Center for Alzheimer Research & Treatment

HARVARD AGING BRAIN

Can we detect and treat Alzheimer's disease a decade before dementia? (And why we must!)

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8/3/2026

Disclosures and Funding

R. Sperling Consultant (over past 3 years, all below NIH guidelines of $5k):

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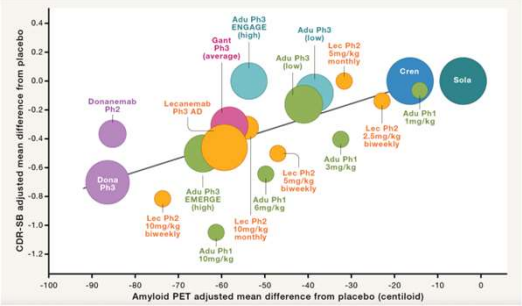
Why have we finally succeeded (at least somewhat) in AD disease modifying therapeutic trials?

- Defining population with target pathology
- Aggressive reduction of amyloid PET below baseline down into "amyloid negative" range
- Moving earlier in the clinical spectrum to MCI/mild dementia
- Initiating treatment at lower levels of AD pathology associated with greater clinical benefit



Boxer A and Sperling R *Cell* 2023

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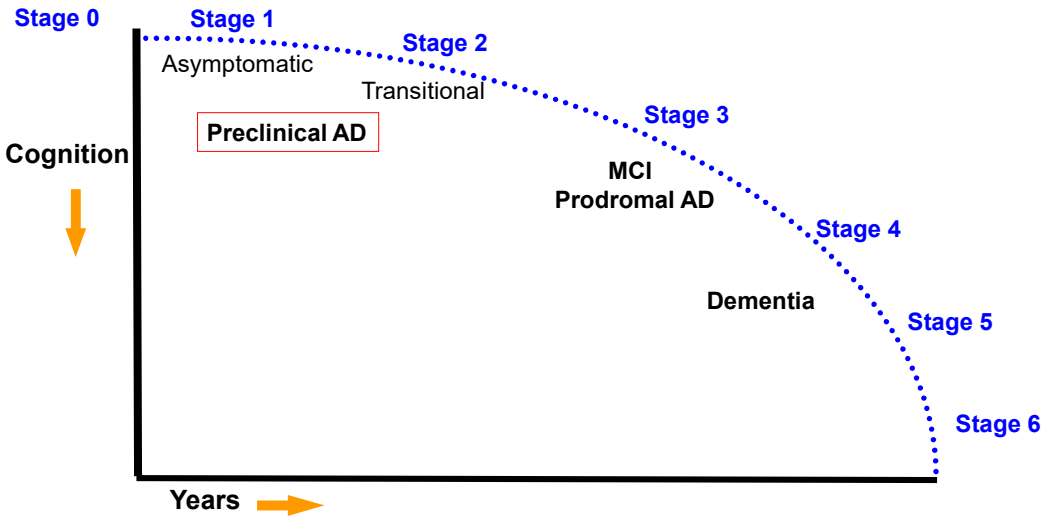
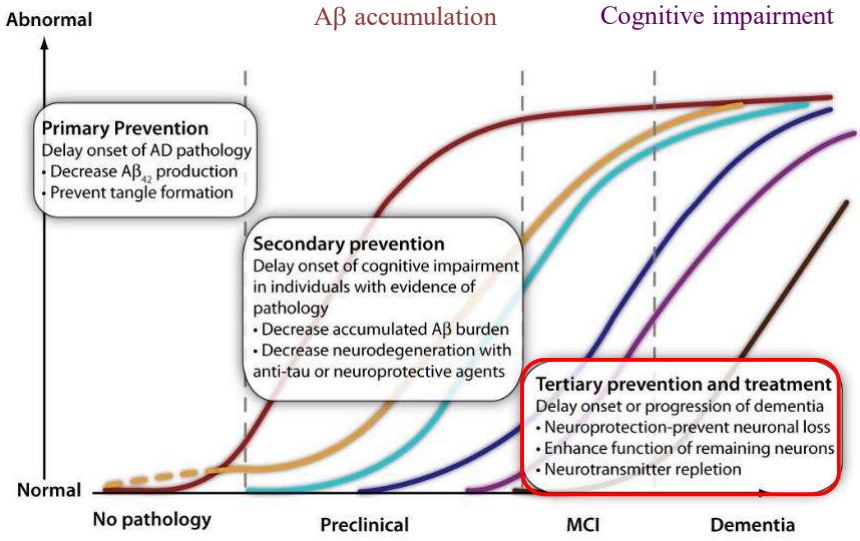
The continuum of Alzheimer's disease



