Wisconsin Alzheimer's Institute
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Blood Biomarkers and Dementia Risk: Clinical Trial Insights Across Sociodemographic Groups

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ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

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Eisai - Public Private Partnership Trial

Alzheimer's Association

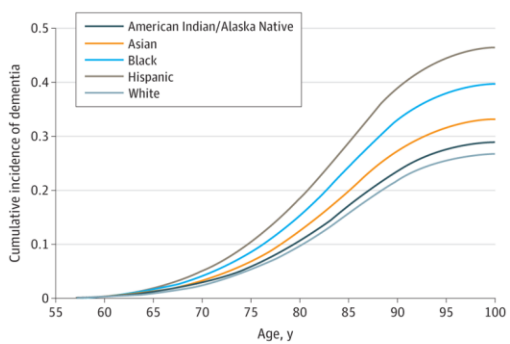
GHR Foundation

Outline

- Disparities in dementia risk across sociodemographic groups
- Advantages of plasma biomarkers over more established biomarkers
- Potential impact of plasma biomarkers in mitigating disparities
- Plasma biomarker use in clinical trials to promote inclusivity
- Insights from ongoing preclinical AD trials
- Future directions

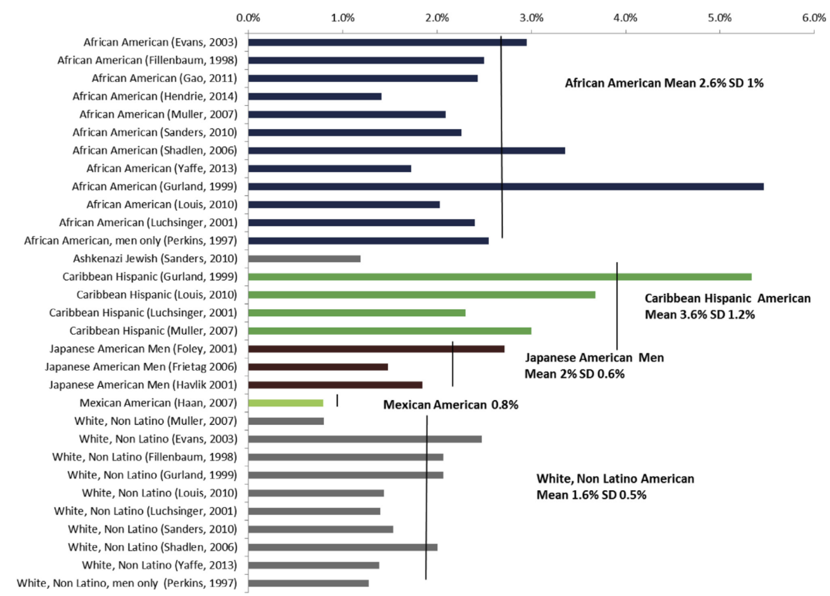
Disparities in Dementia Risk: Race and Ethnicity

- Higher incidence and prevalence of dementia among Black and Hispanic compared to White older adults.
  - Black older adults 2x risk
  - Hispanic older adults 1.5x risk



Kornblith et al., JAMA, 2022

K.M. Mehta and G.W. Yeo / Alzheimer's & Dementia 13 (2017) 72-83



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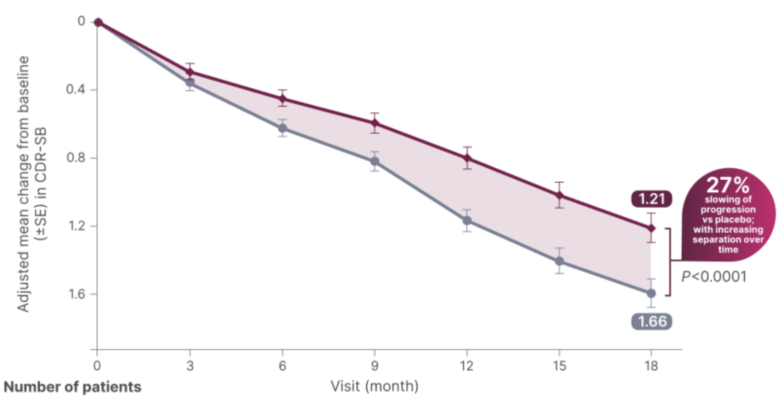
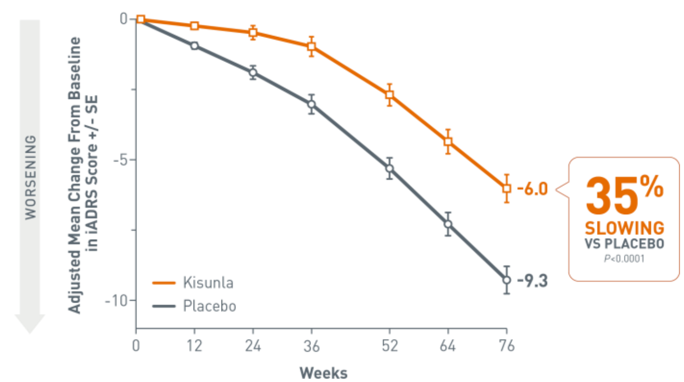
Era of Disease Modifying Treatments: FDA Approved Amyloid Lowering Treatments for Early AD

CLARITY-AD



Number of patients	0	3	6	9	12	15	18
LEQEMBI	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

TRAILBLAZER ALZ-2



No. of Participants	0	12	24	36	52	64	76
Kisunla	533	517	487	459	441	406	418
Placebo	560	549	526	506	474	447	444

Under-researched groups in anti-amyloid trials of FDA approved treatments

- Persistent disparities in dementia treatment are exacerbated by dearth of data in high-risk groups.
- Available FDA-approved, disease-modifying treatments had a low proportion of these populations at high-risk.

