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Authors

Spencer, Barbara E
Digma, Leonardino A
Jennings, Robin G
et al.

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

Barbara E. Spencer[a], **Leonardino A. Digma**[a], **Robin G. Jennings**[a], **James B. Brewer**[a,b,*], **Alzheimer's Disease Neuroimaging Initiative and the A4 Study Team**

[a]Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA;

[b]Department of Radiology, University of California, San Diego, La Jolla, CA, USA

Abstract

INTRODUCTION: Elevated β-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 β-amyloid positivity among clinically normal ADNI participants and applied to an independent ADRC validation cohort. The impact of ADAge enrichment on screening costs was evaluated in A4 trial data.

RESULTS: In the validation cohort, the ADAge-enriched sample had a higher proportion of individuals with elevated β-amyloid (difference[95% CI] 0.19[0.07–0.33]) 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 β-amyloid in clinical trials.

Keywords

Alzheimer's disease; Clinical trial design; Predictive markers; Biomarkers; Genetics; Neuroimaging; PET

1. INTRODUCTION

In clinically normal (CN) individuals, elevated brain β-amyloid (Aβ) is considered to be the earliest detectable indication of Alzheimer's disease (AD) neuropathologic change.[1] Recently, preclinical AD trials began targeting Aβ in CN individuals to test whether decreasing Aβ would slow AD-related decline.[2] As such, these trials require biomarker confirmation of elevated Aβ for enrollment. However, these CN individuals are only identified through the inefficient process of Aβ positron emission tomography (PET)

*Corresponding Author: James B. Brewer, MD, PhD, 9500 Gilman Drive, Mail Code 0949, La Jolla, CA 92093, jbrewer@ucsd.edu, Phone: (858)-534-1237.

screening, which enrolls only ~30% of those screened.[2] Novel enrichment methods leveraging genetic and age-specific risk for AD may improve 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*) ε4 allele are known to modulate AD risk. Risk for AD increases and age of AD onset decreases with an increasing number of *APOE* ε4 alleles.[3,4] Genome-wide association studies have identified additional, more common variants that confer risk for AD,[5,6] 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.[7] Previous work has demonstrated the utility of the PHS for predicting risk of clinical progression and cognitive decline in CN individuals.[8,9] 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 Aβ in CN individuals. We developed a gene- and age-defined ADAge enrichment method and tested the efficiency of such gene- and age-informed Aβ 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 Aβ 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 was 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[7] using MATLAB R2018b.

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 Co 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 1).

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* ε2 and *APOE* ε4 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 Aβ Status Classification

We classified participants as having normal Aβ (Aβ-) or as Aβ positive (Aβ+) based on Florbetapir PET or cerebrospinal fluid (CSF) quantification (Table 1). For the ADNI development cohort, Florbetapir PET summary data were downloaded from ADNI (see Landau et al.[10] for acquisition and processing details). Images were acquired between May 25, 2010 and July 19, 2016. Aβ 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 Aβ quantification by liquid chromatography-tandem mass spectrometry has been described.[11] Aβ positivity was determined using an Aβ-42 to Aβ40 ratio cutoff of 0.16, a threshold value determined to optimally distinguish CN participants from those with AD.[11] Though not completely overlapping, most individuals have concordant amyloid biomarker results

when assessed with both PET and CSF,[12] with even better agreement when using the Aβ42/40 ratio than Aβ42 alone.[13] For the A4 clinical trial cohort, screening Florbetapir PET summary data were downloaded from A4. Aβ 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[14] 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,[14]

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

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.[7]

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

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.

$$\mathrm{ADAge} = \frac{\ln(\frac{\mathrm{PAIR}}{0.084})}{0.142} + 60$$

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 1).

