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Risk Algorithms to Predict Elevated Plasma P-tau217 Status in Cognitively Unimpaired AD: A Cross-sectional Analysis

Nalin Payakachat¹, E. Jolanda Muenzel¹, Dulanji Kuruppu¹, Katie A. Vandergriff¹, Yun-Fei Chen¹, Karen Holdridge¹, Nicolae Done², Urvi Desai², Pete Zuckerman², Michael S. Rafii³, Roy Yaari¹, Reisa A. Sperling⁴ for the A4 and LEARN Study Teams⁵

¹Eli Lilly and Company, Indianapolis, USA; ²Analysis Group, Boston, USA; ³University of Southern California, Los Angeles, USA; ⁴Harvard Medical School, Boston, USA; ⁵A4 and LEARN Study Teams - Alzheimer Clinical Trials Consortium – <https://www.actcinfo.org/a4-study-teamlists/>

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OBJECTIVE

- To develop and internally validate cross-sectional models that identify cognitively unimpaired individuals who have a higher probability of currently elevated plasma P-tau217 levels, using routinely available clinical information as a decision support tool for subsequent testing with a P-tau217 blood test.

KEY TAKEAWAYS

- A simplified cross-sectional model using age, sex, self-reported cognitive concerns, and hypercholesterolemia can serve as a decision support tool for plasma P-tau217 testing without requiring genetic testing.
- By focusing on individuals stratified into the high-risk category for developing AD, the decision support tool achieves **3- to 4-fold enrichment** and reduces the number needed to test from ~4 to ~2.
- This approach is analogous to clinical decision rules used in other screening contexts (e.g., Wells criteria, the CHA₂DS₂-VASc score).
- External validation in diverse, community-based populations is the essential next step.

BACKGROUND

- Plasma phosphorylated tau217 (P-tau217) is emerging as an accurate blood biomarker of Alzheimer's disease (AD) pathology in cognitively unimpaired (preclinical) individuals as well as a prognostic indicator of AD progression.^{1,2}
 - Elevated plasma P-tau217 levels are strongly associated with brain Aβ and tau burden and predict subsequent cognitive decline.^{1,3,4}
- In the absence of universal plasma P-tau217 testing of cognitively unimpaired older adults, practical tools may help guide decisions about who should undergo testing.⁵
 - No validated framework currently exists to triage cognitively unimpaired individuals for P-tau217 testing using routinely available clinical information.

KEY RESULT

Model Specification ¹	Cross-sectional Model 1 Top 5 Predictors ²	Cross-sectional Model 2	Cross-sectional Model 3
	CFI Items (Q01 and Q15) + Age (≥75) + ≥1 APOE ε4 alleles + Hypercholesterolemia	CFI Items (Q01 and Q15) + Age (70–74 and ≥75) + Education (13+ years) + Sex + Ethnicity (Hispanic/Latino) + Hypercholesterolemia	CFI Items (Q01 and Q15) + Age (70 – 74 and ≥75) + Sex + Hypercholesterolemia
Parameter estimates – odds ratio [95% CI ^{3,4}]			
Select CFI items			
CFI Q01 – Memory declined substantially ⁵	1.32 [1.00, 1.73]*	1.33 [1.01, 1.75]*	1.34 [1.02, 1.75]*
CFI Q15 – Seen a doctor about memory concerns ⁵	1.67 [1.15, 2.42]**	1.85 [1.28, 2.67]**	1.86 [1.29, 2.70]**
Age category			
<70 (or <75) ⁶	Reference Category	Reference Category	Reference Category
70 – 74	—	1.86 [1.40, 2.48]**	1.87 [1.40, 2.49]**
75+	2.55 [1.93, 3.36]**	3.12 [2.29, 4.26]**	3.17 [2.33, 4.32]**
Education category			
1 – 12 years (High school at most)	—	Reference Category	—
13+ years (some college)	—	0.75 [0.50, 1.13]	—
Sex – male	—	0.85 [0.66, 1.09]	0.83 [0.65, 1.07]
Ethnicity – Hispanic/Latino	—	1.09 [0.56, 2.12]	—
APOE ε4 carrier	2.22 [1.72, 2.85]**	—	—
Comorbid condition			
Hypercholesterolemia	1.60 [1.16, 2.20]**	1.75 [1.27, 2.40]**	1.75 [1.28, 2.41]**
Model performance ⁷			
AUC	0.662	0.638	0.636
Brier score	0.178	0.181	0.180
Log loss	0.537	0.544	0.544