CLARITY-AD

Table 1. Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Lecanemab (N=859)	Placebo (N=875)
Age — yr	71.4±7.9	71.0±7.8
Sex — no. (%)		
Female	443 (51.6)	464 (53.0)
Male	416 (48.4)	411 (47.0)
Race — no. (%)†		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Other or missing	37 (4.3)	26 (3.0)
Hispanic ethnic group — no. (%)†	107 (12.5)	108 (12.3)

TRAILBLAZER ALZ-2

Table 1. Characteristics of the Participants at Baseline.*

Variable	Donanemab (N=131)	Placebo (N=126)	Total (N=272)†
Female sex — no. (%)	68 (51.9)	65 (51.6)	145 (53.3)
Age — yr	75.0±5.6	75.4±5.4	75.2±5.5
Race or ethnic group — no. (%)‡			
Asian	1 (0.8)	2 (1.6)	3 (1.1)
Black	5 (3.8)	3 (2.4)	8 (2.9)
White	122 (93.1)	121 (96.0)	258 (94.9)
Other	3 (2.3)	0	3 (1.1)
Hispanic ethnic group — no. (%)‡	5 (3.8)	3 (2.4)	9 (3.3)

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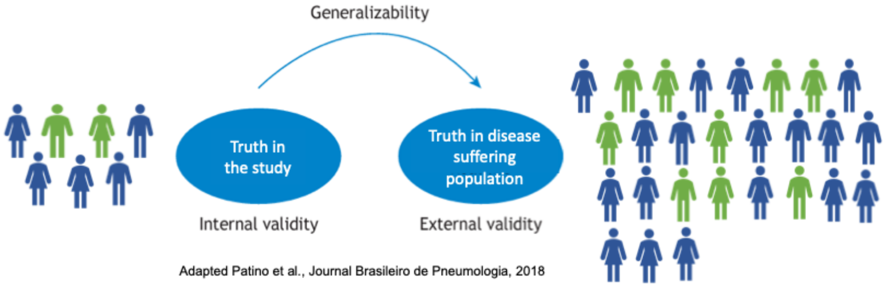
Enhancing External Validity

- Strive for representativeness to **approximate** generalizability
- Prioritize internal validity, maximize external validity

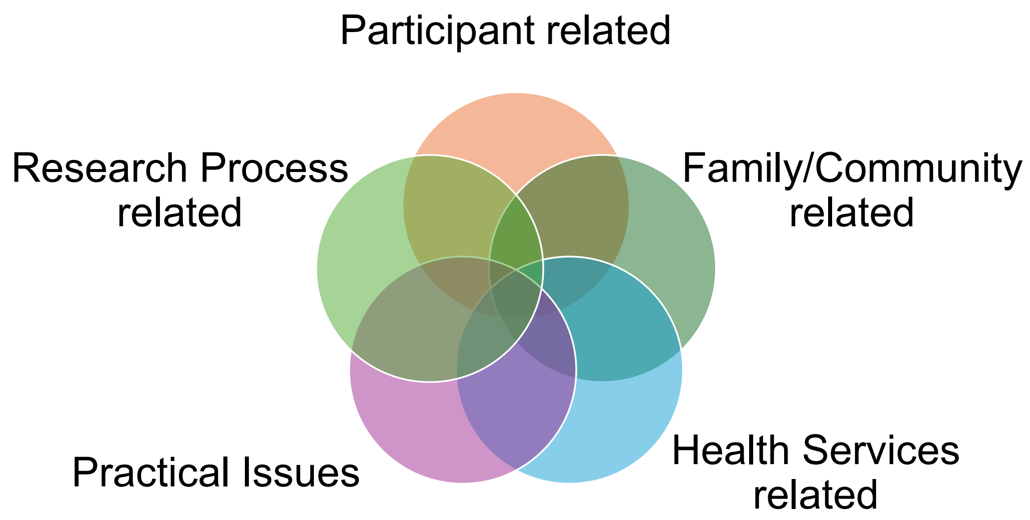


Adapted Patino et al., Journal Brasileiro de Pneumologia, 2018

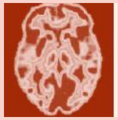
Representativeness of demographic groups for the purpose of conclusive subgroup analyses is not an attainable goal.

Enrollment of Across Sociodemographic Dimensions

*cultural-historical context *socio-political climate *geography



Evolution of Amyloid Biomarkers:



MEASURES IN BRAIN TISSUE FROM DECEDENTS

IN VIVO METHODS: CEREBROSPINAL FLUID, PET SCAN

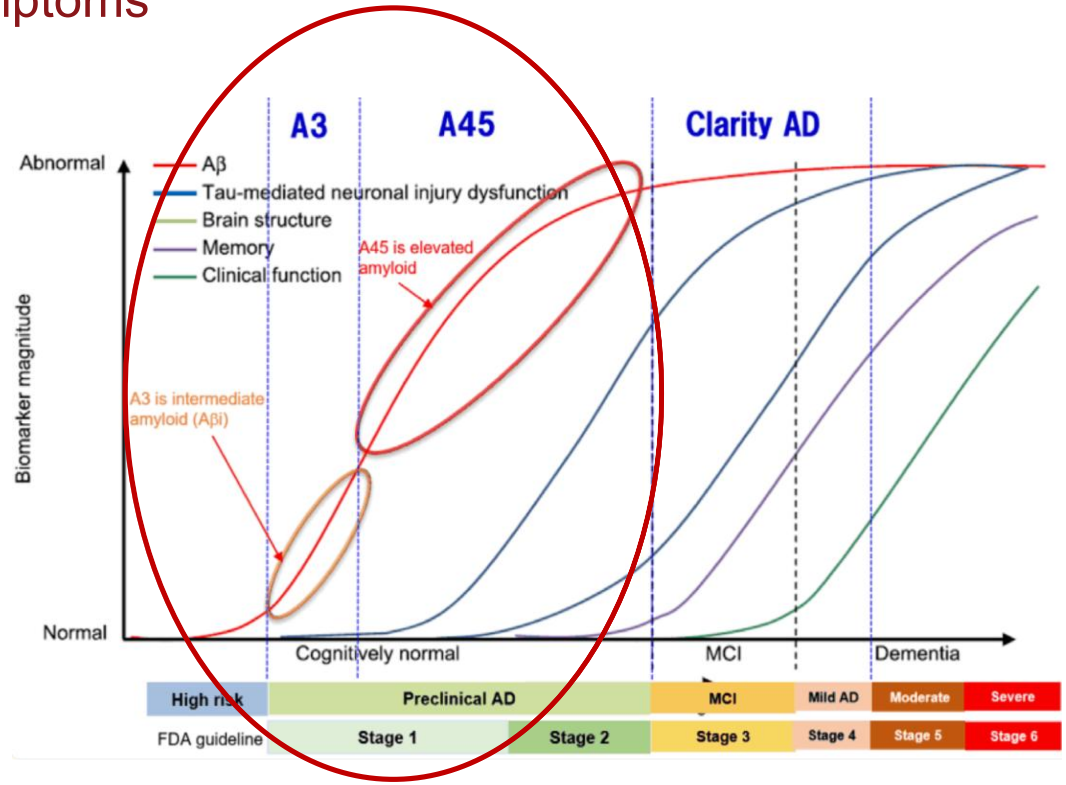
IN VIVO METHODS: BLOOD TESTS

Pre-2000s → Early 2000s → 2010s

Plasma Amyloid Biomarkers May Support More Inclusive Recruitment in Clinical Trials