2.6 Statistical Analyses

Differences in demographics and clinical characteristics by Aβ 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 Aβ than chronological age was in the ADNI development cohort. This test was repeated within CN and *APOE* ε4 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 Aβ 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 Aβ screening for preclinical AD trials as well as to assess demographic differences between such samples. These comparisons were repeated in the theoretical, Aβ+ 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 Aβ+ 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 to verify Aβ status is a function of Aβ positivity within the A4 clinical trial cohort. The proportion of individuals who were Aβ+ under each enrollment strategy was compared, and this comparison was repeated in *APOE* ε3 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. 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[15] 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 – 0.33], $p < .001$) as well as within CN (0.14 [0.08 – 0.21], $p < .001$) and *APOE* ε4 carrier (0.06 [0.02 – 0.11], $p = .006$) subsets of the cohort. Supplementary Figure 2 shows scatterplots for the relationships between Florbetapir SUVR and either chronological age or ADAge.

Supplementary Figure 3 shows the relationships between Aβ positivity and chronological age or ADAge (Supplementary Figure 4 shows this relationship in each diagnostic group). The optimal ADAge cutpoint for predicting Aβ positivity in CN participants in the ADNI development cohort was determined to be 76.4 (Supplementary Figure 5).

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 Aβ 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 Aβ+ individuals (mean [95% CI] 0.46 [0.27 – 0.66] vs 0.28 [0.18 – 0.37], difference 0.19 [0.07 – 0.33]).

Next, we compared the theoretical, Aβ+ 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 – 80.68] vs 73.69 [70.78 – 76.61], difference 3.00 [0.94 – 5.22]). However, the samples were similar in the proportion of *APOE* ε4 carriers (0.75 [0.48 – 1.02] vs 0.64 [0.43 – 0.84], difference 0.11 [−0.04 – 0.28]), the dementia rating scale score (141.33 [140.37 – 142.29] vs 140.95 [140.02 – 141.89], difference 0.38 [−0.28 – 1.14]), and the proportion of female participants (0.75 [0.50 – 1.00] vs 0.59 [0.38 – 0.80], difference 0.16 [0.00 – 0.33]).

Finally, using the A4 clinical trial cohort, we examined the screening necessary to enroll Aβ+ CN participants in the A4 clinical trial with and without ADAge enrichment (Figure 2 and Supplementary Table 2), assuming a cost of $4285 per PET scan[15] and $150 per genotype. Similar to what we observed in the ADRC validation cohort, ADAge enrichment increased the proportion of Aβ+ individuals in the A4 clinical trial cohort from 0.34 (95% CI 0.32 – 0.35) to 0.52 (0.49 – 0.56) (Supplementary Figure 6). When limited to *APOE* ε3 homozygotes, ADAge enrichment again increased the proportion of Aβ+ individuals in the cohort from 0.22 (0.20 – 0.24) to 0.37 (0.31 – 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 lead 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 Aβ 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 Aβ than chronological age and could be used to enrich the proportion of Aβ+ individuals in a sample, leading to an estimated $4.41 million (31.00%) savings.

Strategies that combine age and genetics may be further optimized to enhance efficiency, such as determining age cutoffs for administering genetic screening. An estimated 40–65%[16,17] of healthy adults over 80 are Aβ+. Hence, the likelihood of enrolling Aβ+ 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.[18]

Previous work modeled the prediction of Aβ positivity by PHS in CN individuals usinglogistic regression.[9] Here, we translated this prediction to a practical strategy in which we demonstrated that we can enrich a cohort for Aβ 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* ε4 carriers in our theoretical trial populations with and without ADAge enrichment. As ~60%[3,4] of individuals with late-onset AD are *APOE* ε4 carriers, an approach that sought to enrich for Aβ positivity by enrolling only *APOE* ε4 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.[19] Further, previous work has demonstrated the value of the PHS beyond *APOE,*[7–9] and ADAge enrichment increased the proportion of Aβ+ individuals even within *APOE* ε3 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,[20–22] 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 – 0.39] vs ADAge-enriched 0.55 [0.37 – 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,[23] 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 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.[14] 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 Aβ 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 Aβ+ 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* ε4 carriers.[2]

