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RESEARCH ARTICLE

Plasma GFAP for populational enrichment of clinical trials in preclinical Alzheimer's disease

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Abstract

INTRODUCTION: Cognitively unimpaired (CU) amyloid beta (Aβ)+ individuals with elevated plasma glial fibrillary acidic protein (GFAP) have an increased risk of Alzheimer's disease (AD)-related progression. We tested the utility of plasma GFAP for population enrichment CU populations in clinical trials.

METHODS: We estimated longitudinal progression, effect size, and costs of hypothetical clinical trials designed to test an estimated 25% drug effect on reducing tau

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positron emission tomography (PET) accumulation in the medial temporal lobe (MTL) and temporal neocortical region (NEO-T).

RESULTS: CU GFAP+/Aβ+ individuals present an increased annual rate of change and effect size in tau PET_{MTL} and tau PET_{NEO-T} compared to the other groups. An enrichment strategy selecting CU GFAP+/Aβ+ individuals would require a smaller sample size (≈ 57% reduction) and fewer Aβ PET scans (≈ 74% reduction) than trials enriched with Aβ PET alone, reducing total clinical trial costs by up to 64%.

DISCUSSION: Our results suggest that clinical trials focusing on preclinical AD recruiting Aβ+ individuals with elevated GFAP levels would improve cost effectiveness.

KEYWORDS
clinical trial enrichment, glial fibrillary acidic protein, positron emission tomography imaging, preclinical Alzheimer's disease, tau deposition

Highlights

- Cognitively unimpaired (CU) glial fibrillary acidic protein (GFAP)+/amyloid beta (Aβ)+ shows increased changes in tau positron emission tomography (PET) .
- CU GFAP+/Aβ+ enriched clinical trials require a reduced sample size compared to Aβ+ only.
- CU GFAP+/Aβ+ enrichment reduces Aβ PET scans required and costs.
- CU GFAP+/Aβ+ enrichment allows the selection of individuals at early stages of the Alzheimer's disease continuum.

1 | BACKGROUND

Drug interventions targeting individuals at the preclinical stage of Alzheimer's disease (AD) have the potential to slow or even halt the disease process before the onset of irreversible neurodegeneration and cognitive decline.[1] Enrichment strategies using amyloid beta (Aβ) positron emission tomography (PET) biomarkers have been used to select clinical trial participants with mild cognitive impairment (MCI) or mild dementia. However, cognitively unimpaired (CU) Aβ+ individuals progress slowly, with most remaining cognitively stable over the typical duration of clinical trials.[2] For this reason, exploring drug effects on biomarker endpoints reflecting AD progression, such as tau tangles PET, has been proposed as an alternative to monitoring drug effects on these populations. Yet, most CU Aβ+ individuals may take several years to develop downstream tau tangle deposition.[3,4]

Plasma glial fibrillary acidic protein (GFAP), a marker associated with astrocyte reactivity, has been reported to be elevated in CU Aβ+ compared to Aβ– individuals.[5–7] Moreover, previous studies have shown that plasma GFAP plays a role in mediating early AD progression.[7,8] Our recent findings demonstrated that in the early stages of AD, CU individuals with abnormal Aβ and GFAP biomarkers are at a higher risk of developing tau phosphorylation and aggregation.[9] Together, these results suggest that clinical trials could potentially enroll CU populations presenting abnormalities in both Aβ and GFAP biomarkers to enhance their likelihood of progression during clinical trial periods. However, the potential utility of plasma GFAP for clinical trial enrichment remains speculative.

In this study, we tested the hypothesis that using both plasma GFAP and Aβ PET to select CU individuals who are most likely to show longitudinal changes in tau PET would significantly reduce the required sample size and the number of PET scans needed, thereby lowering the overall costs of clinical trials in these populations.

2 | MATERIALS AND METHODS

2.1 | Participants

This study included participants from two centers, the Translational Biomarkers in Aging and Dementia (TRIAD), McGill University, Canada, and the Wisconsin Registry for Alzheimer's Prevention (WRAP), University of Wisconsin–Madison, USA. The TRIAD cohort comprised 84 older participants (> 50 years old) with a detailed clinical and cognitive assessment. Exclusion criteria included inability to speak English or French; inadequate visual and auditory capacities for neuropsychological assessment; active substance abuse; major surgery; recent head trauma; medical contraindication for PET or magnetic resonance

imaging; currently being enrolled in other studies; and neurological, psychiatric, or systemic comorbidities that were not adequately treated with a stable medication regimen. CU individuals had a Clinical Dementia Rating = 0 and no objective cognitive impairment. The study was approved by the Douglas Mental Health University Institute Research Ethics Board and Montreal Neurological Institute PET working committee. The WRAP cohort is a longitudinal observational study enriched with individuals with a parental history of probable AD dementia. A subset of 128 older participants (> 50 years old) were included who were CU at enrollment and had a complete comprehensive neuropsychological assessment. Cognitive status was established by consensus conference as previously reported.[10] Participants were excluded if they were not fluent in English, if they did not present adequate visual and auditory acuity for neuropsychological testing, or were otherwise not in good health or presented diseases expected to interfere with participation over time. The WRAP data were collected under a University of Wisconsin–Madison Institutional Review Board protocol.[10] All study participants provided written informed consents for all study procedures.