Sperling R et al. 2011; Jack C et al. 2018, 2024
FDA Draft Guidance

Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease



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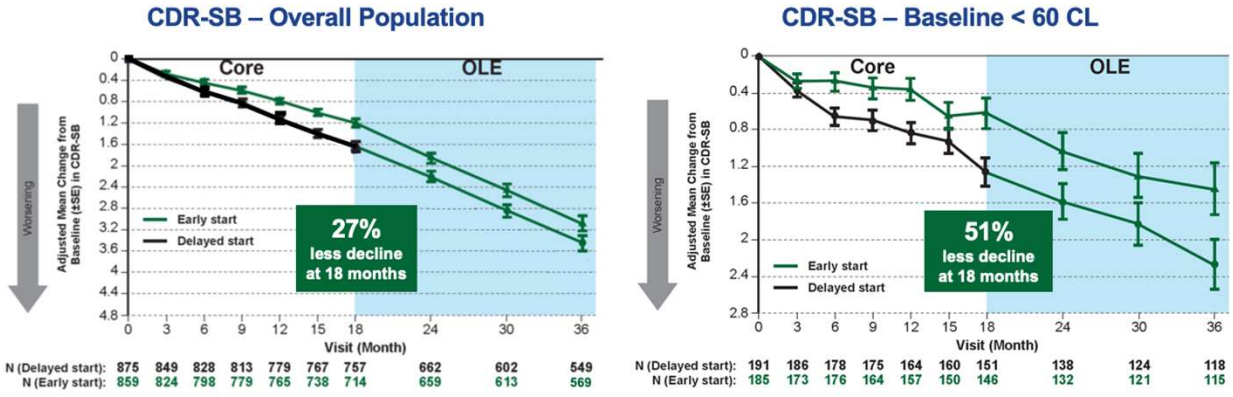
Sperling, Jack, Aisen *Science Trans Med* 2011

Phase 3 Lecanemab Clinical Outcomes Through 36 Month OLE

Lower Baseline Amyloid Group Shows Greater Continued Benefit



Van Dyck C, Sperling R, Johnson K et al. *Alzheimer's & Dementia* 2025

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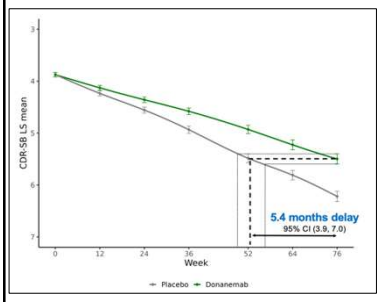
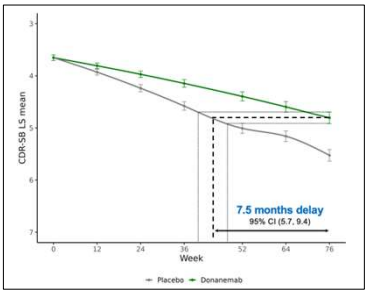
OLE includes those participants on subcutaneous and intravenous formulations.
ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale. ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment. ADNI, Alzheimer's Disease Neuroimaging Initiative. CDR-SB, Clinical Dementia Rating-sum of boxes. CL, Centiloid. OLE, open-label extension. SE, standard error.