In conclusion, ADAge enrichment provides for a more efficient and cost-effective method to enroll Aβ+ 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* ε4 status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Disclosures:

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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Group Information:

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 at: http://adni.loni.usc.edu/wpcontent/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: a4study.org/a4-study-team

Abbreviations:

CN	clinically normal
Aβ	β-amyloid
AD	Alzheimer's disease
PET	positron emission tomography
APOE	apolipoprotein E
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRC	Alzheimer's Disease Research Center
CSF	cerebrospinal fluid
SUVR	standardized uptake value ratio

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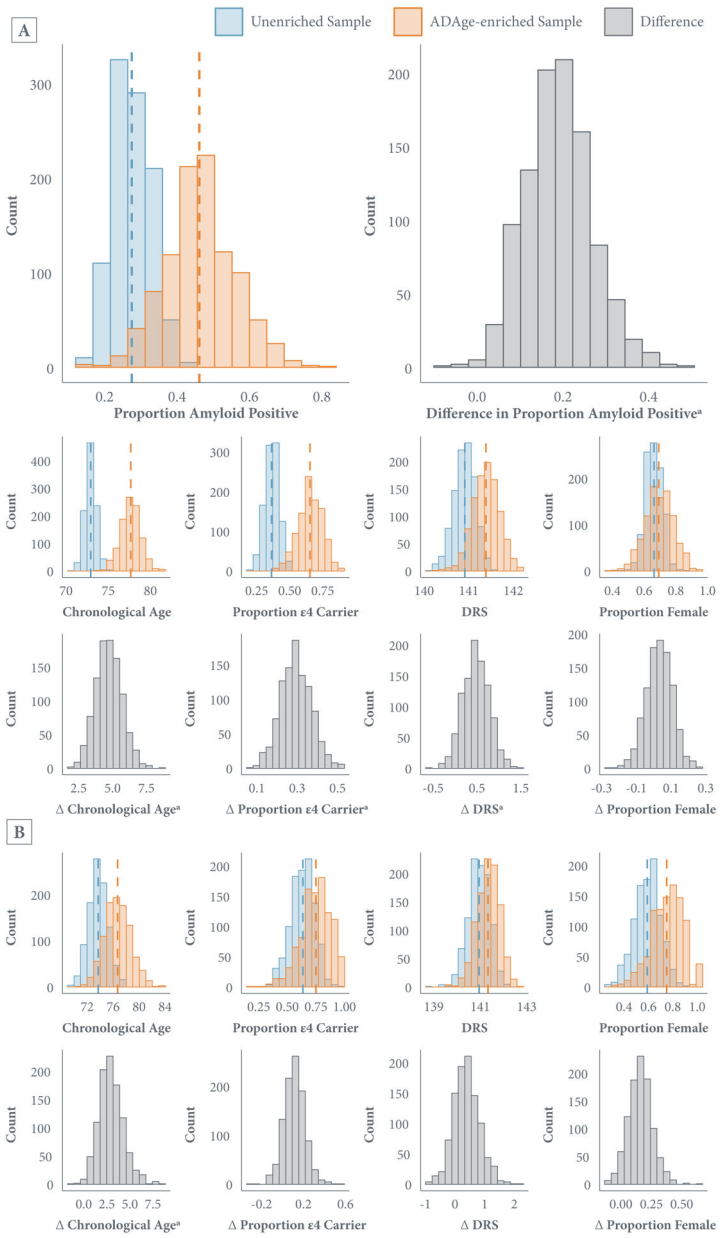

Figure 1. Demographic characteristics of the unenriched (blue) and ADAge-enriched (orange) ADRC validation samples.

