016862), the AD Strategic Fund and the Alzheimer's Association (ADSF-21-831376-C, ADSF-21-831381-C, and ADSF-21-831377-C), the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (FO2019-0228), the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme–Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). K. Blennow is supported by the Swedish Research Council (2017-00915), the Alzheimer Drug Discovery Foundation (RDAPB-201809-2016615), the Swedish Alzheimer Foundation (AF-742881), Hjärnfonden (FO2017-0243), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (ALFGBG-715986), the European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236), the NIH (1R01AG068398-01), and the Alzheimer's Association 2021 Zenith Award (ZEN-21-848495). E.R. Zimmer receives financial support from CNPq (435642/2018-9 and 312410/2018-2), Instituto Serrapilheira (Serra-1912-31365), Brazilian National Institute of Science and Technology in Excitotoxicity and Neuroprotection (465671/2014-4), FAPERGS/MS/CNPq/SESRS–PPSUS (30786.434.24734.231120170), and ARD/FAPERGS (54392.632.30451.05032021) and Alzheimer's Association (AARGD-21-850670). T.A. Pascoal is supported by the NIH (R01AG075336 and R01AG073267) and the Alzheimer's Association (AACSF-20-648075).

Disclosure

P.C.L. Ferreira, J.P. Ferrari-Souza, C. Tissot, B. Bellaver, D.T. Leffa, F.Z. Lussier, G. Povala, J. Therriault, A.L. Benedet, N.J. Ashton, A.D. Cohen, O.L. Lopez, D.L. Tudorascu, W.E. Klunk, and J.P. Soucy report no disclosures relevant to the manuscript. S. Gauthier has served as a scientific advisor to Cerveau Therapeutics. V.L. Villemagne reports no disclosures relevant to the manuscript. H. Zetterberg has served on scientific advisory boards and/or as a consultant for AbbVie, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, reMYND, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K. Blennow has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers; and is a cofounder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the work presented in this paper. P. Rosa-Neto reports no disclosures relevant to the manuscript. E.R. Zimmer serves in the scientific advisory board of Next Innovative Therapeutics. T.K. Karikari and T.A. Pascoal report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Previously published at medRxiv doi: 10.1101/2022.08.17.22278853. Received by *Neurology* August 24, 2022. Accepted in final form January 11, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Pamela C.L. Ferreira, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
João Pedro Ferrari-Souza	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA; Graduate Program in Biological Sciences: Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Cécile Tissot, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA; Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal, Pointe-Claire; Department of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design
Bruna Bellaver, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA; Graduate Program in Biological Sciences: Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Douglas T. Leffa, MD, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Firoza Lussier, MSc	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA; Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal, Pointe-Claire, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Guilherme Povala, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Joseph Therriault, BSc	Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal, Pointe-Claire; Department of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design
Andréa L. Benedet, PhD	Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden	Study concept or design
Nicholas J. Ashton, PhD	Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg; Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden; Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content
Ann D. Cohen, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Oscar L. Lopez, MD	Department of Neurology, School of Medicine, University of Pittsburgh, PA	Analysis or interpretation of data
Dana L. Tudorascu, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA	Analysis or interpretation of data
William E. Klunk, MD, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA	Analysis or interpretation of data
Jean-Paul Soucy, MD, MSc	Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal, Pointe-Claire, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Serge Gauthier, MD	Department of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Victor Villemagne, MD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Henrik Zetterberg, MD, PhD	Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg; Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden; Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology; UK Dementia Research Institute at UCL, United Kingdom; Hong Kong Center for Neurodegenerative Diseases, China	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Kaj Blennow, MD, PhD	Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal; Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden	Drafting/revision of the manuscript for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Pedro Rosa-Neto, MD, PhD	Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal, Pointe-Claire; Department of Neurology and Neurosurgery, Psychiatry and Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada; Department of Pharmacology, Graduate Program in Biological Sciences: Pharmacology and Therapeutics, Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul; Brain Institute of Rio Grande do Sul, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Eduardo R. Zimmer, PhD	Graduate Program in Biological Sciences: Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Thomas K. Karikari, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA; Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Tharick A. Pascoal, PhD	Department of Psychiatry, School of Medicine, University of Pittsburgh, PA; Department of Neurology, School of Medicine, University of Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. *Alzheimers Dement (NY)*. 2021;7(1):e12179.
2. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.
3. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12(3):292-323.
4. Karikari TK, Ashton NJ, Brinkmalm G, et al. Blood phospho-tau in Alzheimer disease: analysis, interpretation, and clinical utility. *Nat Rev Neurol*. 2022;18(7):400-418.
5. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis*. 2022;9(2):197-210.
6. Pontecorvo MJ, Lu M, Burnham SC, et al. Association of donanemab treatment with exploratory plasma biomarkers in early symptomatic Alzheimer disease: a secondary analysis of the TRAILBLAZER-ALZ randomized clinical trial. *JAMA Neurol*. 2022;79(12):1250.
7. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimers Res Ther*. 2021;13(1):80.
8. Cullen NC, Leuzy A, Janelidze S, et al. Plasma biomarkers of Alzheimer's disease improve prediction of cognitive decline in cognitively unimpaired elderly populations. *Nat Commun*. 2021;12(1):3555.
9. Leuzy A, Mattsson-Carlgren N, Palmqvist S, Janelidze S, Dage JL, Hansson O. Blood-based biomarkers for Alzheimer's disease. *EMBO Mol Med*. 2022;14(1):e14408.
10. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19(5):422-433.
11. Moscoso A, Grothe MJ, Ashton NJ, et al. Longitudinal associations of blood phosphorylated tau181 and neurofilament light chain with neurodegeneration in Alzheimer disease. *JAMA Neurol*. 2021;78(4):396-406.
12. Grill JD, Di L, Lu PH, et al. Estimating sample sizes for predementia Alzheimer's trials based on the Alzheimer's Disease Neuroimaging Initiative. *Neurobiol Aging*. 2013;34(1):62-72.
13. Jack CR Jr, Wiste HJ, Schwarz CG, et al. Longitudinal tau PET in ageing and Alzheimer's disease. *Brain*. 2018;141(5):1517-1528.
14. Molinuevo JL, Ayton S, Batrla R, et al. Current state of Alzheimer's fluid biomarkers. *Acta Neuropathol*. 2018;136(6):821-853.
15. Hansson O. Biomarkers for neurodegenerative diseases. *Nat Med*. 2021;27(6):954-963.

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

Pamela C.L. Ferreira, João Pedro Ferrari-Souza, Cécile Tissot, et al.

Neurology 2023;101;38-45 Published Online before print March 6, 2023
DOI 10.1212/WNL.0000000000207115