Phase 3 Donanemab -
Lower Baseline Tau Associated with Greater Clinical Benefit

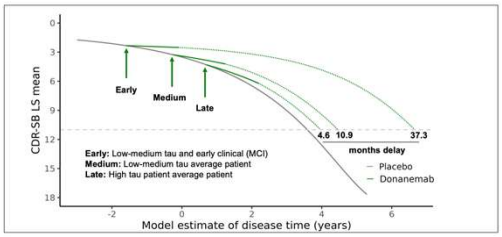
CDR-SB
Overall Population



CDR-SB
Low-Med Tau Population



CDR-SB
Earlier Intervention
Extrapolation Model



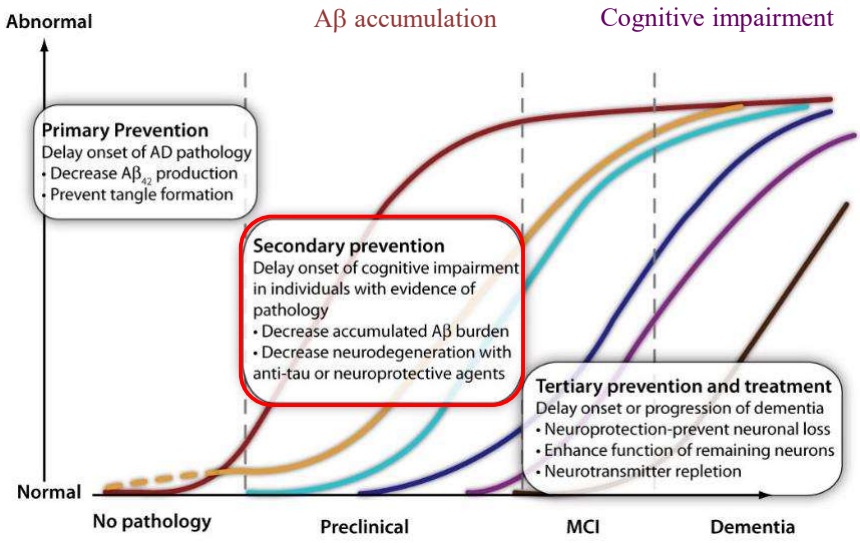
Proportional time slowing PMRM analysis
Error bars indicate +/- 1 standard error
PMRM = Progression Model for Repeated Measures, CI = Confidence Interval

Presented at Donanemab
FDA Advisory Meeting June 2024

Rationale for earlier intervention in “preclinical” AD

- Pathophysiological process of AD begins with the accumulation of Aβ and tau well more than a decade before symptoms
- In the setting of high Aβ, tau can spread rapidly from the medial temporal lobe into the neocortex - the “ca-TAU-strophe” - which heralds imminent progression to Mild Cognitive Impairment (MCI)
- Treatment with anti-amyloid agents have limited efficacy in people with symptomatic AD who have higher amyloid and tau levels
- We need to test whether earlier intervention, reducing Aβ prior to extensive tauopathy and impairment, can demonstrate even greater impact on cognitive decline and prevent progression to cognitive impairment

Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease



Sperling, Jack, Aisen *Science Trans Med* 2011

Secondary Prevention Trials in Sporadic Preclinical AD

- Anti-Amyloid Treatment in Asymptomatic AD (A4) Study (NCT02008357) – solanezumab
  - Completed 2023
- TRAILBLAZER-Alz-3 (NCT05026866) - donanemab
  - Expected to read out sometime within next year
- AHEAD 3-45 (NCT04468659) – lecanemab
  - Expected to read out in 2028
- PrevenTRON (NCT pending) – trontinemab
  - Coming soon!!!

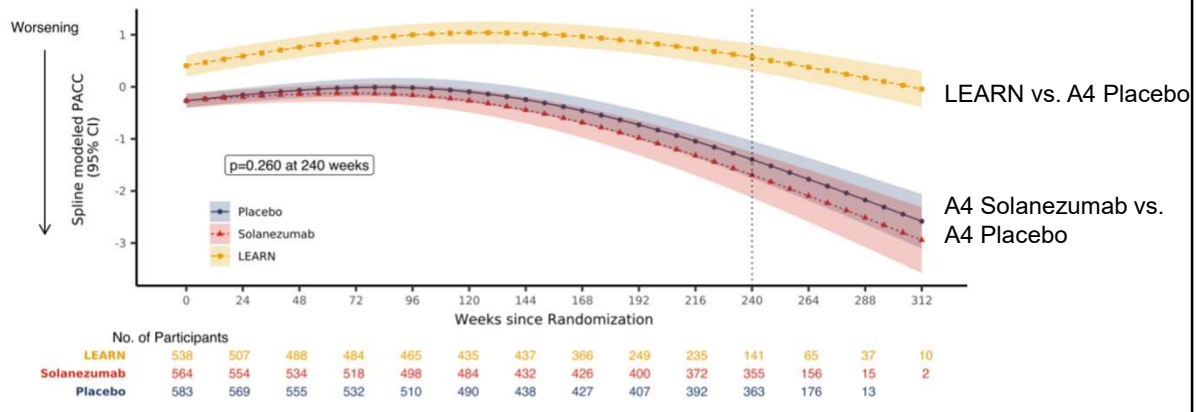
Anti-Amyloid Treatment of Asymptomatic Alzheimer's disease (A4) Study