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 Aβ+ individuals (mean [95% CI] 0.46 [0.27–0.66] vs 0.28 [0.18 – 0.37], difference 0.19 [0.07 – 0.33]), was older (77.67 [75.34 – 80.01] vs 72.92 [71.61 – 74.23], difference 4.75 [3.16 – 6.36]), had a greater proportion of *APOE* ε4 carriers (0.65 [0.47 – 0.84] vs 0.36 [0.25 – 0.47], difference 0.29 [0.17 – 0.42]), and had a higher dementia rating scale score (141.38 [140.79 – 141.98] vs 140.91 [140.43 – 141.39], difference 0.47 [0.01 – 0.97]). The proportion of female participants was similar between ADAge-enriched and unenriched samples (0.69 [0.51 – 0.87] vs 0.66 [0.56 – 0.77], difference 0.03 [−0.09 – 0.15]). **B)** The theoretical, Aβ+ 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 – 80.68] vs 73.69 [70.78 – 76.61], difference 3.00 [0.94 – 5.22]). However, the samples were similar in the proportion of *APOE* ε4 carriers (0.75 [0.48 – 1.02] vs 0.64 [0.43 – 0.84], difference 0.11 [−0.04 – 0.28]), the dementia rating scale score (141.33 [140.37 – 142.29] vs 140.95 [140.02 – 141.89], difference 0.38 [−0.28 –1.14]), and the proportion of female participants (0.75 [0.50 –1.00] vs 0.59 [0.38 – 0.80], difference 0.16 [0.00 – 0.33]).

[a] The difference in means is statistically significant

Abbreviations: Aβ, β-amyloid; *APOE,* apolipoprotein E; DRS, Dementia Rating Scale (score range 0 [worst] to 144 [best])