PET Imaging	**Plasma Biomarkers**
Radioactive tracer injection	Blood draw (minimal burden)
High Cost	Low Cost
Limited to specialized centers	Widely available, even in primary care
Longer processing time due to scheduling and image analysis	Rapid with advanced assays
Considered gold standard for pathology visualization	Advanced plasma markers (e.g., p-tau217) show strong diagnostic accuracy
Less practical for frequent use	Suitable for longitudinal tracking
Often inaccessible due to cost/geography	Feasible in diverse, underserved settings

Earlier intervention is better: Alzheimer's pathology starts decades before symptoms



Rafii, et al. Alzheimers Dement, 2023 Apr;19(4):1227-1233.

Anti-amyloid Treatment in Asymptomatic Disease (A4) Evaluating Eligibility to a Preclinical AD trial

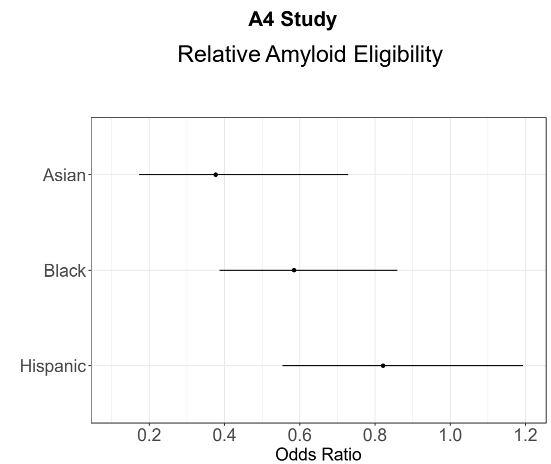
Table 2. Frequency of Screen Failure by Criterion and Racial/Ethnic Group

Characteristic	Total, No.	Race/ethnicity, No. (%)				
		Hispanic	Black	White	Asian	Other
Total participants screened at ScV1	5945	261	323	5107	112	142
ScV1 screen failures[a]						
Screen failures by specific inclusion criteria[a,b]	1683 (28.3)	103 (39.5)	147 (45.5)	1338 (26.2)	43 (38.4)	52 (36.6)
MMSE score	100 (1.7)	16 (6.1)	15 (4.6)	60 (1.2)	4 (3.6)	5 (3.5)
Global CDR score at screening of 0	352 (5.9)	26 (10.0)	41 (12.7)	265 (5.2)	11 (9.8)	9 (6.3)
Logical Memory II score	718 (12.1)	42 (16.1)	62 (19.2)	570 (11.2)	21 (18.8)	23 (16.2)
≥1 of MMSE, CDR or Logical Memory II score	1056 (17.8)	68 (26.1)	99 (30.7)	825 (16.2)	30 (26.8)	34 (23.9)
Screen failures by specific exclusion criteria[a,b]						
Current serious or unstable illness	161 (2.7)	11 (4.2)	10 (3.1)	132 (3)	2 (2)	6 (4)
History of primary or recurrent malignant disease	59 (1.0)	2 (0.8)	2 (0.6)	54 (1.1)	0	1 (0.7)
Clinically significant ECG	106 (1.8)	4 (1.5)	7 (2.2)	93 (1.8)	1 (0.9)	1 (0.7)
History of immunological disorders	56 (0.9)	5 (1.9)	4 (1.2)	43 (0.8)	1 (0.9)	3 (2.1)
Clinically significant lab abnormalities	32 (0.5)	4 (1.5)	6 (1.9)	20 (0.4)	2 (1.8)	0
Total participants screened at ScV3[a]	3937 (66.2)	138 (52.9)	156 (48.3)	3507 (68.7)	62 (55.4)	74 (52.1)
ScV3 screen failures (PET scan showing nonelevated brain amyloid)[a]	2716 (45.7)	100 (38.3)	122 (37.8)	2393 (46.9)	53 (47.3)	48 (33.8)

Abbreviations: CDR, Clinical Dementia Rating; ECG, electrocardiogram; MMSE, Mini-Mental State Exam; ScV, screening visit.

[a] Percentages are based on the total participants screened at ScV1 for a given race/ethnicity.

[b] Limited to inclusion and exclusion criteria that accounted for at least 2% of the total screens within a group or over 50 participants overall.

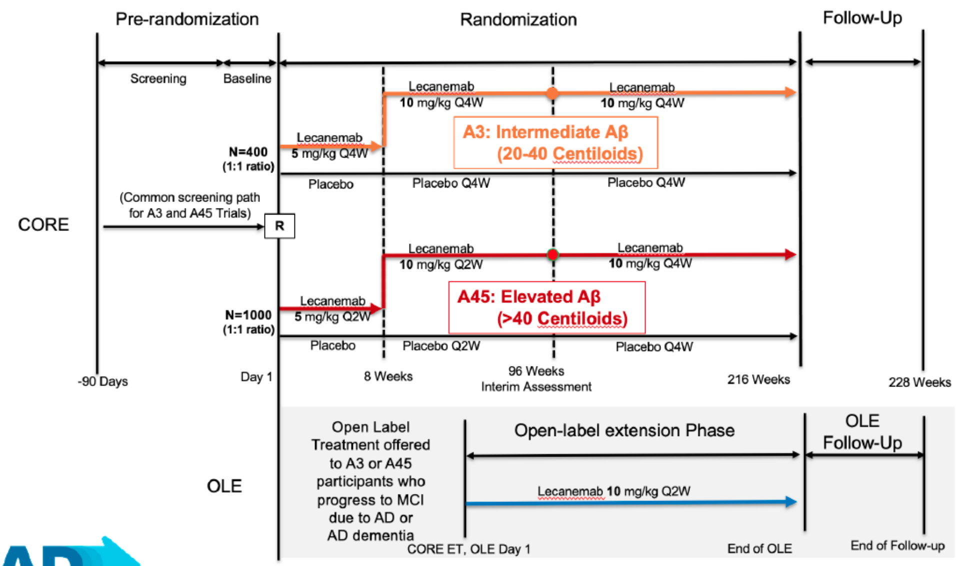


Raman et al., JAMA Netw Open 2021

Harnessing Plasma Biomarkers in Clinical Trials:

The AHEAD 3-45 Study is an ongoing clinical trials program testing lecanemab in cognitively unimpaired adults, 55-80 years old, with biomarker evidence of amyloid.