- Secondary prevention trial in clinically normal older individuals (age 65-85y) with elevated Aβ screening PET
- Phase 3 randomized, double-blind, placebo-controlled trial of solanezumab vs. placebo – 240 weeks (4.5 years)
- 67 sites in U.S., Canada, Japan, Australia,
- Enrollment N=1150; 575 per arm, stratified by APOE
- LEARN companion study of Aβ- (not elevated Aβ)
- Amyloid Disclosure Ethics Substudy

The A4 Study
NOW IS THE TIME

No treatment difference on cognitive decline in A4
No cognitive decline observed in LEARN

Preclinical Alzheimer Cognitive Composite (PACC)

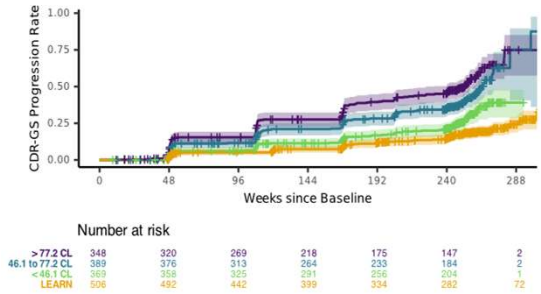


Mean (95% CI) derived from spline model of Preclinical Alzheimer's Cognitive Composite (PACC).

Sperling R et al *New England Journal Medicine* 2023

High Risk of Progression to MCI/Dementia in Cognitively Unimpaired with Elevated AD Biomarkers

Baseline Amyloid PET

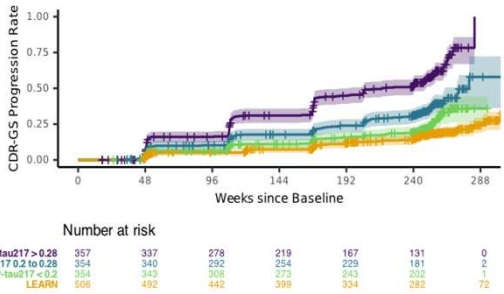


Number at risk

>77.2 CL	348	320	269	218	175	147	2
46.1 to 77.2 CL	389	376	313	264	233	184	2
<46.1 CL	369	358	325	291	256	204	1
LEARN	506	492	442	399	334	282	72

LEARN
< 46.1 CL
46.1 to 77.2 CL
> 77.2 CL

Baseline Plasma P-tau 217



Number at risk

P-tau217 > 0.28	357	337	278	219	167	131	0
P-tau217 0.2 to 0.28	354	340	292	254	229	181	2
P-tau217 < 0.2	354	343	308	279	243	202	1
LEARN	506	492	442	399	334	282	72

LEARN
P-tau217 < 0.2
P-tau217 0.2 to 0.28
P-tau217 > 0.28

More than 50% of people in highest levels of AD biomarker progressed to MCI or dementia within 5 years

The A4 Study
NOW IS THE TIME

Sperling R et al *JPAD* 2024

AHEAD STUDY

www.aheadstudy.org

The AHEAD Study

The AHEAD Study is testing whether an investigational treatment can lower people's risk of memory loss due to Alzheimer's disease.

View Participation Requirements

We are looking for people ages 55-80 who do not yet have symptoms of Alzheimer's disease, but who are interested in participating in clinical trials aiming to help prevent memory problems in the future. You can answer a few short questions to learn if you may be eligible to participate in the AHEAD Study.