^{*} p<0.05; ^{**} p<0.01; ^{***} p<0.001. "—" indicates predictor not included in the model specification.
¹Prediction models were estimated using an elastic net penalized logistic regression with k-fold cross-validation. Predictors were first screened using a weak penalty (α=0.10) to remove variables with little signal, then re-estimated using a ridge penalty (α=0) to obtain stable coefficients and ORs.
²The "Top 5 Predictors" label on Cross-sectional Model 1 refers to the 5 highest-ranked variables from the random forest variable importance screening.
³95% CIs for ORs were estimated via 500 bootstrap replicates, stratified by outer cross-validation folds.
⁴P-values were based on Wald tests from the penalized logistic regression models.
⁵CFI Q01: "Compared to one year ago, do you feel that your memory has declined substantially?" with response options of Yes, No, Maybe; CFI Q15: "In the past year, have you seen a doctor about memory concerns?" with response options of Yes and No.
⁶Cross-sectional Model 1 categorized age as <75 (reference category) and ≥75 years.
⁷Model performance was obtained from nested 7-fold cross-validation, with an inner 5-fold loop used for weak-lasso screening of predictors. Out-of-fold predictions were used to ensure unbiased estimates of model discrimination and calibration.

Methods

Study population

- The current analysis is based on retrospective cohorts from the A4 (NCT02008357) and LEARN (NCT02488720) studies.
 - Eligible participants were 65–85 years old, cognitively unimpaired at study entry defined by MMSE 27–30 and CDR-GS = 0, and with available plasma P-tau217 levels at first assessment (week 0 for A4 and week 72 for LEARN) (**Figure 1**).
- Elevated plasma P-tau217 was defined as ≥0.28 U/mL at first assessment.
 - This threshold corresponded to the upper tertile of baseline P-tau217 value in the A4 cohort, a subgroup previously shown to exhibit more rapid cognitive decline.¹
 - Plasma P-tau217 was quantified using an analytically validated electrochemiluminescence immunoassay (Meso Scale Discovery) at the Lilly Clinical Diagnostics Laboratory.

Predictors

- Baseline predictors (**Figure 2**) were selected to include information that may be available or obtainable in clinics.
- Potential predictors were identified using random forest models and clinical relevance, followed by algorithm development via penalized logistic regression.