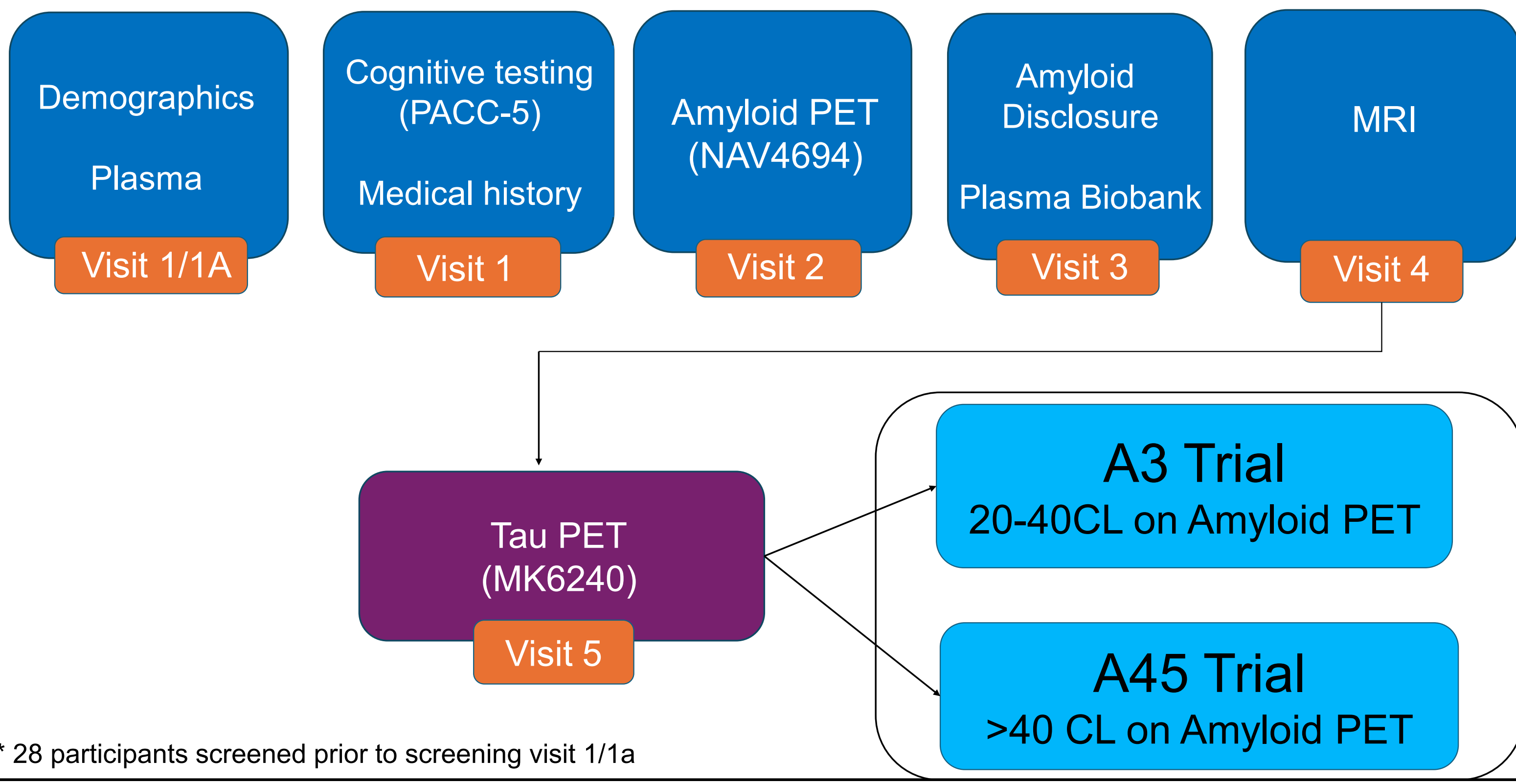
AHEAD 3-45 Study Design



ACTC NIA and Eisai Public Private Partnership

AHEAD 3-45 Study: Shared screening platform

Total consent N = 20721*



* 28 participants screened prior to screening visit 1/1a

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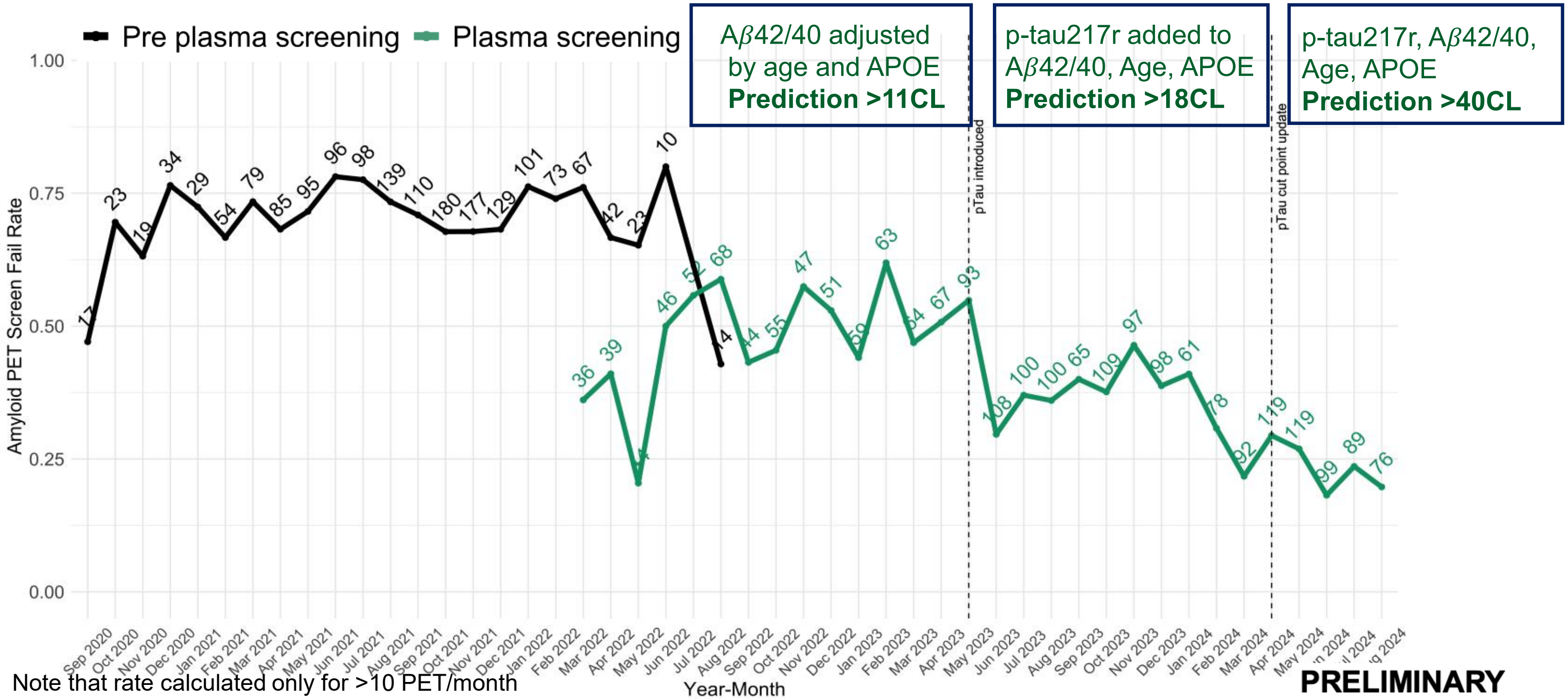
Minimizing screening ineligibility on PET – Introduction of plasma algorithms in AHEAD