Join the Study

8/3/2026

AHEAD 3-45 Design Overview

- AHEAD 3-45 Study is composed of two sister trials spanning the continuum of early-late preclinical AD on the basis of screening amyloid PET level
- AHEAD Study testing targeted dosing of lecanemab - a monoclonal antibody targeting protofibrillar forms of Aβ

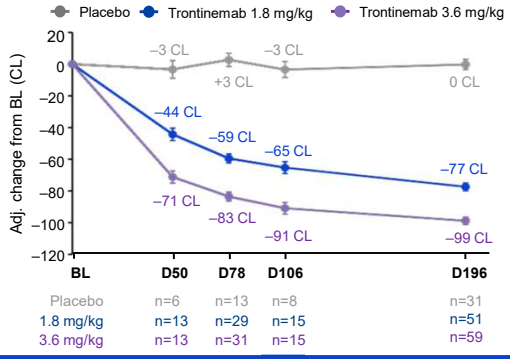
- **A3 – Intermediate amyloid (20-40 centiloids) aimed at slowing Aβ accumulation**
  - 4 year Phase 2 trial – 10mg/kg monthly lecanemab (n=200/arm)
  - Amyloid PET primary outcome – Tau PET key secondary
  - Cognition exploratory (PACC-5 and C3)

- **A45 – Elevated amyloid (>40 centiloids) aimed at preventing cognitive decline**
  - 4 year Phase 3 trial – 10mg/kg lecanemab biweekly then monthly maintenance (n=500/arm)
  - Cognitive primary outcome (PACC-5)
  - Amyloid and Tau PET key secondary (potential interim for accelerated approval)
  - Additional cognitive, participant reported, plasma and CSF biomarker outcomes

PrevenTRON – Phase 3 trial in 1600 cognitively unimpaired participants at high risk of cognitive impairment testing trontinemab (brain shuttle)

Trontinemab demonstrates rapid and robust amyloid reduction with low ARIA incidence

PET change from BL with trontinemab 1.8 mg/kg and 3.6 mg/kg*,†



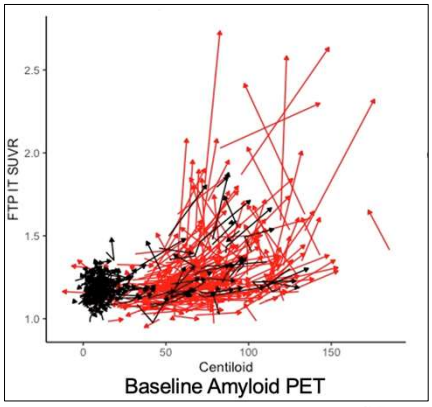
Total number of participants, n (%)	Cohort 3 1.8 mg/kg or placebo (n=76)	Cohort 4 3.6 mg/kg or placebo (n=75)
ARIA-E‡	3 (3.9)	1 (1.3)
Symptomatic ARIA-E	1 (1.3)	0
ARIA-H	5 (6.6)	3 (4.0)
Microhaemorrhage	2 (2.6)	2 (2.7)
Superficial siderosis	3 (3.9)	1 (1.3)
Concurrent ARIA-E + ARIA-H	0	0
Other significant MRI findings		
Cerebral macrohaemorrhage[c]	1 (1.3)	0

In the Phase Ib/IIa Brainshuttle™ AD study of participants with MCI due to AD and mild-to-moderate AD dementia, rapid and robust amyloid load reduction, as measured by amyloid PET, was observed with trontinemab from baseline to Day 196. The incidence of ARIA-E and ARIA-H was low, and all ARIA-E events were mild/mild+ in radiologic severity

Trontinemab is an investigational product not approved for use in any market. Data from Part 1+2 of the Phase Ib/IIa study Brainshuttle™ AD (NCT04639050). *Part 1+2 combined. †Values at each time point were based on an MMRM model, with change from baseline in amyloid PET burden (CL) as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction and baseline amyloid PET. 'n' represents the number of participants contributing to the model with available change from baseline at each visit. p<0.0001 vs placebo for both active dose groups and all post-BL time points via MMRM. All p-values are exploratory. ‡Radiological ARIA-E severity according to five-point grading scale. Adj., adjusted; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-oedema/effusion; ARIA-H, amyloid-related imaging abnormalities-microhaemorrhages and hemosiderin deposition; BL, baseline; CL, Centiloid; D, day; MCI, mild cognitive impairment; MMRM, mixed models for repeated measures; MRI, magnetic resonance imaging; PET, positron emission tomography.
Kulic L, et al. Presented at CTAD 2025.