2.2 | PET biomarkers

Aβ and tau PET images were processed at each site.[11,12] Aβ status was determined using Centiloid value cutoff for [^{18}F]AZD4694 in TRIAD and [^{11}C]Pittsburgh compound B (PiB) in WRAP. We used a Centiloid cutoff > 12 to determine positivity for both tracers, which identifies moderate-to-frequent neuritic plaques as classified by the Consortium to Establish a Registry for Alzheimer's Disease.[13] Tau PET was performed using [^{18}F]MK-6240 in both cohorts. We computed the tau PET standardized uptake value ratio (SUVR) for the medial temporal lobe (MTL, an unweighted average of bilateral entorhinal cortex and amygdala) and a temporal neocortical (NEO-T, a weighted average of bilateral middle temporal, inferior temporal gyri, and inferior parietal gyri) regions of interest based on the Desikan–Killiany–Tourville (DKT) atlas.[14] All participants had baseline and follow-up [^{18}F]MK-6240 with a mean of 2.46 years between visits. In a sensitivity analysis, the ComBat method was applied for harmonization to eliminate scanner differences between sites in tau PET.[15]

2.3 | Plasma biomarkers

Plasma GFAP was measured using a commercially available immunoassay from Quanterix using single molecule array (Simoa) in TRIAD and WRAP. In TRIAD, plasma phosphorylated tau (p-tau)217 was quantified by scientists at Janssen Research & Development.[16] In WRAP, plasma p-tau217 was quantified at the Department of Psychiatry and Neurochemistry, University of Gothenburg, using the commercial ALZpath Ptau217 assay.[17] Head-to-head studies have demonstrated that these plasma p-tau217 assays present similar analytical performance.[18,19] GFAP and p-tau217 positivity was determined using the mean plasma GFAP/p-tau217 concentration of the youngest 15% of Aβ− individuals plus two standard deviations (SDs) as reported elsewhere.[9]

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional sources. Drug interventions targeting the preclinical stage of Alzheimer's disease (AD) hold promise to halt disease progression before cognitive symptoms appear, but selecting participants at higher risk to progress remains challenging. Evidence suggests that CU amyloid beta (Aβ)+ individuals with elevated plasma glial fibrillary acidic protein (GFAP) levels are at increased risk of AD-related progression. However, the utility of plasma GFAP for population enrichment in clinical trials focusing on CU populations has not yet been explored.
2. **Interpretation**: In this study involving two cohorts, we found that combining plasma GFAP with Aβ for participant selection increases the effect size required to detect changes in tau positron emission tomography (PET) accumulation. This approach reduces the required sample size, the number of Aβ PET scans, and trial costs.
3. **Future directions**: Our findings suggest that clinical trials targeting tau pathology in preclinical AD could benefit from recruiting individuals positive for both Aβ and GFAP biomarkers, improving participant selection and cost effectiveness.

2.4 | Statistical analysis

The statistical analyses were performed using R statistical software version 4.2.1. (http://www.r-project.org/). Tau PET values for each region of interest (i.e., MTL and NEO-T) were *z* scored within each cohort and for baseline and follow-up separately.[20] The annual rate of change in tau PET was calculated as the difference between follow-up and baseline uptake values divided by the time between scans. Differences between groups in continuous variables were assessed using analysis of variance with Tukey correction. For the calculation of effect size, sample size, and trial costs individuals were divided into biomarker negative (GFAP−/Aβ−), Aβ+ (regardless of their GFAP status), and GFAP+/Aβ+ categories. Effect sizes were calculated as the mean of the annual rate of change for each group divided by the SD accounting for age, sex, and cohort.[21,22] Additional analyses were corrected by Centiloid values and GFAP/p-tau levels when applicable. We estimated the sample size required for a clinical trial designed to test a hypothesized 25% drug effect on longitudinal reduction in tau PET.[21–23] To calculate the number of individuals recruited in the population enrichment strategy we considered a prevalence of 30% of GFAP+ in CU older adults.[9] In addition, for clinical trial cost calculation, in the proposed enrich-

TABLE 1 Demographics and key characteristics of participants.