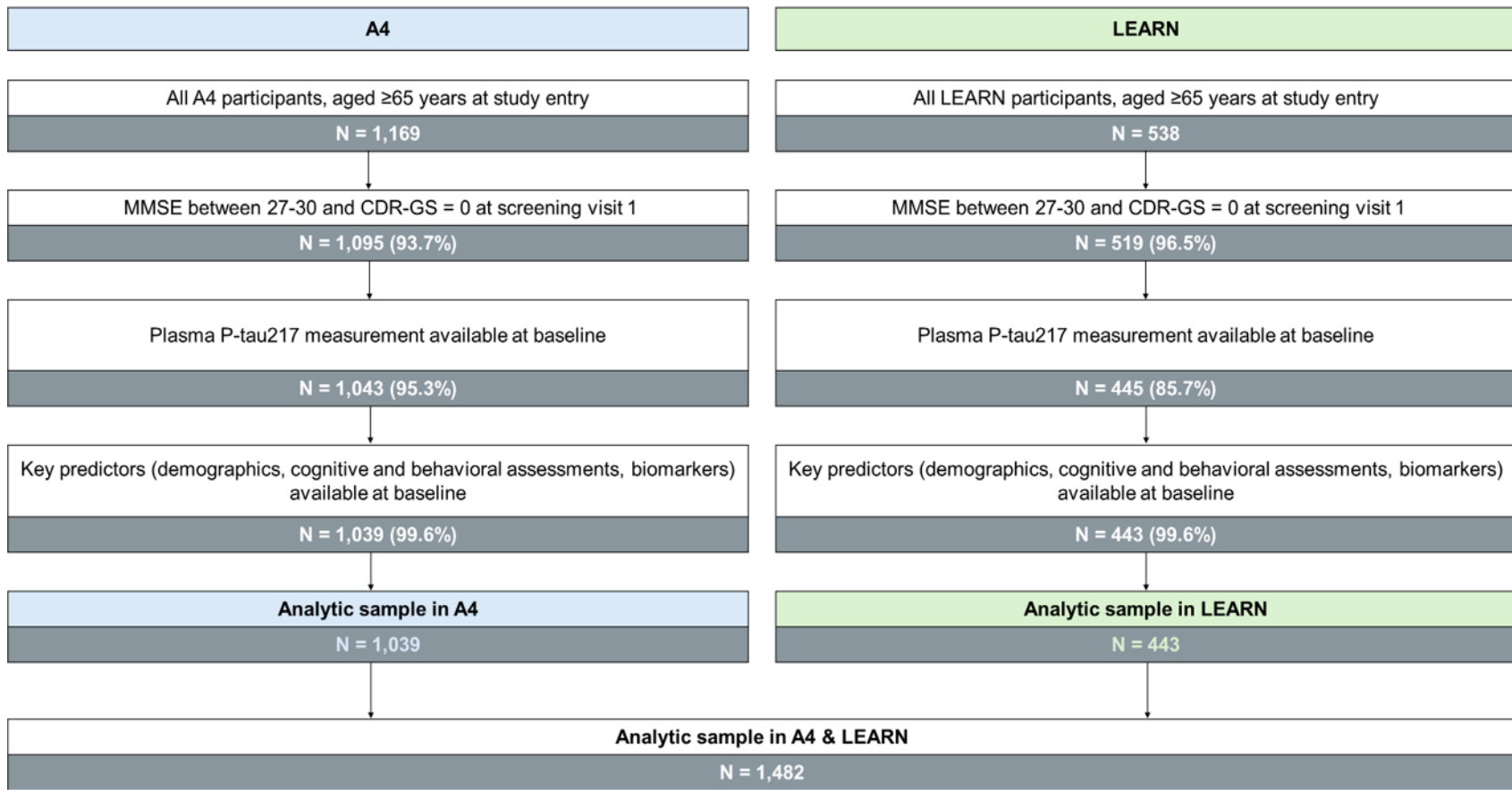
Risk score algorithm

- A risk score algorithm was developed to estimate the likelihood of elevated plasma P-tau217 levels.
 - Each predictor was assigned a weighted score, reflecting its log odds ratio from the penalized logistic regression model. The total risk score was derived by summing risk scores contributed by each predictor.
- Participants were stratified into risk groups (e.g., tertiles or clinically relevant categories) based on the probability of elevated plasma P-tau217 levels.

Statistical analyses

- Model predictive performance was assessed with k-fold cross-validation using AUC, Brier score, and log loss.

Figure 1. Sample selection flowchart



Note: Percentages are calculated with regards to the preceding step in the flowchart.