Note that rate calculated only for >10 PET/month

PRELIMINARY

Higher rates of ineligibility in RE-URGs in North America using Aβ42/40 ratio, but same PET eligibility rates in plasma-eligible

Received: 26 December 2023 | Revised: 27 February 2024 | Accepted: 28 February 2024
DOI: 10.1002/alz.13803
Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Racial and ethnic differences in plasma biomarker eligibility for a preclinical Alzheimer's disease trial

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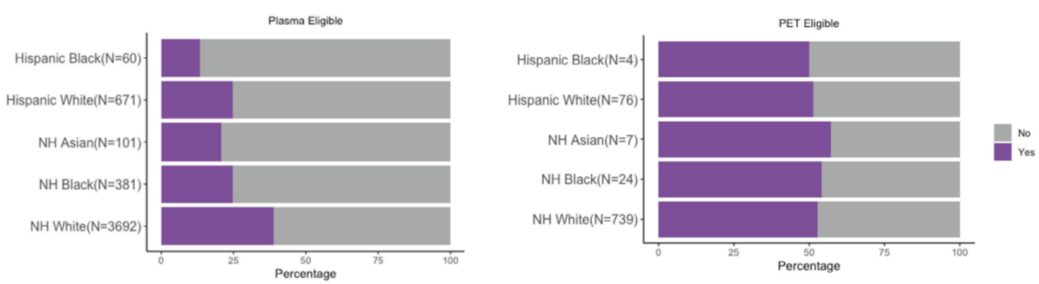
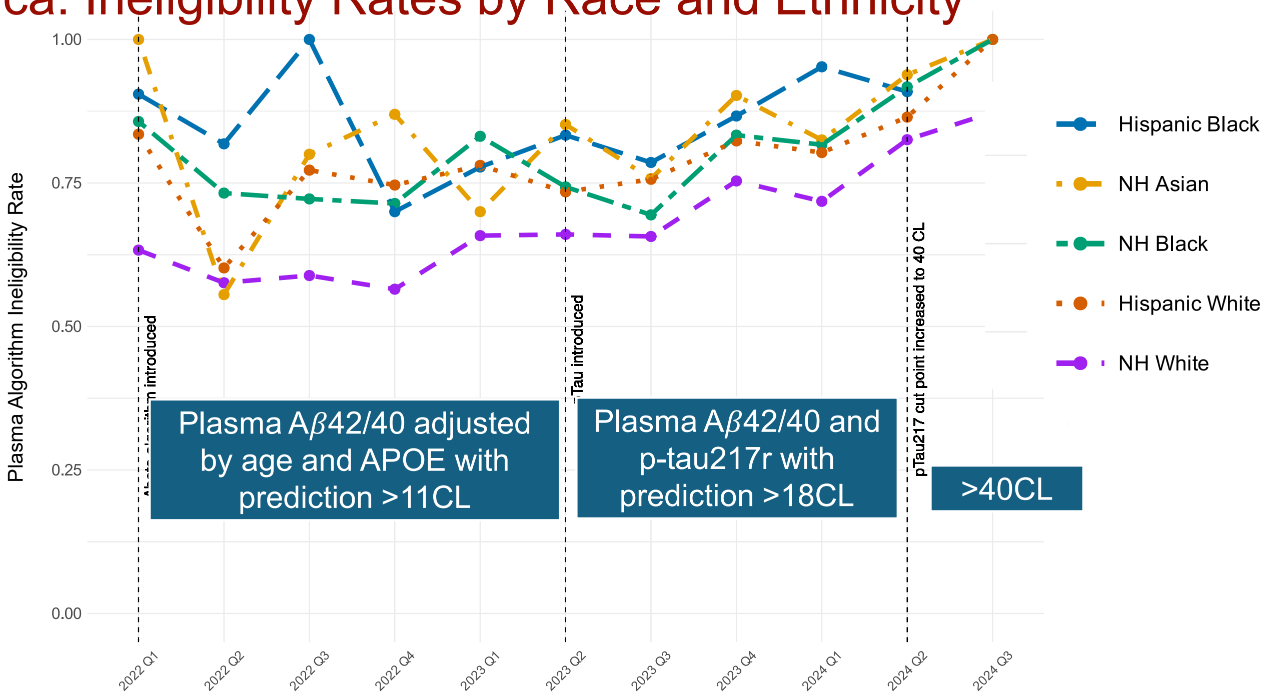


