

## RESEARCH ARTICLE

## Gene- and age-informed screening for preclinical Alzheimer's disease trials

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## Abstract

**Introduction:** Elevated  $\beta$ -amyloid is used to enroll individuals into preclinical Alzheimer's disease trials, but the screening process is inefficient and expensive. Novel enrichment methods are needed to improve efficiency of enrollment.**Methods:** Alzheimer's disease incidence rates and a polygenic hazard score were used to create a gene- and age-defined ADAge. An ADAge cutpoint was chosen to optimally predict  $\beta$ -amyloid positivity among clinically normal Alzheimer's Disease Neuroimaging Initiative participants and applied to an independent Alzheimer's Disease Research Center validation cohort. The impact of ADAge enrichment on screening costs was evaluated in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease trial data.**Results:** In the validation cohort, the ADAge-enriched sample had a higher proportion of individuals with elevated  $\beta$ -amyloid (difference [95% CI] 0.19[0.07 to 0.33]) than the unenriched sample. ADAge enrichment lowered screening costs by \$4.41 million (31.00%) in the real-world clinical trial scenario.**Discussion:** ADAge enrichment provides for a more efficient and cost-effective means to enroll clinically normal individuals with elevated  $\beta$ -amyloid in clinical trials.

## KEYWORDS

Alzheimer's disease, biomarkers, clinical trial design, genetics, neuroimaging, PET, predictive markers

## 1 | INTRODUCTION

In clinically normal (CN) individuals, elevated brain  $\beta$ -amyloid ( $A\beta$ ) is considered to be the earliest detectable indication of Alzheimer's disease (AD) neuropathologic change.<sup>1</sup> Recently, preclinical AD trials began targeting  $A\beta$  in CN individuals to test whether decreasing  $A\beta$  would slow AD-related decline.<sup>2</sup> As such, these trials require biomarker confirmation of elevated  $A\beta$  for enrollment. However, these CN individuals are only identified through the inefficient process of  $A\beta$  positron emission tomography (PET) screening, which enrolls only  $\approx$ 30% of those screened.<sup>2</sup> Novel enrichment methods leveraging genetic and age-specific risk for AD may improve the speed and

efficiency of preclinical AD trial enrollment while reducing screening costs by identifying those CN individuals who are at greatest risk for AD.

Genetic variants such as the apolipoprotein E (APOE)  $\epsilon$ 4 allele are known to modulate AD risk. Risk for AD increases and age of AD onset decreases with an increasing number of APOE  $\epsilon$ 4 alleles.<sup>3,4</sup> Genome-wide association studies have identified additional, more common variants that confer risk for AD,<sup>5,6</sup> and polygenic scores have been developed to capture an individual's risk for AD as an aggregate of their risk across many variants. Recently, a polygenic hazard score (PHS) based on 31 variants and APOE was developed and validated that better predicts the age of AD onset than does APOE alone.<sup>7</sup> Previous work

has demonstrated the utility of the PHS for predicting risk of clinical progression and cognitive decline in CN individuals.<sup>8,9</sup> However, for a given individual, aging is the single most important risk factor for AD, regardless of genetic background. Therefore, instantaneous risk for developing AD is better understood as a function of both genetic and baseline age-specific risk for AD.

We hypothesized that by combining PHS- and age-specific risk for AD we could predict elevated A $\beta$  in CN individuals. We developed a gene- and age-defined ADAge enrichment method and tested the efficiency of such gene- and age-informed A $\beta$  screening for preclinical AD trials in an independent cohort, while evaluating its impact on hypothetical trial population demographics. We then applied the ADAge enrichment method to real-world clinical trial screening data and compared the screening and associated costs necessary to enroll CN participants with elevated A $\beta$  into the trial with or without ADAge enrichment.

## 2 | METHODS

### 2.1 | Participants

The development cohort comprised 939 participants (306 CN, 469 with mild cognitive impairment, and 164 with AD) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (Supplementary Methods). ADNI participants who completed a florbetapir PET scan and had PHS calculated were included.

For the validation cohort, an independent sample of 80 participants was selected from the Shiley-Marcos Alzheimer's Disease Research Center (ADRC) of the University of California, San Diego. All CN participants who had undergone a lumbar puncture and genotyping were included.

The real-world clinical trial cohort comprised 3322 screened participants from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) trial who had undergone genotyping and a florbetapir PET scan.

The research protocol was approved by each local institutional review board and written informed consent was obtained from each participant or participant's guardian.