Figure 2. Candidate predictors included in the analysis

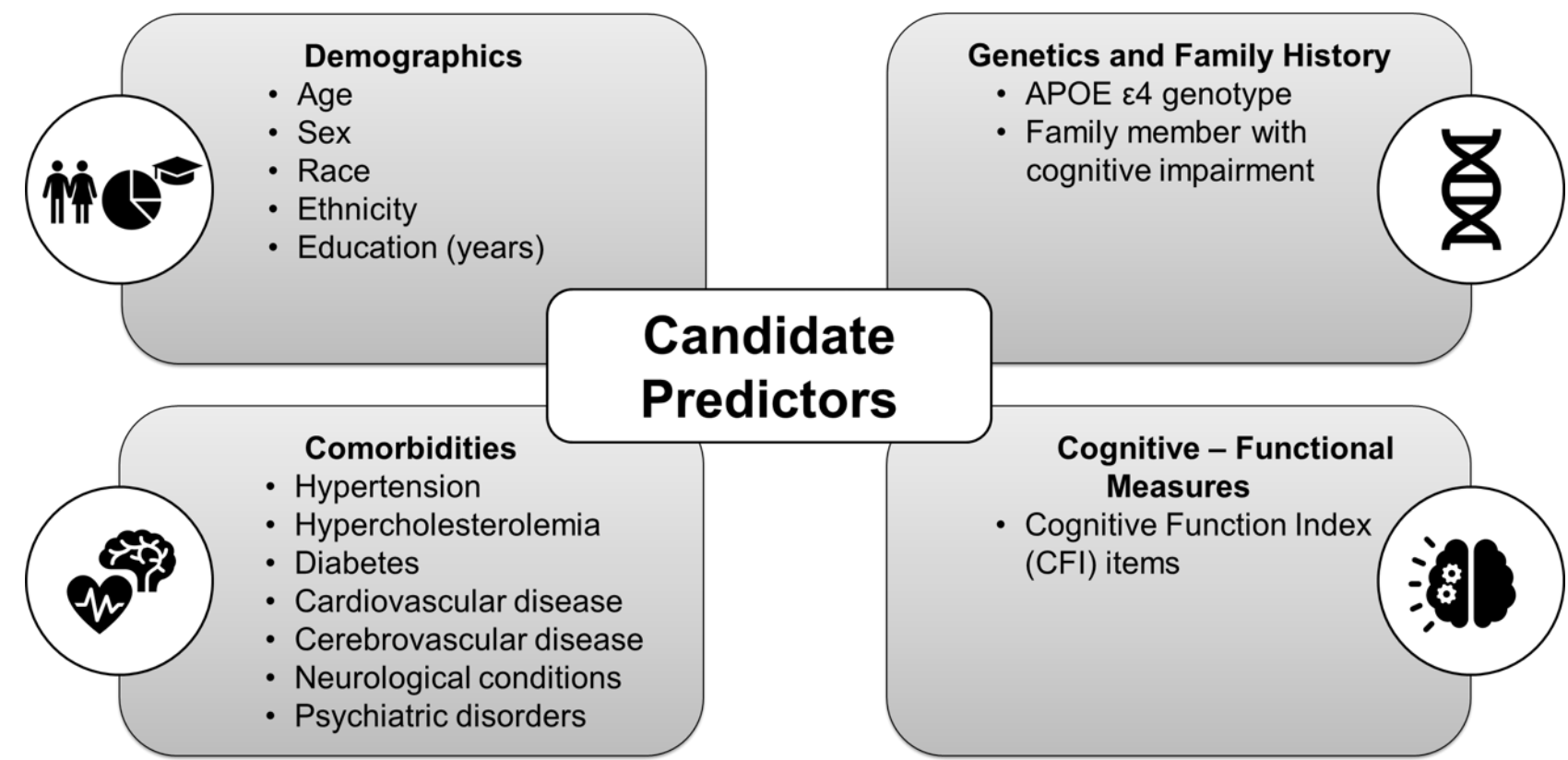


Table 2: Baseline participant demographics and biomarker or genetic characteristics

	Overall N = 1482	A4 N = 1039	LEARN N = 443
Demographics			
Age in years, mean (SD)	71.37 (4.66)	71.77 (4.75)	70.43 (4.28)
Age category in years, n (%)			
<70	683 (46.1%)	441 (42.4%)	242 (54.6%)
70–74	485 (32.7%)	341 (32.8%)	144 (32.5%)
≥75	314 (21.2%)	257 (24.7%)	57 (12.9%)
Sex, n (%)			
Female	900 (60.7%)	627 (60.4%)	273 (61.6%)
Male	582 (39.3%)	412 (39.7%)	170 (38.4%)
Race, ^a n (%)			
White	1407 (94.9%)	989 (95.2%)	418 (94.4%)
Black/African American	31 (2.1%)	22 (2.1%)	9 (2.0%)
Asian	27 (1.8%)	19 (1.8%)	8 (1.8%)
American Indian/Alaska Native	5 (0.3%)	2 (0.2%)	3 (0.7%)
Multiracial	12 (0.8%)	7 (0.7%)	5 (1.1%)
Ethnicity, n (%)			
Hispanic/Latino	44 (3.0%)	30 (2.9%)	14 (3.2%)
Not Hispanic/Latino	1438 (97.0%)	1009 (97.1%)	429 (96.8%)
Education in years, mean (SD)	16.7 (2.7)	16.6 (2.8)	16.8 (2.6)
Biomarker and genetic characteristics			
Plasma P-tau217 (U/mL), mean (SD)	0.24 (0.15)	0.28 (0.16)	0.15 (0.05)
≥1 APOE ε4 allele, n (%)	716 (48.3%)	617 (59.4%)	99 (22.3%)

^aNo participants self-identified as Hawaiian/Pacific Islander thus counts are omitted from this table.
[†]The overall participants were enriched for amyloid positive due to the large proportion of A4 patients in the study sample.