	GFAP−/Aβ− (*n* = 105)	GFAP+/Aβ− (*n* = 38)	GFAP−/Aβ+ (*n* = 41)	GFAP+/Aβ+ (*n* = 28)
Age, mean (SD)	66.7 (6.2)	71.5 (6.2)[a]	69.5 (4.7)[a]	73.4 (6.3)[a]
Sex, *n* (% female)	67 (63.8)	32 (84.2)	19 (46.3)	22 (78.6)
APOE ε4 (% of carriers)	26 (24.8)	8 (21.1)	18 (43.9)	13 (46.4)
Education, years (SD)	16.2 (3.4)	15.9 (3.5)	16.9 (3.3)	15.0 (2.6)
Aβ PET (Centiloid)	1.48 (5.13)	2.87 (5.03)	43.8 (31.3)[a,b]	47.0 (25.2)[a,b]
p-tau217 (*z* score)	−0.38 (0.43)	−0.32 (0.39)	0.54 (1.15)[a,b]	1.06 (1.62)[a,b,c]

Note: Nine individuals did not have plasma p-tau217 available.
Abbreviations: *APOE*, apolipoprotein; Aβ, amyloid beta; GFAP, glial fibrillary acidic protein; PET, positron emission tomography; p-tau, phosphorylated tau; SD, standard deviation.
[a]Different from GFAP−/Aβ−.
[b]Different from GFAP+/Aβ−.
[c]Different from GFAP−/Aβ+.

ment strategy with GFAP, we considered that only GFAP+ individuals would undergo clinical assessments. We estimated that 10% of individuals who would be prescreened without suspected cognitive decline would present some degree of cognitive impairment and would have to be excluded after clinical assessments. Only individuals without cognitive impairment would undergo an Aβ PET scan. We estimated the cost of each step based on research settings for: recruitment = $100, prescreening with plasma GFAP = $200, clinical assessments = $1000, Aβ PET = $3000, and tau PET = $3000 for each time point (i.e., baseline and follow-up).[21]

3 | RESULTS

We studied 212 CU individuals (mean age = 69.0 ± 6.4 years, 32.5% Aβ+) with plasma GFAP, Aβ PET, as well as longitudinal tau PET (follow-up duration of 2.48 ± 0.84 years). Demographic and clinical characteristics of the population are summarized in Table 1.

3.1 | CU GFAP+/Aβ+ show increased longitudinal changes in tau PET deposition

GFAP−/Aβ+ and GFAP+/Aβ+ groups showed a statistically significant longitudinal increase in tau PET_{MTL} uptake (Figure 1A). The effect size of the annual rate of change in tau PET_{MTL} was numerically higher in GFAP+/Aβ+ than in Aβ+ only individuals (0.75 vs. 0.66, respectively; Figure 1B) and both were higher than those observed in the GFAP−/Aβ− group (0.12; Figure 1B). For tau PET_{NEO-T}, only the GFAP+/Aβ+ group showed an annual rate of change that was significantly different from zero, with the GFAP+/Aβ+ group also presenting a significantly higher annual rate of change compared to GFAP−/Aβ+ (Figure 1D). The effect size of the rate of change in tau PET_{NEO-T} was numerically higher in the GFAP+/Aβ+ group compared to Aβ+ (0.56 vs. 0.35, respectively; Figure 1E) and GFAP−/Aβ− (0.56 vs. −0.08, respectively; Figure 1E) groups. When analyzing the cohorts individually, we observed that the overall effect sizes of changes in tau PET_{MTL} and tau PET_{NEO-T} were higher in the WRAP cohort than in the TRIAD cohort (Figure S1 in supporting information). Harmonization of tau PET with ComBat rendered similar effect sizes for changes in tau PET_{MTL} and tau PET_{NEO-T} (Figure S2 in supporting information).

3.2 | CU GFAP+/Aβ+ enriched clinical trials require a reduced sample size

Clinical trials aiming to detect changes in tau PET_{MTL} as a secondary outcome using CU GFAP+/Aβ+ would require 433 individuals per study arm, while a trial including CU Aβ+ only (regardless of GFAP status) would require 507 individuals per arm (Figure 1C), rendering a reduction of 15% in the sample size required. Clinical trials aiming to detect changes in tau PET_{NEO-T} as an outcome using CU GFAP+/Aβ+ individuals would require 891 individuals per study arm, while a trial including CU Aβ+ only would require 2068 individuals per study arm (reduction of 57%; Figure 1F).

3.3 | CU GFAP+/Aβ+ enrichment reduces resource use

We propose an enrichment strategy in which prescreening with plasma GFAP is performed and only GFAP+ individuals undergo clinical assessment (to confirm the absence of cognitive impairment), followed by an Aβ PET scan only for individuals with a confirmed absence of cognitive impairment (Figure 2A). The inclusion of the GFAP+ prescreening step increased the total number of individuals required to be recruited for trials targeting tau PET_{MTL} (2886 vs. 1619, if using Aβ only; Figure 2B). However, the number of Aβ PET scans necessary for these trials after GFAP prescreening was reduced by up to 49% (866 vs. 1619; Figure 2B). For clinical trials targeting tau PET_{NEO-T}, the GFAP+ prescreening step reduced the total number of individuals required to be recruited (5937 vs. 6892; Figure 2C) and of Aβ PET scans required by up to 74% (1781 vs. 6892 if using Aβ only; Figure 2C). We calculated the estimated costs of clinical trials using the two dif-