### 2.2 | Genetic data

All participants in the ADNI development, ADRC validation, and A4 clinical trial cohorts were genotyped using a commercially available Illumina BeadChip array. For a description of the imputation and quality control process for the genetic data see Supplementary Methods.

### 2.3 | PHS

PHS data were downloaded from ADNI for each participant in the ADNI development cohort. For the ADRC validation and A4 clinical trial cohorts, the PHS was calculated as described<sup>7</sup> using MATLAB R2018b.

### RESEARCH IN CONTEXT

1. Systematic review: We searched the literature using PubMed. While previous work established the potential utility of the polygenic hazard score in clinically normal individuals, it was unknown whether we could enrich a cohort for  $\beta$ -amyloid positivity using gene- and age-informed inclusion decisions at the individual level.
2. Interpretation: We demonstrated that gene- and age-informed  $\beta$ -amyloid screening could be used to significantly enrich the proportion of clinically normal individuals with elevated  $\beta$ -amyloid in a sample (from 0.28 to 0.46), leading to a \$4.41 million (31.00%) reduction in screening costs in a real-world clinical trial screening scenario. Gene- and age-informed  $\beta$ -amyloid screening is a novel preclinical Alzheimer's disease trial enrichment method that may help address the current expense and inefficiency of participant selection and enrollment.
3. Future directions: Due to observed differences in Alzheimer's disease genetic risk across racial and ethnic groups, future work is needed to develop Alzheimer's disease polygenic scores in diverse populations.

Briefly, AD-associated single-nucleotide polymorphisms (SNPs) were identified in the International Genomics of Alzheimer's Project (IGAP) cohort at  $P < 10^{-5}$ . These SNPs were then integrated into a stepwise Cox proportional hazards model using a subset of the Alzheimer's Disease Genetics Consortium (ADGC) phase 1 genetic data, which excluded individuals from the National Alzheimer's Coordinating Center and ADNI samples. This stepwise procedure identified 31 SNPs that most improved the model prediction (Supplementary Table S1).

A PHS was calculated for each participant as the vector product of that individual's genotype for the 31 SNPs and the corresponding parameter estimates from the ADGC phase 1 Cox proportional hazard model, choosing the effect allele to be consistent with the direction of the beta in the IGAP summary statistics, in addition to the APOE  $\epsilon$ 2 and APOE  $\epsilon$ 4 effects.

Because the development and validation of the PHS has been largely limited to white, non-Hispanic cohorts, for the purposes of this analysis only white, non-Hispanic participants were included in the ADNI development and ADRC validation cohorts. This resulted in the exclusion of 29 otherwise eligible ADNI participants and 10 ADRC participants. However, all participants were included in the real-world A4 clinical trial cohort, which comprised 340 participants that were Hispanic, not white, or both.

### 2.4 | A $\beta$ status classification

We classified participants as having normal A $\beta$  (A $\beta$ -) or as A $\beta$  positive (A $\beta$ +) based on florbetapir PET or cerebrospinal fluid (CSF)

**TABLE 1** Demographics and clinical characteristics of the ADNI development, ADRC validation, and A4 clinical trial cohorts split by A $\beta$  status