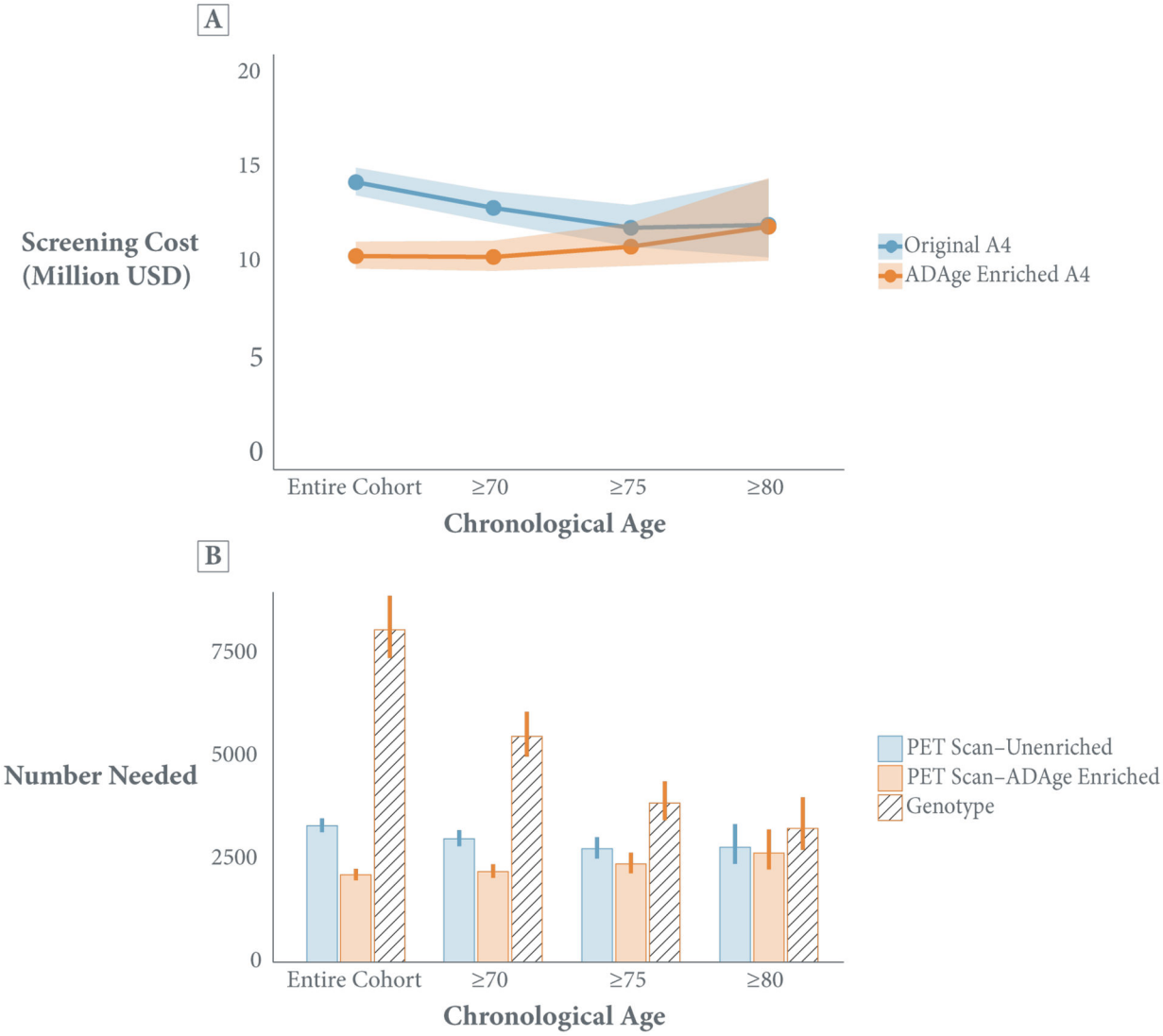

Figure 2. ADAge-enriched Aβ screening more efficiently enrolls clinically normal individuals in the A4 preclinical AD trial.

The figure outlines the screening necessary to enroll 1115 Aβ+ 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 to verify Aβ 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 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 Aβ positivity within the A4 clinical trial cohort. The number needed to genotype is a function of the proportion of the sample with an ADAge greater than the 76.4 cutpoint within the A4 clinical trial cohort.

Abbreviations: USD, United States Dollar; PET, positron emission tomography; Aβ, β-amyloid; AD, Alzheimer's disease; CN, clinically normal

Table 1.

Demographics and clinical characteristics of the ADNI development, ADRC validation, and A4 clinical trial cohorts split by Aβ status.

	ADNI Development Cohort			
	Entire Cohort n=939	**Aβ+ n=507**	**Aβ− n=432**	***P* value Aβ+ vs Aβ−**
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, years	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 ε4 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 *	1.21 (0.23)	1.39 (0.17)	1.00 (0.06)	< .001
	ADRC Validation Cohort			
	Entire Cohort n=80	**Aβ+ n=22**	**Aβ− n=58**	***P* value Aβ+ vs Aβ−**
Age, years	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 ε4 carrier, No. (%)	29 (36)	14 (64)	15 (26)	.002
PHS	0.01 (0.88)	0.51 (0.92)	−0.18 (0.80)	.004
Aβ 42/40 Ratio †	0.20 (0.06)	0.13 (0.02)	0.22 (0.05)	< .001
	A4 Clinical Trial Cohort			
	Entire Cohort n=3322	**Aβ+ n=1115**	**Aβ− n=2207**	***P* value Aβ+ vs Aβ−**
Age, years	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 ε4 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 *	1.09 (0.19)	1.31 (0.17)	0.98 (0.06)	< .001

NOTE 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.

* Aβ positivity was determined using a cutoff of 1.11 SUVR.

† Aβ positivity was determined using an Aβ1-42 to Aβ40 ratio cutoff of 0.16.

Abbreviations: Aβ, β-amyloid; CN, clinically normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; *APOE,* apolipoprotein E; PHS, polygenic hazard score; SUVR, standardized uptake value ratio; CSF, cerebrospinal fluid