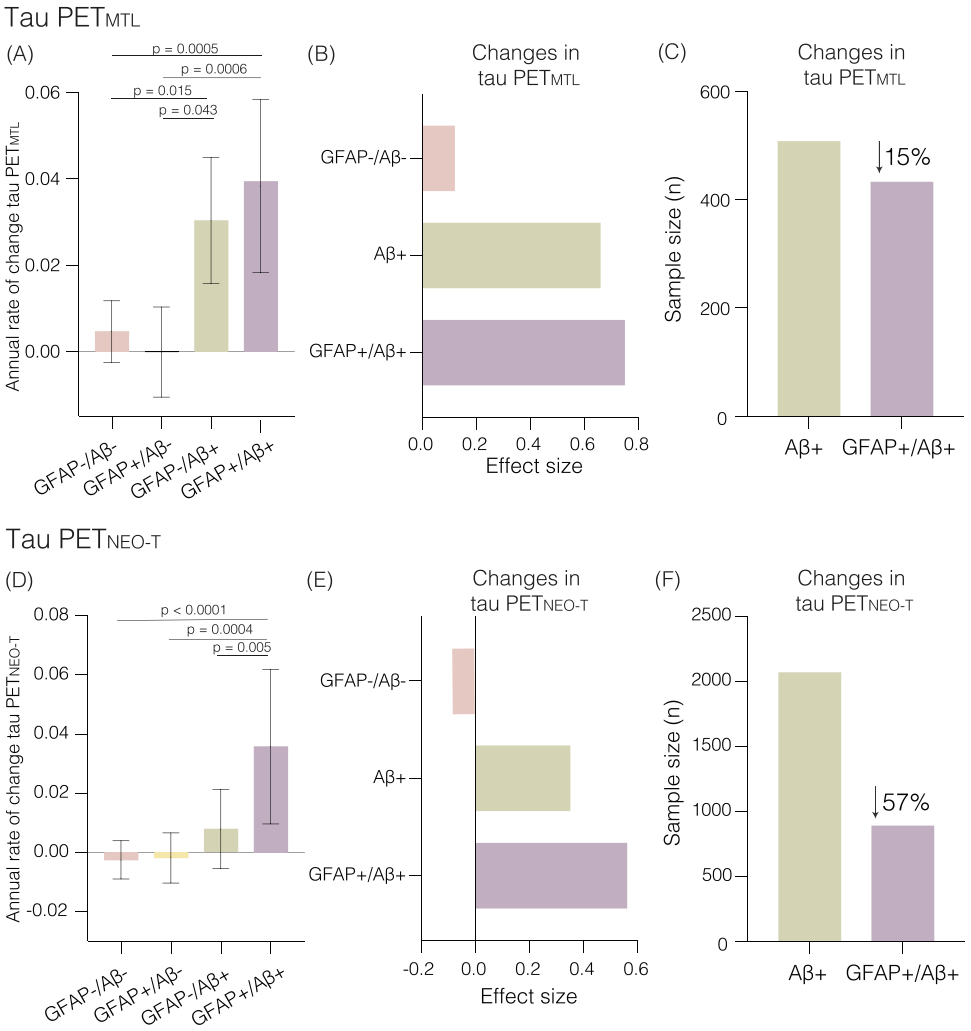

FIGURE 1 Longitudinal changes and effect size of tau PET according to Aβ and GFAP status. A, Annual rate of change in tau PET_{MTL}, (B) effect size of changes in tau PET_{MTL}, and (C) sample size required for detecting changes in tau PET_{MTL} in CU stratified by Aβ and GFAP status. D, Annual rate of change in tau PET_{NEO-T}, (E) effect size of changes in tau PET_{NEO-T}, and (F) sample size required for a study detecting changes in tau PET_{NEO-T} in CU individuals stratified by Aβ and GFAP status. Group comparisons were assessed using analysis of variance accounting for age, sex, and cohort, with Tukey correction. The graphs show the mean and 95% confidence interval. Effect sizes were calculated adjusting for age, sex, and cohort. For effect size and sample size calculation, the Aβ+ group was divided regardless their GFAP levels. Aβ, amyloid beta; CU, cognitively unimpaired; GFAP, plasma glial fibrillary acidic protein; MTL, medial temporal lobe region; NEO-T, temporal neocortical region; PET, positron emission tomography.

ferent strategies for population enrichment using: (1) only Aβ PET+ and (2) GFAP+ prescreening plus Aβ PET (Figure 2A). For the hypothetical trial targeting changes in tau PET_{MTL}, the total estimated cost reduction was 28% using the GFAP+/Aβ+ strategy compared to using Aβ PET only (Figure 3A). For trials targeting changes in tau PET_{NEO-T}, the cost reduction was as high as 64% using the GFAP+/Aβ+ strategy (Figure 3B).