	ADNI development cohort			P value A $\beta$ + versus A $\beta$ -
	Entire cohort n = 939	A $\beta$ + n = 507	A $\beta$ - n = 432	
Clinical diagnosis				<.001
CN, no. (%)	306 (32.59)	102 (20.12)	204 (47.22)	
MCI, no. (%)	469 (49.95)	264 (52.07)	205 (47.45)	
AD, no. (%)	164 (17.47)	141 (27.81)	23 (5.32)	
Age, y	74.05 (7.47)	74.79 (7.19)	73.18 (7.71)	<.001
ADAge	76.29 (8.49)	79.21 (7.91)	72.86 (7.84)	<.001
Female, no. (%)	423 (45.05)	236 (46.55)	187 (43.29)	.32
APOE $\epsilon$ 4 carrier, no. (%)	414 (44.09)	329 (64.89)	85 (19.68)	<.001
PHS	0.32 (0.76)	0.63 (0.76)	-0.05 (0.58)	<.001
Florbetapir SUVR <sup>a</sup>	1.21 (0.23)	1.39 (0.17)	1.00 (0.06)	<.001
	ADRC validation cohort			P value A $\beta$ + versus A $\beta$ -
	Entire cohort n = 80	A $\beta$ + n = 22	A $\beta$ - n = 58	
Age, y	72.92 (5.95)	73.69 (6.88)	72.63 (5.59)	.80
ADAge	73.01 (8.34)	77.28 (8.77)	71.40 (7.65)	.009
Female, no. (%)	53 (66)	13 (59)	40 (69)	.40
APOE $\epsilon$ 4 carrier, no. (%)	29 (36)	14 (64)	15 (26)	.002
PHS	0.01 (0.88)	0.51 (0.92)	-0.18 (0.80)	.004
A $\beta$ 42/40 ratio <sup>b</sup>	0.20 (0.06)	0.13 (0.02)	0.22 (0.05)	<.001
	A4 clinical trial cohort			P value A $\beta$ + versus A $\beta$ -
	Entire cohort n = 3322	A $\beta$ + n = 1115	A $\beta$ - n = 2207	
Age, y	71.34 (4.74)	71.98 (4.88)	71.02 (4.64)	<.001
ADAge	71.86 (7.20)	74.77 (7.13)	70.40 (6.78)	<.001
Female, no. (%)	1992 (59.96)	674 (60.45)	1318 (59.72)	.69
APOE $\epsilon$ 4 carrier, no. (%)	1166 (35.10)	651 (58.39)	515 (23.33)	<.001
PHS	0.07 (0.84)	0.40 (0.88)	-0.09 (0.77)	<.001
Florbetapir SUVR <sup>a</sup>	1.09 (0.19)	1.31 (0.17)	0.98 (0.06)	<.001

Reported as mean (SD) unless otherwise noted. *P*-value based on Pearson's chi-squared test, Welch's two-sample *t* test, or independent two-group Mann-Whitney *U* test as appropriate.

AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ADRC, Alzheimer's Disease Research Center; APOE, apolipoprotein E; A $\beta$ ,  $\beta$ -amyloid; CN, clinically normal; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PHS, polygenic hazard score; SUVR, standardized uptake value ratio; A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease.

<sup>a</sup>A $\beta$  positivity was determined using a cutoff of 1.11 SUVR.

<sup>b</sup>A $\beta$  positivity was determined using an A $\beta$ 1-42 to A $\beta$ 40 ratio cutoff of 0.16.

quantification (Table 1). For the ADNI development cohort, florbetapir PET summary data were downloaded from ADNI (see Landau et al.<sup>10</sup> for acquisition and processing details). Images were acquired between May 25, 2010 and July 19, 2016. A $\beta$  positivity was determined using a cutoff of 1.11 standardized uptake value ratio (SUVR, whole cerebellum reference region) for the summary cortical grey matter region of interest. For the ADRC validation cohort, CSF was collected between June 30, 2011 and November 17, 2017. CSF sample collection and A $\beta$  quantification by liquid chromatography-tandem mass spec-

trometry has been described.<sup>11</sup> A $\beta$  positivity was determined using an A $\beta$ 1-42 to A $\beta$ 40 ratio cutoff of 0.16, a threshold value determined to optimally distinguish CN participants from those with AD.<sup>11</sup> Though not completely overlapping, most individuals have concordant amyloid biomarker results when assessed with both PET and CSF,<sup>12</sup> with even better agreement when using the A $\beta$ 42/40 ratio than A $\beta$ 42 alone.<sup>13</sup> For the A4 clinical trial cohort, screening florbetapir PET summary data were downloaded from A4. A $\beta$  positivity was determined using a cutoff of 1.11 SUVR for the composite summary region of interest.

## 2.5 | ADAge

We used the United States (US) population baseline AD incidence rate<sup>14</sup> in combination with PHS to calculate an individualized genetic assessment of age-specific AD risk in the form of a predicted annualized incidence rate. For a given rate, the ADAge is defined as the age at which there is an equivalent risk in the baseline population.

At chronological age  $t$ , where IR is the US population baseline AD incidence rate,<sup>14</sup>

$$IR = 0.084e^{0.142(t-60)}.$$

This population baseline incidence rate can be combined with the PHS to generate an individualized predicted annualized incidence rate (PAIR), which was found to be associated with empirical rates of progression to AD.<sup>7</sup>

$$PAIR = e^{PHS} \times IR.$$

Like the IR, the PAIR gives an estimate of an individual's age-associated AD risk, but, in this case, also incorporates genetic information. For a given individual's PAIR, the ADAge is defined as the age at which there is equivalent risk in the baseline population.

$$ADAge = \frac{\ln\left(\frac{PAIR}{0.084}\right)}{0.142} + 60.$$

For example, if a participant whose chronological age is 67 has a PAIR that is equivalent to the population baseline IR for an 81-year-old, this participant's ADAge would be 81 (Supplementary Figure S1).