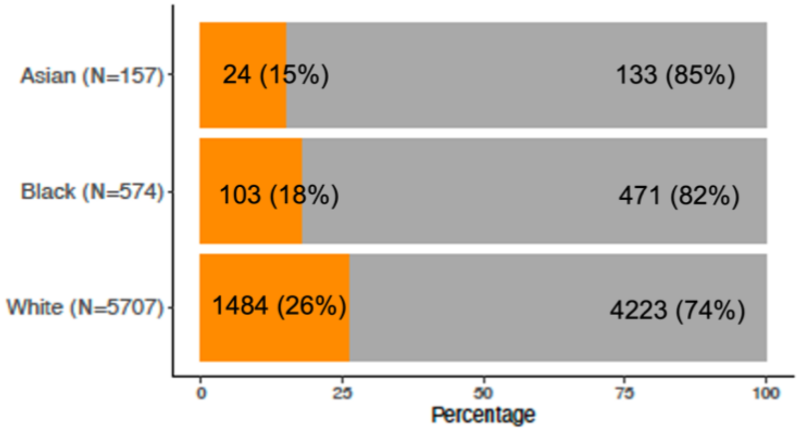
Plasma Screening Timeline for Participants Screened in North America: Ineligibility Rates by Race and Ethnicity



Higher ineligibility rates across all racial and ethnic under-researched groups compared to non-Hispanic White (NHW) adults across all algorithmic adjustments

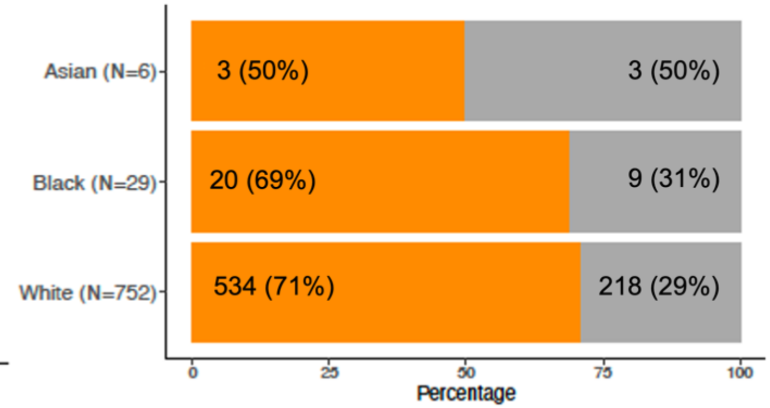
Plasma and PET Eligibility Rates by Race

Plasma Eligibility by Race



Unadjusted Fisher's exact test
p-value < 0.001

PET Eligibility by Race of 'Plasma Eligible'



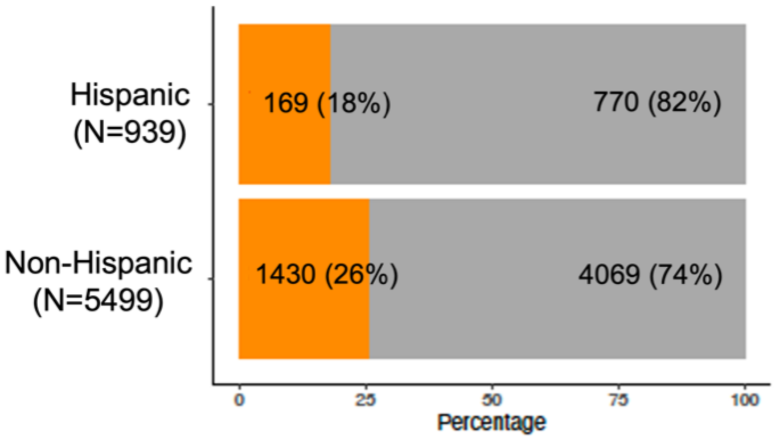
Yes No

Unadjusted Fisher's exact test
p-value = 0.56

Plasma eligibility rates were lower in racial URG but PET eligibility rates did not among plasma eligible.

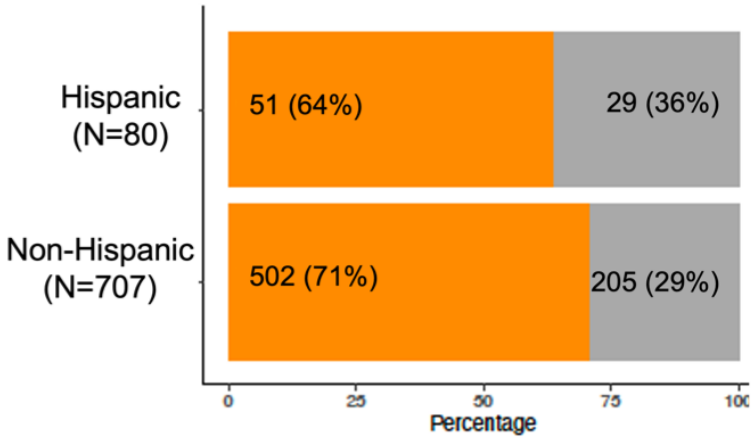
Plasma and PET Eligibility Rates by Ethnicity

Plasma Eligibility by Ethnicity



Unadjusted Fisher's exact test
p-value < 0.001

PET Eligibility by Ethnicity of 'Plasma Eligible'



Yes No

Unadjusted Fisher's exact test
p-value = 0.16

Plasma eligibility rates were lower in ethnic URG but PET eligibility rates did not among plasma eligible.

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Lower Eligibility Rates Underrepresented Populations Among Overall AHEAD Screened

Participant Characteristics	**Screened Participants (N=20721*)**	**Randomized Participants**	
		A3 (N=448)	**A45 (N=1173)**
Race, n (%)			
White	16490 (79.7%)	393 (87.7%)	1070 (91.2%)
Black or African American	1442 (7.0%)	14 (3.1%)	22 (1.9%)
Asian	2153 (10.4%)	35 (7.8%)	62 (5.3%)
American Indian or Alaska Native	56 (0.3%)	0 (0.0%)	2 (0.2%)
Native Hawaiian or Other Pacific Islander	22 (0.1%)	0 (0.0%)	2 (0.2%)
More than one race	236 (1.1%)	2 (0.4%)	5 (0.4%)
Other race	189 (0.9%)	4 (0.9%)	9 (0.8%)
Unknown or Not Reported	96 (0.5%)	0 (0.0%)	1 (0.1%)
Hispanic or Latino Ethnicity	2638 (12.7%)	41 (9.2%)	82 (7.0%)
Race and Ethnic Underrepresented Groups (North America only)	4534 (26.9%)	57 (15.2%)	108 (11.0%)