3.4 | CU GFAP+/Aβ+ enrichment allows selection of individuals at early stages of the AD continuum

We compared strategies using Aβ+ plus GFAP+ versus Aβ+ plus p-tau+ for selecting individuals at the earliest stages of AD. We found that GFAP+/Aβ+ had lower Aβ pathology compared to p-tau+/Aβ+ individuals (Figure 4A). Although no statistically significant differences in plasma p-tau217 were observed between populations (Figure 4B), a sensitivity analysis removing one outlier showed that p-tau+/Aβ+ individuals had statistically significantly higher levels of plasma p-tau217 than GFAP+/Aβ+ individuals (Figure S3 in supporting information). No statistically significant differences were observed between GFAP+/Aβ+ and p-tau+/Aβ+ in the annual rate of change on tau PET_{MTL} or tau PET_{NEO-T} (Figure S4 in supporting information). The effect size on the rate of change in tau PET_{MTL} was numerically higher in the p-tau+/Aβ+ compared to the GFAP+/Aβ+ group (0.93 vs. 0.77, respectively; Figure 4C). However, when accounting for Aβ levels, the effect size of GFAP+/Aβ+ was higher than p-tau+/Aβ+ (GFAP+/Aβ+ = 0.49 vs. p-tau+/Aβ+ = 0.40; Figure 4E). This repre-

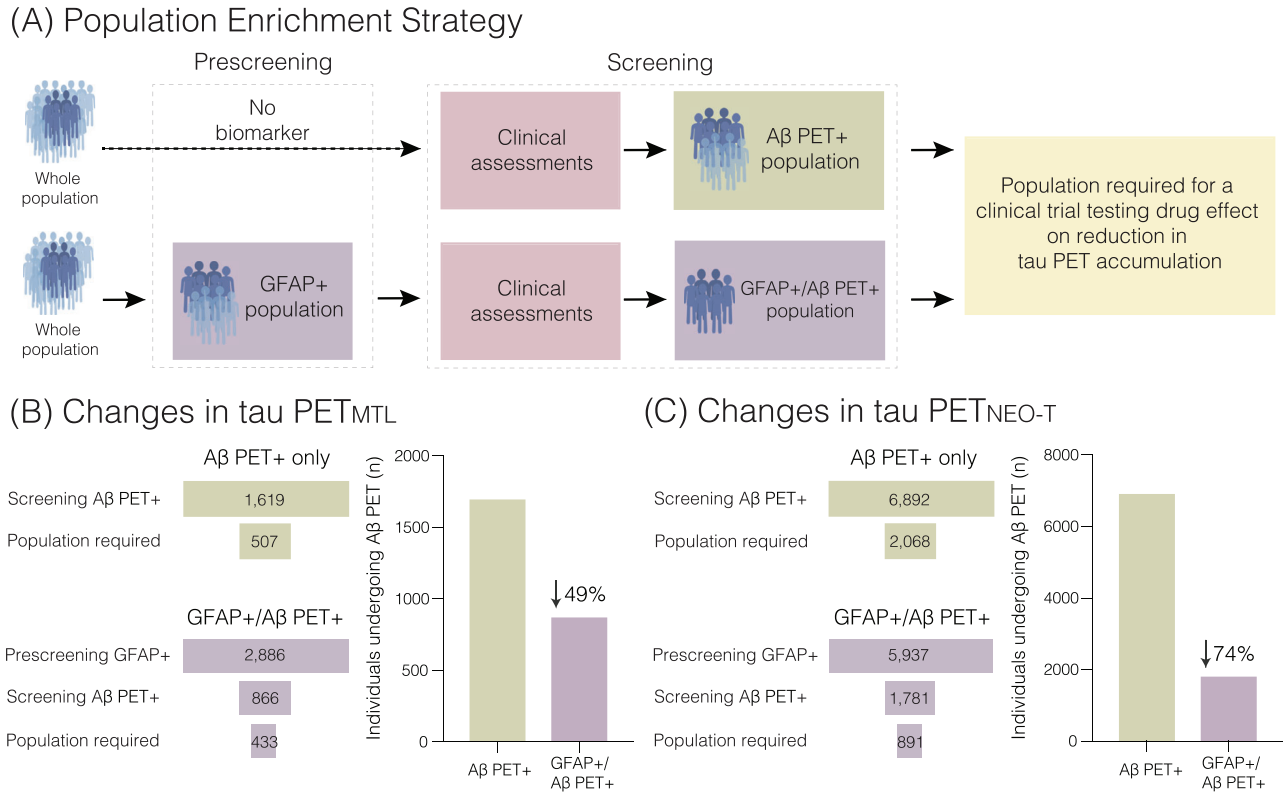

FIGURE 2 Plasma GFAP enrichment strategy for participant selection in clinical trials focusing on CU individuals. A, Schematic representation of population enrichment strategies with and without prescreening using plasma GFAP before clinical and Aβ PET assessments. B, C, Comparison of number of individuals in each step of clinical trial workflow using only Aβ+ biomarker and GFAP+ plus Aβ+ biomarkers to select participants in hypothetical clinical trials aiming at detecting changes in tau (B) PET_{MTL} and (C) PET_{NEO-T}. Aβ, amyloid beta; CU, cognitively unimpaired; GFAP, plasma glial fibrillary acidic protein; MTL, medial temporal lobe region; NEO-T, temporal neocortical region; PET, positron emission tomography.