## 2.6 | Statistical analyses

Differences in demographics and clinical characteristics by A $\beta$  status were evaluated in the ADNI development, ADRC validation, and A4 clinical trial cohorts using Pearson's chi-squared tests, Welch's two-sample  $t$  tests, or independent two-group Mann-Whitney  $U$  tests as appropriate.

We used Meng's test for comparing two or more correlated correlations to assess whether the ADAge was more correlated with A $\beta$  than chronological age in the ADNI development cohort. This test was repeated within CN and APOE  $\epsilon$ 4 carrier subsets of the ADNI development cohort to further evaluate this difference. We then chose an ADAge cutpoint by maximizing the Youden index for predicting A $\beta$  positivity in CN participants in the ADNI development cohort.

We applied the ADNI development cohort-derived ADAge cutpoint to 1000 bootstrap samples of the ADRC validation cohort. Using these bootstrap samples, 95% confidence intervals (CI) for the differences in means between samples enrolled by each strategy (ADAge enrichment vs no enrichment) were calculated to determine the efficiency of ADAge-informed A $\beta$  screening for preclinical AD trials as well as to assess demographic differences between such samples. These com-

parisons were repeated in the theoretical, A $\beta$ + end trial populations that would be enrolled by each strategy within the ADRC validation cohort to determine the impact of ADAge enrichment on trial population demographics.

All statistical analyses were performed using R (version 3.6.2).

## 2.7 | A4 clinical trial screening scenario

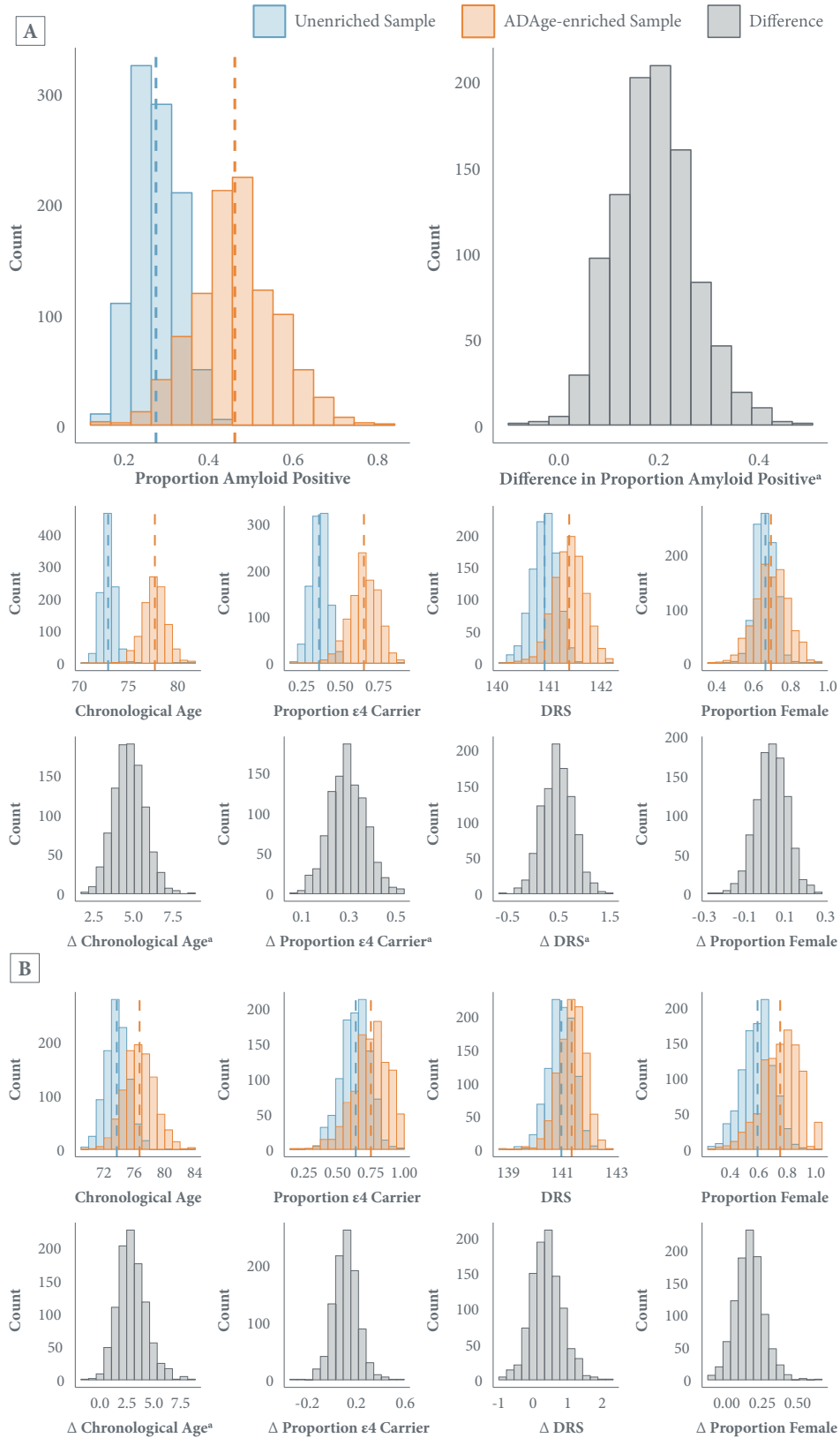
We compared the screening necessary to enroll A $\beta$ + CN participants in the A4 clinical trial cohort using each enrollment strategy (ADAge enrichment vs no enrichment). For both strategies, the number needed to PET scan in order to verify A $\beta$  status is a function of A $\beta$  positivity within the A4 clinical trial cohort. The proportion of individuals who were A $\beta$ + under each enrollment strategy was compared, and this comparison was repeated in APOE  $\epsilon$ 3 homozygotes to evaluate the impact of enrichment beyond APOE. For the ADAge enrichment strategy, the number needed to genotype (to recruit those with an ADAge greater than the cutpoint) is a function of the proportion of the sample with an ADAge greater than the cutpoint within the A4 clinical trial cohort. Values of the 95% CI for the mean screening and associated costs necessary to enroll participants by each strategy (ADAge enrichment vs no enrichment) were calculated. The screening cost assumes \$4285 per PET scan<sup>15</sup> and \$150 per genotype. The performance of ADAge enrichment was compared across racial and ethnic groups in the A4 clinical trial cohort.