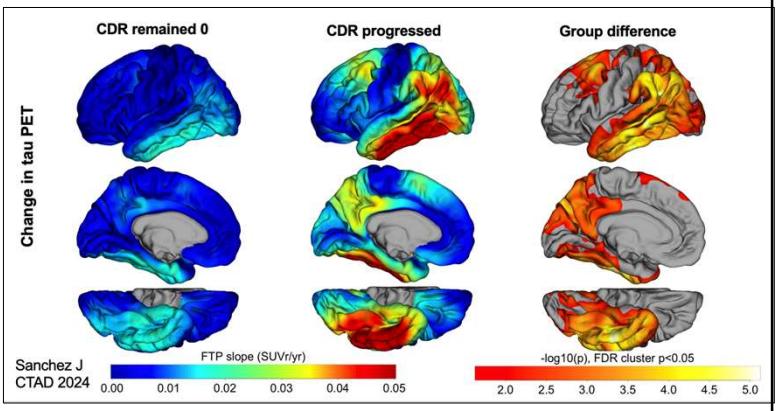
Need to prevent the "ca-TAU-strophe" in preclinical AD

Change in Inferior Temporal Tau by Baseline Amyloid Level



A4 Study and Harvard Aging Brain Study

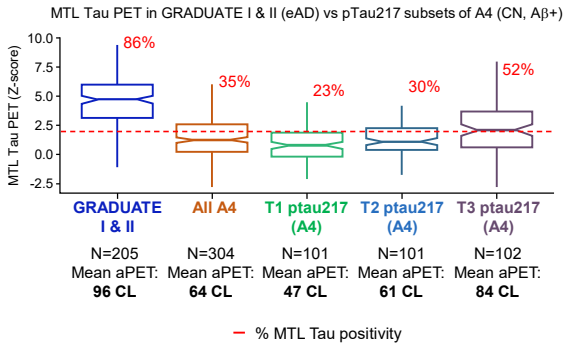
Longitudinal Tau PET in A4 CDR Progressors



Keith Johnson

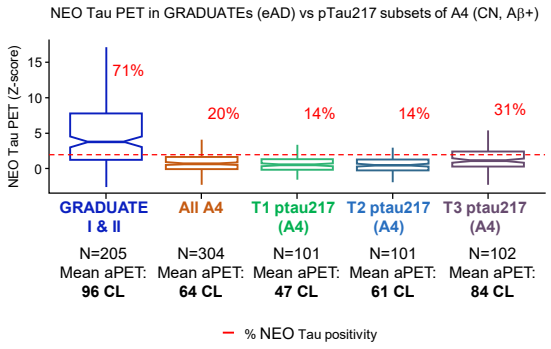
Baseline Tau PET in GRADUATE (symptomatic AD) vs. A4 (preclinical AD)

Medial Temporal Lobe (MTL)



MTL : weighted mean of ERC and amygdala SUVrs
Z–score for A4 : (SUVr – mean(SUVrs LEARN)) / sd(SUVrs LEARN)
Z–score for GRADUATE I & II : using mean and sd of CN AB– GTP1 cohort in DOI: 10.1002/alz.13908
T : Tercile
Elecsys pTau217

Neocortical (NEO)



NEO : weighted mean of inferior and middle temporal SUVrs
Z–score for A4 : (SUVr – mean(SUVrs LEARN)) / sd(SUVrs LEARN)
Z–score for GRADUATE I & II : using mean and sd of CN AB– GTP1 cohort in DOI: 10.1002/alz.13908
T : Tercile
Elecsys pTau217