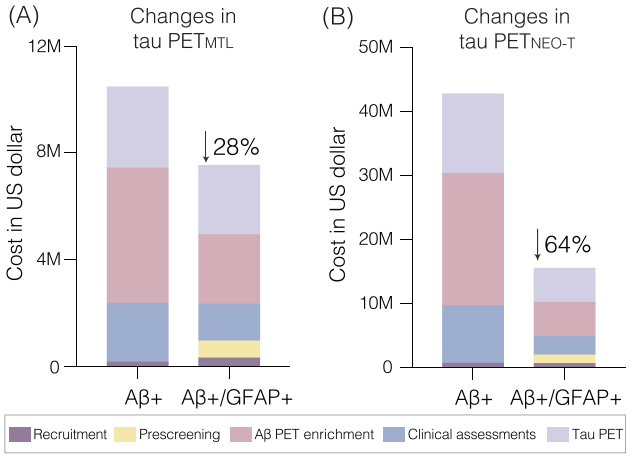

FIGURE 3 Plasma GFAP cost-efficiency impact in CU trials. Estimated costs are based on a hypothetical 25% drug effect on changes in (A) tau PET_{MTL} and (B) tau PET_{NEO-T}. For the calculation, we estimated the following costs: recruitment = $100; plasma GFAP = $200; Aβ PET or tau PET = $3000; clinical assessments = $1000. Tau PET and clinical assessments were calculated to two time points (baseline and follow-up to determine change). Aβ, amyloid beta; CU, cognitively unimpaired; GFAP, plasma glial fibrillary acidic protein; MTL, medial temporal lobe region; NEO-T, temporal neocortical region; PET, positron emission tomography.

sented a 36% reduction in the effect size of GFAP+/Aβ+ group and a 57% reduction in the effect size of the p-tau+/Aβ+ group (Figure S5 in supporting information). The effect size of the rate of change in tau PET_{NEO-T} was numerically higher in the GFAP+/Aβ+ group compared to the p-tau+/Aβ+ group (0.57 vs. 0.52, respectively; Figure 4D). When accounting for continuous Aβ levels, the effect size of the GFAP+/Aβ+ group remained substantially higher than of the p-tau+/Aβ+ group (0.38 vs. 0.20; Figure 4F; Figure S5), suggesting that the effect size of the p-tau+/Aβ+ group is strongly influenced by their elevated Aβ load. Interestingly, when further accounting for plasma p-tau217 levels (in addition to Aβ) in the GFAP+/Aβ+ group the effect sizes on tau PET_{MTL} and tau PET_{NEO-T} only slightly changed (Figure 4E,F; Figure S5), suggesting little influence of underlying p-tau217 levels on the effect size of the GFAP+/Aβ+ group. Similarly, for the p-tau+/Aβ+ group, additional correction for GFAP levels had only a slight impact on the effect sizes of change in tau PET (Figure 4E,F; Figure S5). Aiming to target the earliest stages of the AD continuum, we evaluated the effect size on tau PET changes in individuals with Centiloid levels between 12 and 50 (Figure S6 in supporting information). Our findings revealed that GFAP+/Aβ+ individuals demonstrated greater effect sizes in tau PET changes in both tau PET_{MTL} and PET_{NEO-T} compared to p-tau+/Aβ+ individuals. Specifically, the effect sizes for tau PET_{MTL} were 0.95 in GFAP+/Aβ+ individuals versus 0.84 in p-tau+/Aβ+ individuals, while