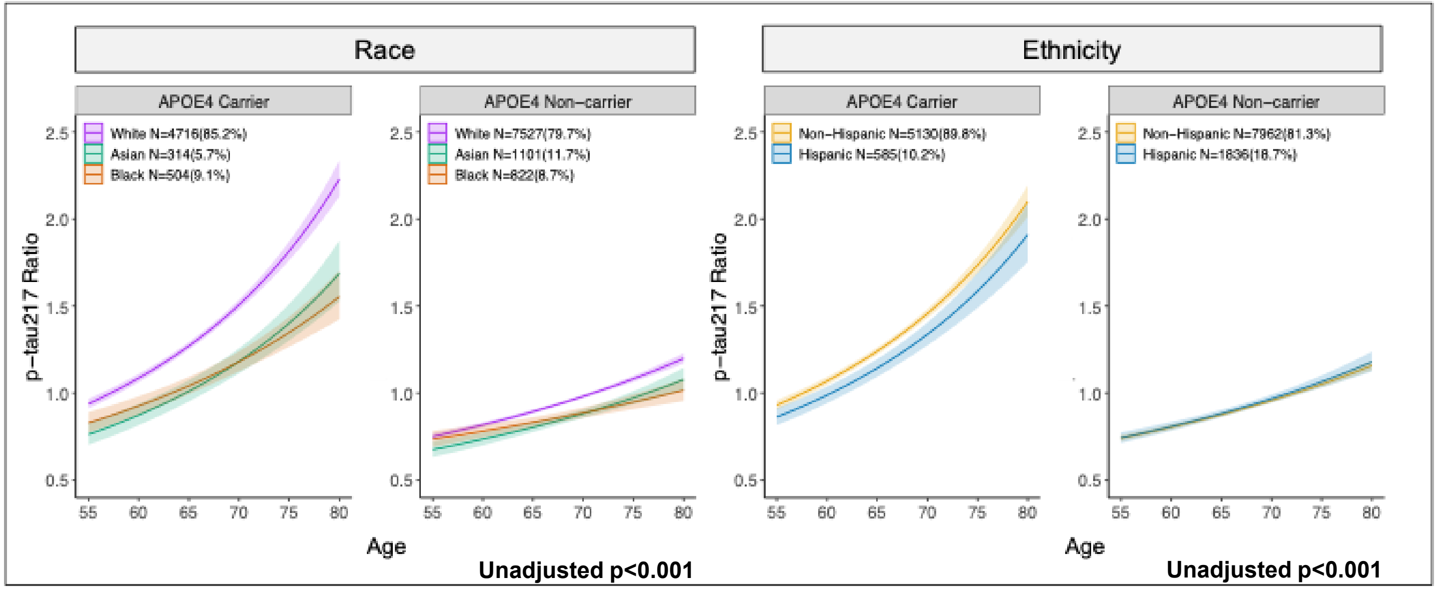
Aisen et al., 2024 CTAD

Results: Characteristics of AHEAD 3-45 Participants with P-tau217r Screened Globally

Population Characteristics	Population with p-tau217r (N=15609)
Region	
North America	13320 (85.3%)
Asia	1073 (6.9%)
Europe	1144 (7.3%)
Australia	72 (0.5%)
Age (y)	
Mean (SD)	68.41 (6.23)
Sex	
Female	9944 (63.7%)
Education (y)	
Mean (SD)	15.79 (3.15)
APOE ε4	
Carrier	5753 (36.9%)
pTau217 Ratio	
Mean (SD)	1.42 (1.10)

Sociodemographic characteristics	Population with p-tau217r (N=15609)
Race	
White	12307 (78.8%)
Asian	1424 (9.1%)
Black	1334 (8.5%)
Ame. Indian/Alaskan	51 (0.3%)
Pacific Islander	19 (0.1%)
Other	175 (1.1%)
Multiple	219 (1.4%)
Unknown	80 (0.5%)
Ethnicity	
Hispanic	2432 (15.6%)
Non-Hispanic	13176 (84.4%)
Hollingshead	
Lower SES	2776 (17.9%)
Higher SES	12742 (82.1%)
Rurality	
Rural	545 (4.4%)
Urban	11809 (95.6%)

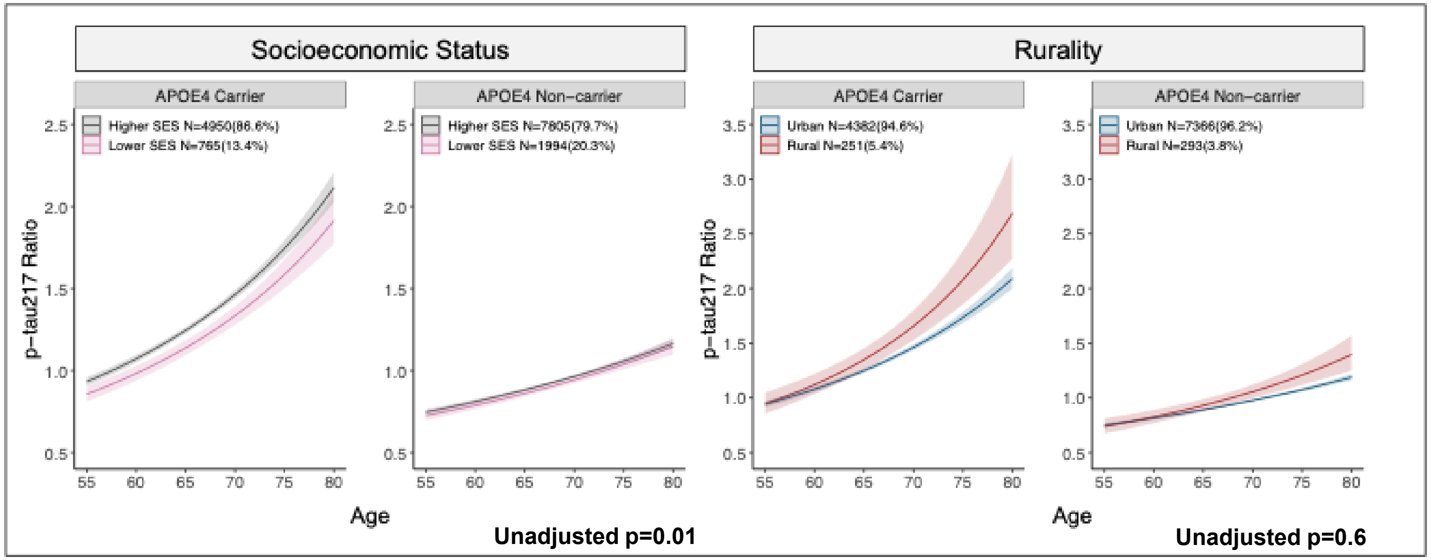
The Effect of Race and Ethnicity on P-tau217r Differs by APOE4 Status



P-values reflect 2-way interactions of group x APOE

Across racial and ethnic groups, p-tau217r was higher with age.
APOE4 carriers have higher p-tau217r.
Asian, Black and Hispanic populations have lower ratios compared to White and non-Hispanic.