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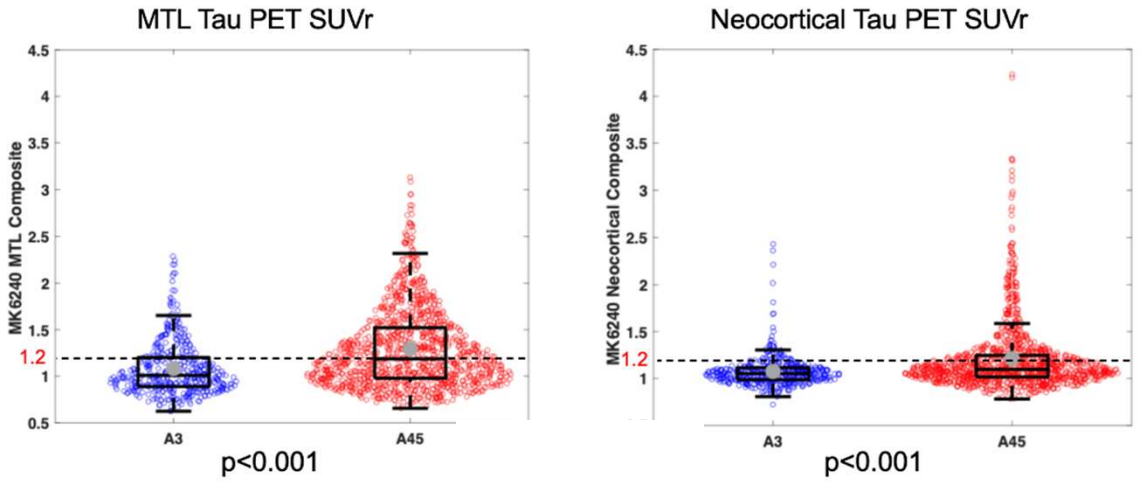
AHEAD A3 and A45 Preclinical AD Screening Data
Tau PET (^{18}F-MK6240) Composite Regions



AHEAD 3-45 STUDY

A3 20-40CL Amyloid PET **N=429**
A45 >40CL Amyloid PET **N=1106**

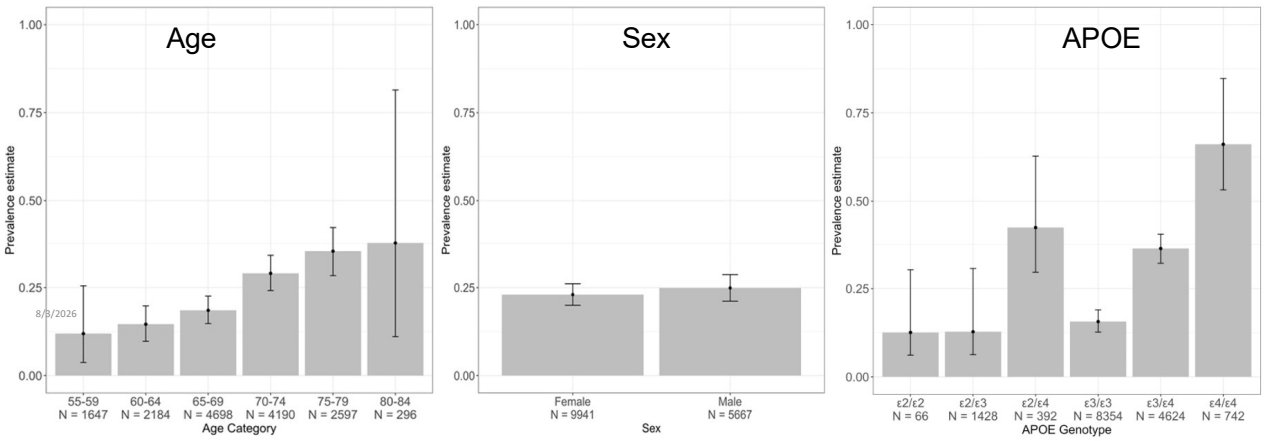
Combination Prevention Trials and ADAD

- Dominantly Inherited Alzheimer Network (NCT05269394) E2814 (antibody targeting MTBR domain) plus lecanemab
  - Expected to read out in 2028
- DIAN Primary Prevention (NCT06647498) – Remternetug
  - Expected to read out in 2034
- ACTC Alzheimer Tau Platform (ATP) – (NCT06957418)
  - Phase 2 - Factorial combination platform in preclinical and prodromal AD based on biological diagnosis
  - First tau agent Axon active immunization plus donanemab
  - Second Tau agent selection underway

Why does this matter?