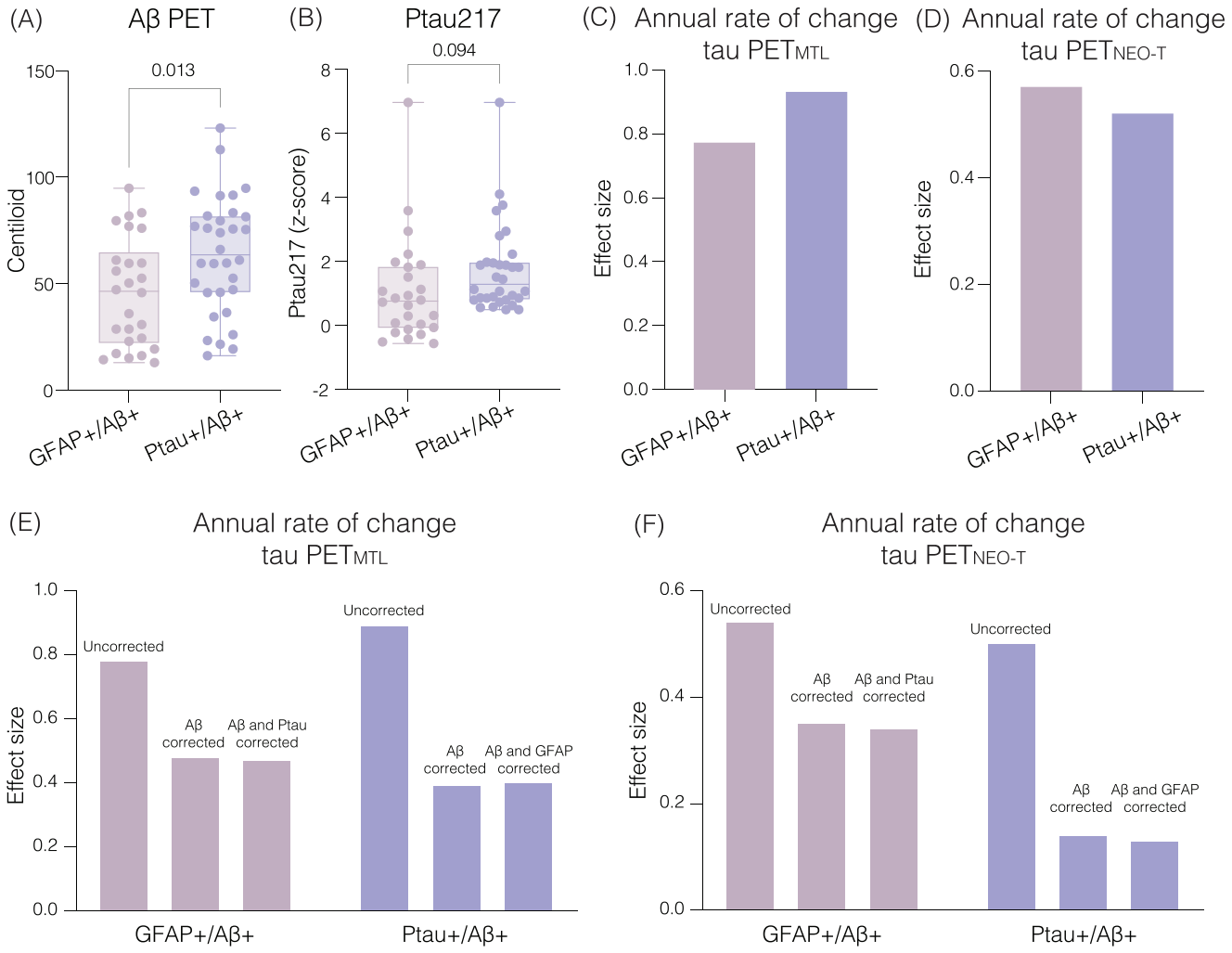

FIGURE 4 Population enrichment with GFAP+/Aβ+ allows the selection of CU individuals with similar tau progression levels compared to p-tau+/Aβ+ but who are earlier in the AD continuum. A, Baseline Aβ PET Centiloid and (B) plasma p-tau217 values in GFAP+/Aβ+ and p-tau+/Aβ+ CU individuals. Effect size of changes in tau (C) PET_{MTL} and (D) PET_{NEO-T} in CU individuals stratified according to their Aβ and/or GFAP and p-tau217 status. Effect sizes of changes in tau (E) PET_{MTL} and (F) PET_{NEO-T} adjusting for Aβ levels, Aβ and p-tau levels (only for the GFAP+/Aβ+ group), and Aβ and GFAP levels (only for the p-tau+/Aβ+ group). Effect sizes were further adjusted for age, sex, and cohort. Nine individuals without plasma p-tau217 available were removed from this analysis. Group comparisons were assessed using analysis of variance. Aβ, amyloid beta; AD, Alzheimer's disease; CU, cognitively unimpaired; GFAP, plasma glial fibrillary acidic protein; MTL, medial temporal lobe region; NEO-T, temporal neocortical region; PET, positron emission tomography; p-tau, phosphorylated tau.

tau PET_{NEO-T} effect sizes were 0.48 versus 0.29, respectively (Figure S6).

4 | DISCUSSION

We show that using plasma GFAP in addition to Aβ PET for CU population enrichment in clinical trials designed to detect changes in tau PET reduces the (1) required sample size, (2) number of Aβ PET scans, and (3) overall costs of these trials. Furthermore, this enrichment strategy selects participants at earlier stages of AD compared to using plasma p-tau.

CU GFAP+/Aβ+ individuals showed a significant increase in longitudinal tau accumulation in the MTL and NEO-T regions, while GFAP−/Aβ+ individuals only showed significant tau accumulation in the MTL. Longitudinal tau accumulation in AD-related brain regions has been consistently and strongly associated with cognitive decline.[24–26] *Post mortem* and clinical imaging studies suggest that the accumulation of tau neurofibrillary tangles in AD follows a stereotypical pattern, with early deposition in the MTL that spreads later to the neocortex.[12,27,28] While tau accumulation confined to the MTL has been associated with subtle age-related cognitive effects, lateral spread of tau pathology over NEO-T regions has been linked to marked cognitive impairment.[2,29] Indeed, it has recently been demonstrated that the clinical progression of individuals from CU to MCI is more pronounced in those who have tau deposition in NEO-T than in MTL.[2] Our results showed that GFAP+ individuals exhibit more prominent tau accumulation in brain regions highly associated with dementia

symptoms (i.e., NEO-T), highlighting that GFAP positivity indicates Aβ+ individuals who are more likely to experience AD-related progression.