## 3 | RESULTS

Cohort demographics are displayed in Table 1. Spearman's correlations were calculated for the relationships between florbetapir PET SUVR and either chronological age or ADAge across ADNI development cohort subsets. Compared to chronological age, ADAge was more correlated with florbetapir SUVR in the entire cohort (difference in correlation [95% CI] 0.28 [0.25 to 0.33],  $P < .001$ ) as well as within CN (0.14 [0.08 to 0.21],  $P < .001$ ) and APOE  $\epsilon$ 4 carrier (0.06 [0.02 to 0.11],  $P = .006$ ) subsets of the cohort. Supplementary Figure S2 shows scatterplots for the relationships between florbetapir SUVR and either chronological age or ADAge.

Supplementary Figure S3 shows the relationships between A $\beta$  positivity and chronological age or ADAge (Supplementary Figure S4 shows this relationship in each diagnostic group). The optimal ADAge cutpoint for predicting A $\beta$  positivity in CN participants in the ADNI development cohort was determined to be 76.4 (Supplementary Figure S5).

We generated 1000 bootstrap samples of the ADRC validation cohort (Figure 1). To test whether ADAge enrichment increased the proportion of CN individuals with elevated A $\beta$  in the sample, we applied the ADAge cutpoint to each of these bootstrap samples and compared these enriched samples to the original, unenriched samples. The ADAge-enriched sample had a higher proportion of A $\beta$ + individuals (mean [95% CI] 0.46 [0.27 to 0.66] vs 0.28 [0.18 to 0.37], difference 0.19 [0.07 to 0.33]).



**FIGURE 1** Demographic characteristics of the unenriched (blue) and ADage-enriched (orange) ADRC validation samples. Histograms display the means of 1000 bootstrap samples of the ADRC validation cohort and the difference in those means (gray). (A) At baseline, the ADage-enriched sample had a higher proportion of A $\beta$ + individuals (mean [95% CI] 0.46 [0.27 to 0.66] vs 0.28 [0.18 to 0.37], difference 0.19 [0.07 to 0.33]), was older (77.67 [75.34 to 80.01] vs 72.92 [71.61 to 74.23], difference 4.75 [3.16 to 6.36]), had a greater proportion of APOE  $\epsilon 4$  carriers (0.65 [0.47 to 0.84] vs 0.36 [0.25 to 0.47], difference 0.29 [0.17 to 0.42]), and had a higher dementia rating scale score (141.38 [140.79 to 141.98] vs 140.91