- We are doing a very good job at keeping people alive longer and are facing a tsunami of AD
  - One third of people >65 have evidence of AD biomarkers
  - One third of people >80 will die with dementia, largely due to AD
- We can now accurately detect AD beginning in the brain >10 years before impairment
- Cognitively unimpaired individuals with high levels of AD biomarkers are at high risk of progression to MCI/dementia

Proportion of Abnormal Plasma %p-tau217 by Age and APOE Global Screening Data from AHEAD (N=15,609)



C_2N Mass Spec – plasma % phosphorylated tau217/non-phosphorylated tau217
Prevalence estimates based on optimal %p-tau217 threshold
based on Youden index as reported in Rissman R et al *Alz & Dem* 2024

Sperling R et al *HAI* 2026

JAMA | Original Investigation

Prognostic Value of Blood-Based P-Tau217 Levels for Progression to Cognitive Impairment

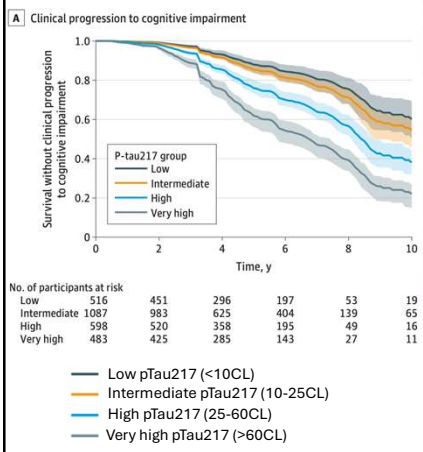


Table 2. Absolute Risk of Incident Cognitive Impairment by Time Horizon[a]

	P-tau217 group, % (95% CI)			
	Low	Intermediate	High	Very high
Absolute risk of incident cognitive impairment according to time horizon, y[b]				
2	1 (1-1)	1 (1-1)	2 (1-3)	4 (3-5)
5	12 (9-15)	15 (12-17)	24 (20-28)	38 (33-43)
10	40 (31-49)	45 (37-52)	62 (52-69)	78 (69-84)
5-y Absolute risk of incident cognitive impairment according to sex[c]				
Female	10 (6-14)	11 (8-14)	21 (17-25)	36 (30-41)
Male	16 (12-21)	20 (16-24)	30 (24-38)	43 (35-48)
5-y Absolute risk of incident cognitive impairment at selected ages, y[d]				
65	11 (7-14)	12 (8-14)	17 (12-23)	39 (31-46)
75	13 (10-19)	19 (15-22)	29 (25-33)	43 (39-47)
85	17 (5-34)	30 (20-42)	39 (45-58)	47 (36-57)

Estimates of absolute risk of incident cognitive impairment by plasma p-tau217 group derived from a Cox proportional hazards model including baseline plasma p-tau217 group and adjusted for cohort, baseline age, sex, APOEε4 carrier status, and years of education.

Six cohorts: Harvard Aging Brain Study, A4 Study, LEARN, HABS-HD, ADNI, WRAP
Total N = 2684 Cognitively Unimpaired at Baseline

8/3/2026

Buckley R et al *JAMA* 2026

Encouraging history from other fields

- Think about what has changed in cancer, stroke, HIV, osteoporosis, diabetes …. when we detect disease BEFORE symptoms?
- Delaying dementia by just 5 years would reduce projected Medicare costs by nearly 50%
- Serious diseases require aggressive treatments
  - Many older people fear Alzheimer's disease more than cancer
  - But we need to determine which people with preclinical AD need what kind of treatment and when they need it
- Alzheimer's disease is a formidable opponent – We must be even bolder!
- But we are getting there…

8/3/2026

Acknowledgments

- **Keith Johnson** and colleagues from Harvard Aging Brain Study
- **Paul Aisen** and colleagues from ACTC
- A4 Teams at Eli Lilly and ACTC: https://www.actcinfo.org/trial/a4-open-label-extension/
- AHEAD Teams at Eisai and ACTC: https://www.actcinfo.org/trial/ahead-study/
- PrevenTRON Planning Teams at Roche
- Clinical Trial Site investigators and staff
- **Most importantly - the dedicated research participants and their study partners!**