We estimated that enriching clinical trials with CU GFAP+/Aβ+ individuals can substantially reduce the sample size and costs of AD clinical trials targeting decreases in tau accumulation, especially in the NEO-T region. This biomarker profile identifies CU individuals at higher risk of short-term tau tangle accumulation. Our proposed enrichment strategy begins with recruiting participants without known cognitive impairment. Initially, these participants will undergo prescreening with plasma GFAP. Then, only GFAP+ individuals undergo clinical assessment to confirm the absence of objective cognitive impairment. Conducting GFAP prescreening in CU populations prior to formal clinical assessments led to a significant reduction in the number of participants required to undergo detailed clinical evaluations, which resulted in a reduction in trial costs (of up to 64%) and the time required for prescreening. After the clinical assessments, CU GFAP+ individuals will undergo Aβ PET scans. We estimate that the initial participant selection steps could reduce the number of Aβ PET scans required by up to 80%, which not only lowers the clinical trial costs but also has the potential to speed up the participant screening. However, it is important to consider that for trials using tau PET_{MTL} as an outcome, the initial recruitment step using this strategy requires the enrollment of a substantially higher number of individuals for prescreening with plasma GFAP. Although the estimated total cost of these trials is lower compared to the strategy without prescreening, the additional time required for recruitment should be considered. Altogether, these results suggest that the use of plasma GFAP offers a cost-effective alternative to population enrichment for clinical trials in preclinical AD.

We demonstrate that GFAP+/Aβ+ individuals had a lower overall burden of AD pathology than p-tau+/Aβ+ populations while presenting a similar increase in longitudinal tau PET deposition. This finding may have important implications for clinical trial participant selection. Our results suggest that selecting GFAP+/Aβ+ individuals may help identify individuals who are more likely to progress in the disease but have a lower Aβ burden (mean Centiloid of 46) compared to the selection of p-tau+/Aβ+ individuals (mean Centiloid of 65). This approach is particularly relevant for trial enrichment if we consider the TRAILBLAZER-ALZ study, which demonstrated that individuals with lower baseline Aβ levels were more likely to achieve complete Aβ clearance.[30] Additionally, early clearance of Aβ plaques was associated with greater slowing of tau accumulation over the course of the trial. Relying solely on Aβ PET for participant selection for preclinical AD trials may be insufficient to identify individuals at risk of progression, as the solanezumab study found that disease progression occurred in individuals with high baseline Aβ deposition (i.e., Centiloid > 77).[31] These results suggest that using GFAP+ rather than p-tau+ in combination with Aβ PET could help select individuals most likely to benefit from anti-Aβ therapies.

The strengths of our study include replicating the results using two well-characterized cohorts, both of which had tau PET measured with the same high-affinity tau tracer, which facilitated the interpretation of changes in tau PET between cohorts. However, limitations should be considered when interpreting our results. Both cohorts consist of a selective population of highly educated, mostly White participants, which does not represent a more diverse general world population, a problem also observed with most recent clinical trials in AD. Additionally, the effect sizes and sample sizes determined here might not be generalizable to other tau PET tracers that present distinct intrinsic characteristics and off-target binding, which could result in varying rates of changes between tracers.

To conclude, clinical trials focusing on preclinical AD would benefit from recruiting individuals positive for Aβ and GFAP biomarkers to improve their population selection and cost effectiveness.

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CONFLICT OF INTEREST STATEMENT

H.Z. 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 co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K.B. has served as a consultant and on advisory boards for Abbvie, AC Immune, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Neurimmune, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served on data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials, and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai, and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. S.G. received consulting fees as a member of the scientific advisory boards in Abbvie, Alzheon, AmyriAD, Eisai, Enigma/Meilleur, Lilly, Okutsa, Novo Nordisk, TauRx; honoraria for educational videos from Lundbeck; and reimbursement for AD/PD 2024 travel expenses by TauRx. S.G. is a board member at the Sharon and Robert Francis Foundation, Toronto, Canada, and the Canadian Conference on Dementia (CCD). E.R.Z. has served on the scientific advisory board of Nintx, Novo Nordisk, and Masima. He is also a co-founder and a minority shareholder at Masima. P.R-N. has served on scientific advisory boards and/or as a consultant for Roche, Novo Nordisk, Eisai, and Cerveau radiopharmaceuticals. N.J.A. has given lectures in symposia sponsored by Lilly and Quanterix. J.T. has served as a consultant for the Neurotorium educational platform and for Alzheon Inc. P.V. has served on scientific advisory boards for Novo Nordisk, Eisai, and Lilly. G.T.B. receives salary and has stocks from Janssen R&D. S.C.J. serves on advisory boards for AlzPATH and Enigma Biomedical. The other authors declare that they have no conflict of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All study participants provided written informed consents for all study procedures.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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