Next, we compared the theoretical, A $\beta$ + trial populations enrolled by each strategy (ADAge enrichment vs no enrichment) within the ADRC validation cohort to determine the impact of ADAge enrichment on trial cohort demographics. The ADAge-enriched sample was older than the unenriched sample (76.70 [72.71 to 80.68] vs 73.69 [70.78 to 76.61], difference 3.00 [0.94 to 5.22]). However, the samples were similar in the proportion of APOE  $\epsilon$ 4 carriers (0.75 [0.48 to 1.02] vs 0.64 [0.43 to 0.84], difference 0.11 [−0.04 to 0.28]), the dementia rating scale score (141.33 [140.37 to 142.29] vs 140.95 [140.02 to 141.89], difference 0.38 [−0.28 to 1.14]), and the proportion of female participants (0.75 [0.50 to 1.00] vs 0.59 [0.38 to 0.80], difference 0.16 [0.00 to 0.33]).

Finally, using the A4 clinical trial cohort, we examined the screening necessary to enroll A $\beta$ + CN participants in the A4 clinical trial with and without ADAge enrichment (Figure 2 and Supplementary Table S2), assuming a cost of \$4285 per PET scan<sup>15</sup> and \$150 per genotype. Similar to what we observed in the ADRC validation cohort, ADAge enrichment increased the proportion of A $\beta$ + individuals in the A4 clinical trial cohort from 0.34 (95% CI 0.32 to 0.35) to 0.52 (0.49 to 0.56) (Supplementary Figure 6). When limited to APOE  $\epsilon$ 3 homozygotes, ADAge enrichment again increased the proportion of A $\beta$ + individuals in the cohort from 0.22 (0.20 to 0.24) to 0.37 (0.31 to 0.43). By leveraging low-cost genetic screening as inclusion criteria for subsequent high-cost PET, the ADAge-enriched sample reduced the number of PET scans needed by 1196.68 (36.02%). Despite needing to genetically screen a large number of participants, ADAge enrichment lowered the total screening cost by \$3.91 million (27.50%). This reduction in total screening cost assumes no genetic screening was completed in the A4 clinical trial. In fact, the 3322 participants were genotyped through the trial, meaning the ADAge enrichment approach would have led to a total screening savings of \$4.41 million (31.00%). ADAge-enrichment did not reach significance outside the non-Hispanic white participant subgroup (Supplementary Table 3).

## 4 | DISCUSSION

Given the high-cost, effort-intensive process of broad screening for A $\beta$  positivity and the availability of low-cost genetic screening, ADAge warrants further evaluation as an enrichment method to address the current inefficiency in preclinical AD trial enrollment. We demonstrated that ADAge was more correlated with A $\beta$  than chronological age and could be used to enrich the proportion of A $\beta$ + individuals in a sample, leading to an estimated \$4.41 million (31.00%) savings in a real-world clinical trial scenario.