Limitations

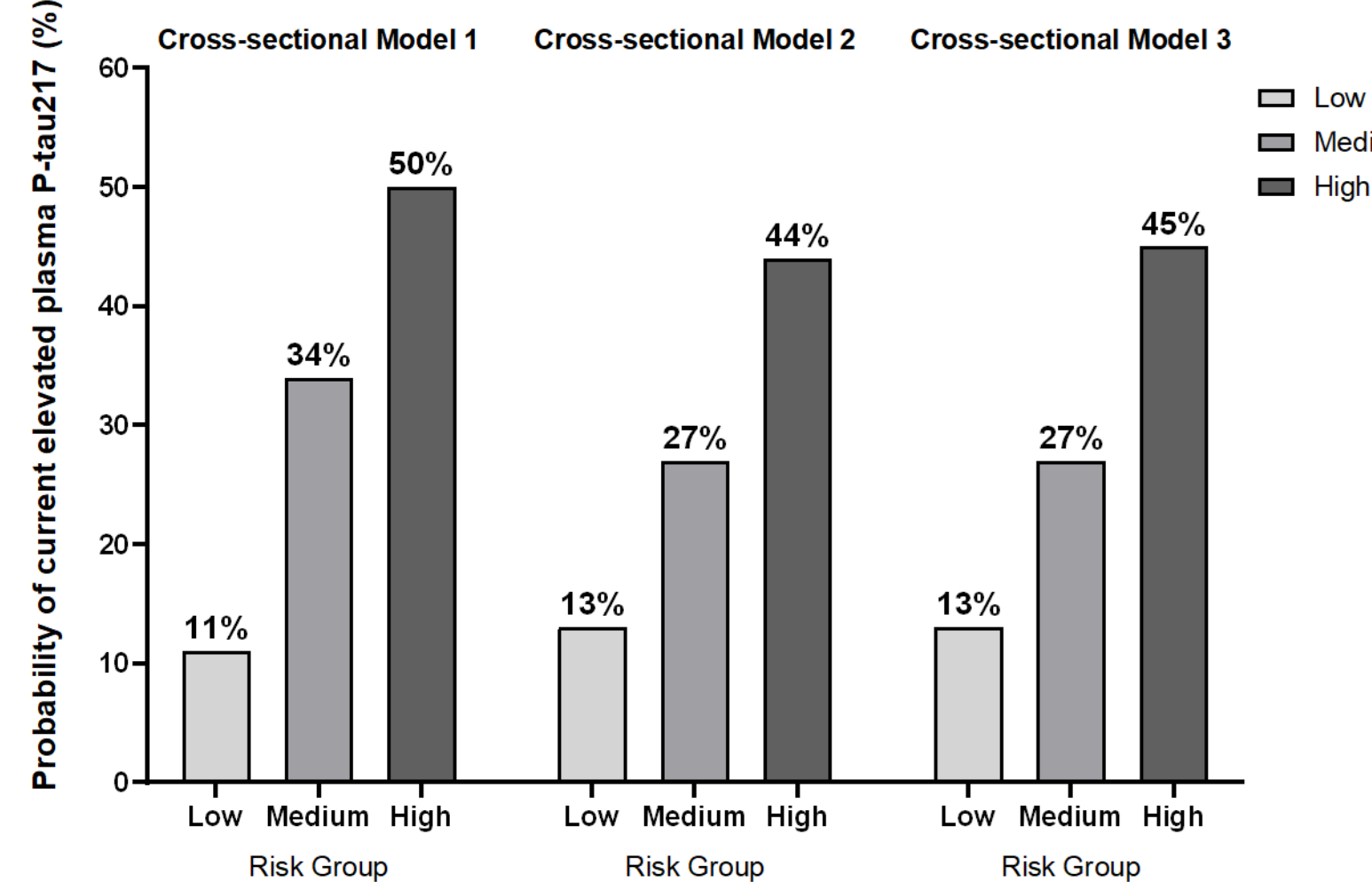
- Models were developed and internally validated using A4/LEARN cohorts, which were predominantly White and highly educated; external validation in more diverse, community-based populations will be needed to confirm broader applicability.
- The cross-sectional design cannot distinguish transient from persistent plasma P-tau217 elevation, potentially introducing outcome misclassification.
- The elevation threshold (≥0.28 U/mL) was derived from the A4 cohort upper tertile and will require recalibration for other assay platforms or populations.
- The models are intended for risk-based stratification and should not replace clinical evaluation.