The Effect of SES on P-tau217r Differs by APOE4 Status



P-values reflect 2-way interactions of group x APOE

Across SES and Rurality, p-tau217r was higher with age.
Lower p-tau217r among lower SES and urban populations.
Adjustment for SES did not attenuate the effect of race and ethnicity.

Summary and Future Directions

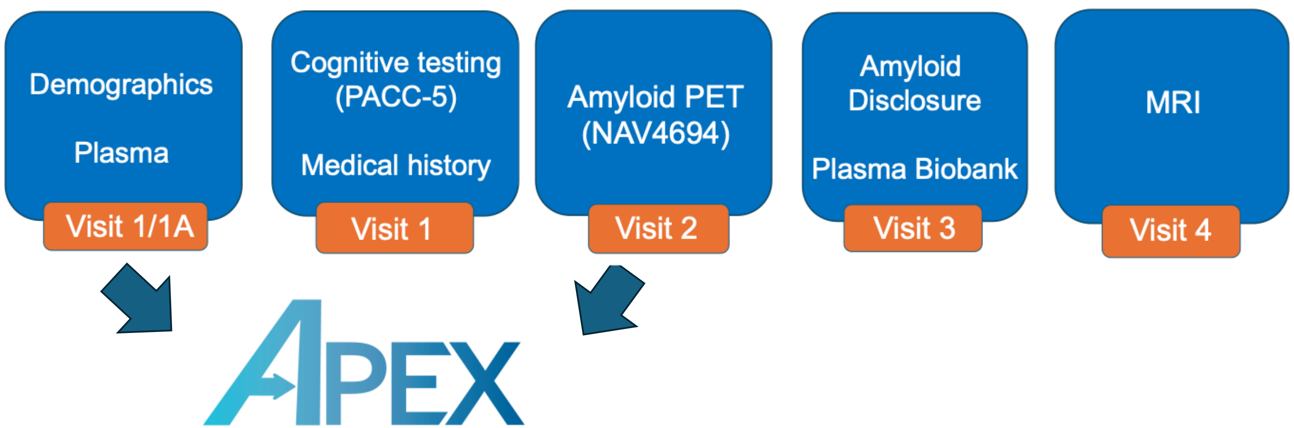
- Group-level differences in p-tau217r by race, ethnicity and SES modulated by APOE4.
  - SES does not explain race and ethnic differences.
- Lower prevalence of elevated amyloid in some populations
  - Co-pathologies (vascular, inflammatory) may be drivers of greater risk across race, ethnicity and SES

- Limitations: Cross-sectional data; limited representativeness across SES and Rural groups

- Future epidemiological studies and longitudinal studies, like the Alzheimer's Plasma Extension Study will be critical to continue to inform on the performance of biomarkers across these populations.

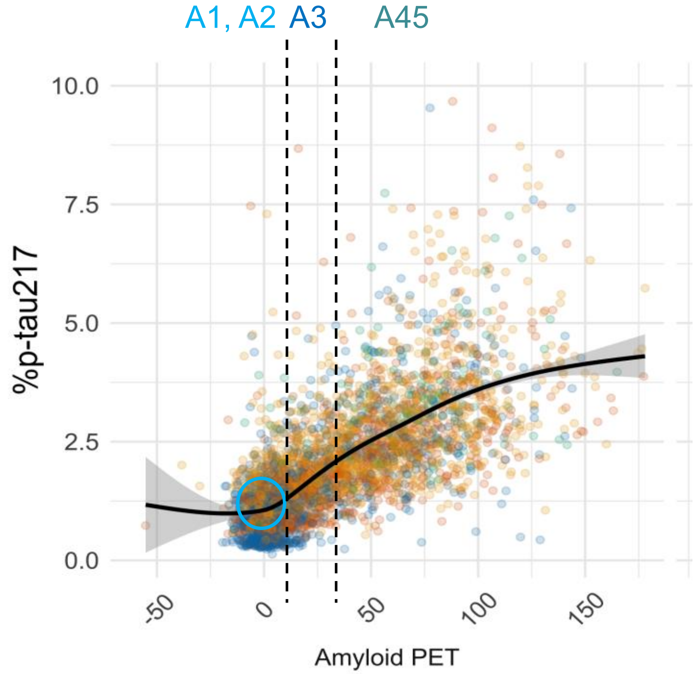
Alzheimer's Prevention Study (APEX)

- Invited participants who did not qualify to be randomized to the AHEAD trials but leverages previously collected plasma and PET data.
- Evaluate longitudinal plasma and cognitive trajectories



Ineligible to proceed at different stages of screening process

APEX Study: Plasma amyloid abnormalities are detectable prior to 20CL



AHEAD 3-45 Screens with %ptau-217 and Amyloid PET
(N=3811)

APEX

- Within-individual validation over time
- Oversampling of low amyloid prevalence but at risk of dementia groups.
- Explore contributions of social factors
- Explore contributions of other co-pathologies

	APEX (N=1314)
Age	
- Mean (SD)	68.25 (6.22)
Sex	
- Female	872 (66.4%)
Education (years)	
- Mean (SD)	16.0 (3.0)
Race	
- American Indian or Alaska Native	7 (0.53%)
- Asian	83 (6.3%)
- Black or African American	275 (20.9%)
- More than one race	75 (5.7%)
- Native Hawaiian or Other Pacific Islander	5 (0.38%)
- Other	41 (3.1%)
- Unknown or Not Reported	11 (0.84%)
- White	816 (62.0%)
Ethnic group	
- Hispanic or Latino	305 (23.3%)
- Not Hispanic or Latino	1008 (76.8%)
Racial and Ethnic URG	
- Non-URG	741 (56.4%)
- URG	572 (43.5%)

Key Insights on Plasma Biomarkers in AD Clinical Research

- Increase **efficiency** in trials, **minimize** participant burden
- Greater potential for **scalability** and **longitudinal** data collection.
- Bridging **access gaps** for all populations at risk
- **Promising tool** for identifying individuals who may progress at the earliest asymptomatic stages
- More **data across different populations** to better understand differences in disease trajectories and contributions to dementia risk

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[1] ACTC Lead and [2] Eisai Lead representing the ACTC and Eisai AHEAD study team

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AHEAD STUDY

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And the AHEAD 3-45 study participants and their families!!