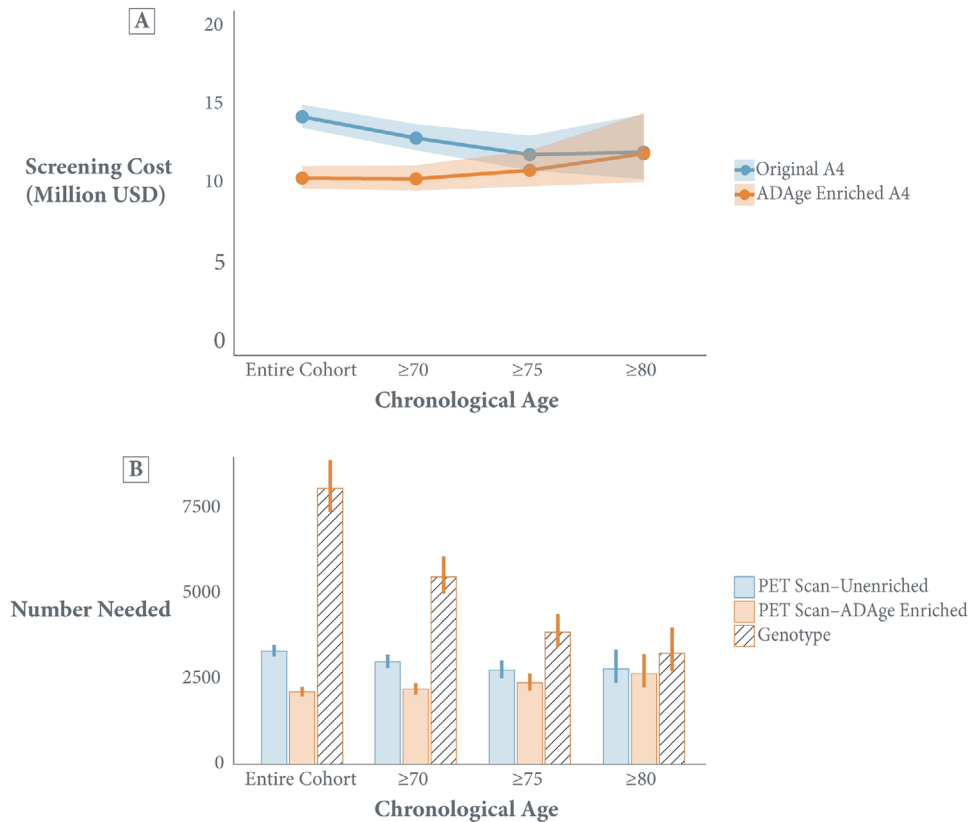
Strategies that combine age and genetics may be further optimized to enhance efficiency, such as determining age cutoffs for administering genetic screening. An estimated 40% to 65%<sup>16,17</sup> of healthy adults over 80 are A $\beta$ +. Hence, the likelihood of enrolling A $\beta$ + participants in this age group is high and less dependent on genetic risk, diminishing the value of genetic prescreening in this older population. However, with advanced age also comes a higher likelihood of concomitant pathologies such as vascular disease and the recently described Limbic-predominant age-related TDP-43 encephalopathy.<sup>18</sup>

Previous work modeled the prediction of A $\beta$  positivity by PHS in CN individuals using logistic regression.<sup>9</sup> Here, we translated this prediction to a practical strategy in which we demonstrated that we can enrich a cohort for A $\beta$  positivity based on inclusion decisions made at an individual level. Further, ADAge enrichment does not rely on PHS alone. Rather, older individuals with low to average genetic risk are included alongside younger individuals with high risk under the ADAge enrichment method.

We found a similar proportion of APOE  $\epsilon$ 4 carriers in our theoretical trial populations with and without ADAge enrichment. As  $\approx$ 60%<sup>3,4</sup> of individuals with late-onset AD are APOE  $\epsilon$ 4 carriers, an approach that sought to enrich for A $\beta$  positivity by enrolling only APOE  $\epsilon$ 4 carriers would disproportionately represent this group in a trial. Given the heterogeneous nature of AD, it is important to consider additional variants that modulate AD risk. The PHS includes genes associated with multiple biological processes implicated in AD, such as inflammation, synaptic function, and epigenetic regulation.<sup>19</sup> Further, previous work has demonstrated the value of the PHS beyond APOE,<sup>7-9</sup> and ADAge enrichment increased the proportion of A $\beta$ + individuals even within APOE  $\epsilon$ 3 homozygotes in the A4 clinical trial cohort.

Although we validated our findings in an independent research sample and real-world clinical trial data, the ADRC validation cohort was small and both cohorts were relatively homogeneous. Due to observed differences in AD genetic risk across racial and ethnic groups,<sup>20-22</sup> these findings are largely limited to white, non-Hispanic individuals. Future work is needed to develop AD polygenic scores in diverse populations. In the small subset of A4 participants who were not non-Hispanic whites, ADAge enrichment was most promising in white Hispanic or Latino participants (unenriched mean [95% CI] 0.29 [0.20 to 0.39] vs ADAge-enriched 0.55 [0.37 to 0.73]). However US Latinos are not a single, homogenous group but have Amerindian, European, and African admixture, which contributes to genetic heterogeneity within this population,<sup>23</sup> warranting further investigation within genetically determined Latino subgroups. Validation in more diverse samples is required to provide evidence that an ADAge enrichment strategy could be successfully implemented into screening for clinical trials, especially