Cross-sectional Model 3 performed adequately in prediction of current elevation of plasma P-tau217 compared with the other two models.

- Cross-sectional models may function as decision support tools to guide selective plasma P-tau217 testing using routinely available clinical information.
 - The simplified model (Cross-sectional Model 3) using age, sex, self-reported cognitive concerns, and hypercholesterolemia may be best suited for clinical implementation (AUC 0.636), as these clinical characteristics are readily available in the primary care setting and do not require additional steps such as APOE genotyping.
 - Cross-sectional Model 1, adding APOE ε4 status, provided only modestly higher discrimination (AUC 0.662 vs 0.636) with similar risk group separation, offering an option where genetic data are available.
 - Cross-sectional Model 2, which includes education and ethnicity in addition to variables in Model 3, only marginally improves the performance (AUC 0.638 vs. 0.636).

Figure 3. Observed prevalence of current elevated plasma P-tau217 status by risk groups

The observed prevalence of elevated plasma P-tau217 in the study sample was 25%, which would require to test 4 individuals to identify one with elevated plasma P-tau217. Using the risk algorithm models, Individuals classified as high risk had approximately 3- to 4-fold higher prevalence of current plasma P-tau217 elevation compared with those classified as low risk.



- Risk stratification resulted in 3- to 4-fold enrichment of observed P-tau217 elevation prevalence, from 11–13% in low-risk groups to 44–50% in high-risk groups.
 - The number needed to test was reduced from approximately 4 to approximately 2 in individuals classified as high risk using the cross-sectional models.
- Early identification of at-risk individuals supports timely biomarker evaluation and early intervention strategies.

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease; Aβ, amyloid β; AD, Alzheimer’s disease; APOE4, apolipoprotein E ε4; AUC, area-under-curve; CDR-GS, Clinical Dementia Rating, Global Scale; CFI, Cognitive Function Index; CI, confidence interval; LEARN, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration; MMSE, Mini-Mental State Examination; OR, odds ratio; P-tau217, phosphorylated tau217; Q, question; SD, standard deviation.

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Acknowledgments: The authors would like to thank the entire A4 and LEARN study teams. The authors are also grateful to all participants involved in the A4 and LEARN clinical trials, as well as their care partners and families. Medical writing and editorial services were provided by Gillispie Minhas and Antonia Baldo, employees of Syneos Health, and were funded by Eli Lilly and Company.

Disclosures: NP, EJMJ, DK, KAV, YFC, KH, and RY are employees and minor shareholders of Eli Lilly and Company. ND, UD, and PZ are employees of Analysis Group, Inc., which received funding from Eli Lilly and Company for the conduct of the present study. MSR has received grants from Esai and Eli Lilly and Company; has received consulting fees from AC Immune and Ionis; and has participated in data safety monitoring boards or advisory boards for Alzheon, Aptah Bio, Biohaven, Keystone Bio, Prescient Imaging, Positrogo, and Embic. RAS has received grants from NIA, GHR Foundation, Alzheimer’s Association, and Eisai; has received institutional funding from Eli Lilly and Company; and has received consulting fees from AC Immune, Acumen, Anylam, AbbVie, Genentech, Janssen, Bristol Myers Squibb, Merck, Prothena, Shionogi, Alector, Ionis, Vaxxinity, and Roche.