[140.43 to 141.39], difference 0.47 [0.01 to 0.97]). The proportion of female participants was similar between ADAge-enriched and unenriched samples (0.69 [0.51 to 0.87] vs 0.66 [0.56 to 0.77], difference 0.03 [−0.09 to 0.15]).B) The theoretical, A $\beta$ + end trial populations that would be enrolled by each strategy (ADAge enrichment vs no enrichment) were compared. The ADAge-enriched sample remained older than the unenriched sample (76.70 [72.71 to 80.68] vs 73.69 [70.78 to 76.61], difference 3.00 [0.94 to 5.22]). However, the samples were similar in the proportion of APOE  $\epsilon$ 4 carriers (0.75 [0.48 to 1.02] vs 0.64 [0.43 to 0.84], difference 0.11 [−0.04 to 0.28]), the dementia rating scale score (141.33 [140.37 to 142.29] vs 140.95 [140.02 to 141.89], difference 0.38 [−0.28 to 1.14]), and the proportion of female participants (0.75 [0.50 to 1.00] vs 0.59 [0.38 to 0.80], difference 0.16 [0.00 to 0.33]).<sup>a</sup>The difference in means is statistically significant. A $\beta$ ,  $\beta$ -amyloid; ADRC, Alzheimer's Disease Research Center; APOE, apolipoprotein E; DRS, Dementia Rating Scale (score range 0 [worst] to 144 [best])



**FIGURE 2** ADage-enriched  $A\beta$  screening more efficiently enrolls clinically normal individuals in the A4 preclinical AD trial. The figure outlines the screening necessary to enroll 1115  $A\beta+$  CN participants in the A4 clinical trial for each enrollment strategy, split into bins by chronological age. (A) The screening cost for each strategy (unenriched [blue] vs ADage-enriched [orange]), assumes \$4285 per PET scan and \$150 per genotype. Shading represents 95% confidence intervals. (B) The number needed to PET scan in order to verify  $A\beta$  status is shown for each enrollment strategy (unenriched [blue] vs ADage-enriched [orange]) by chronological age bin. Error bars represent 95% confidence intervals. The number needed to genotype in order to recruit those with an ADage greater than the cutpoint is shown for the ADage-enriched strategy (diagonal pattern) by each age bin. The number needed to PET scan is a function of the  $A\beta$  positivity within the A4 clinical trial cohort. The number needed to genotype is a function of the proportion of the sample with an ADage >76.4 cutpoint within the A4 clinical trial cohort. AD, Alzheimer's disease;  $A\beta$ ,  $\beta$ -amyloid; CN, clinically normal; PET, positron emission tomography; A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease

those whose cohort demographics better reflect the underlying population diversity. Further, the studies used to estimate the US population baseline AD incidence rate underrepresented African American and Hispanic populations.<sup>14</sup> Additionally, the relationship between PHS and baseline AD incidence is multiplicative, but we acknowledge that there are other models that could be used to estimate the absolute risk. Large-scale population-based samples are needed to clarify the true prevalence of  $A\beta$  positivity across the lifespan and examine differences between genders and between racial and ethnic groups. One would expect that incorporating such information or that pertaining to other risk factors for dementia would improve the performance of ADage enrichment at the individual level. However, the proportion of  $A\beta+$  CN individuals in our ADRC validation cohort (.28) closely matches what has been observed in the screening process of the A4 trial (.30) in similarly aged participants, with a similar proportion of  $APOE \epsilon 4$  carriers.<sup>2</sup>

In conclusion, ADage enrichment provides for a more efficient and cost-effective method to enroll  $A\beta+$  CN participants in clinical trials. Enrolled cohorts are expected to be 3 years older on average than their

unenriched counterparts, but similar in sex, cognition, and  $APOE \epsilon 4$  status.

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Group Information: Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative database ([adni.loni.usc.edu](http://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

at: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf). The A4 Study is a secondary prevention trial in preclinical Alzheimer's disease, aiming to slow cognitive decline associated with brain amyloid accumulation in clinically normal older individuals. The A4 and LEARN Studies are led by Dr. Reisa Sperling at Brigham and Women's Hospital, Harvard Medical School and Dr. Paul Aisen at the Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California. The A4 and LEARN Studies are coordinated by ATRI at the University of Southern California, and the data are made available through the Laboratory for Neuro Imaging at the University of Southern California. The participants screening for the A4 Study provided permission to share their de-identified data in order to advance the quest to find a successful treatment for Alzheimer's disease. We would like to acknowledge the dedication of all the participants, the site personnel, and all of the partnership team members who continue to make the A4 and LEARN Studies possible. The complete A4 Study Team list is available on: <http://a4study.org/a4-study-team>.

#### CONFLICT OF INTEREST

Dr. Brewer has served on advisory boards for Elan, Bristol-Myers Squibb, Avanir, Novartis, Genentech, and Eli Lilly and holds stock options in CorTechs Labs, Inc. and Human Longevity, Inc.

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#### SUPPORTING INFORMATION

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

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