Center for Alzheimer
Research & Treatment

Towards precision medicine in preclinical Alzheimer's disease: Who should be treated when and with what?

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Massachusetts General Hospital
Harvard Medical School

Disclosures and Funding

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

Abbvie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol-Myers Squibb, Roche, Ionis, Janssen, Merck, Oligomerix, Prothena, Vaxxinity

Spouse (K. Johnson) Consultant to:

Bristol-Myers-Squibb, Janssen, Novartis, Merck, Prothena

Research funding from:

National Institute on Aging:

P01AG036694; R01AG095009

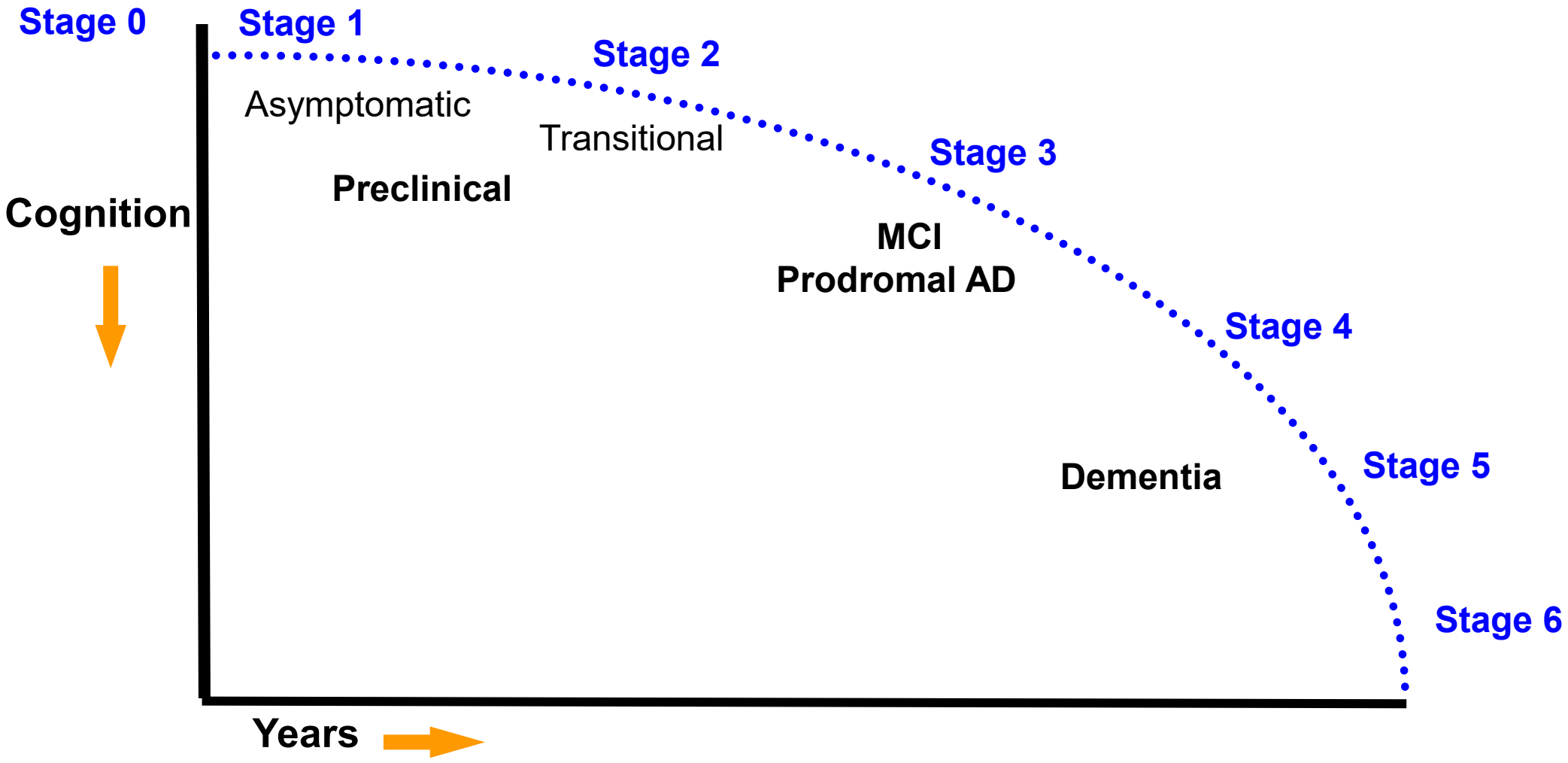
U24AG057437; R01AG063689

Alzheimer's Association

GHR Foundation, Fidelity Biosciences, Gates Ventures

Eli Lilly, Eisai – Public Private Partnership Trials Funding to Sites

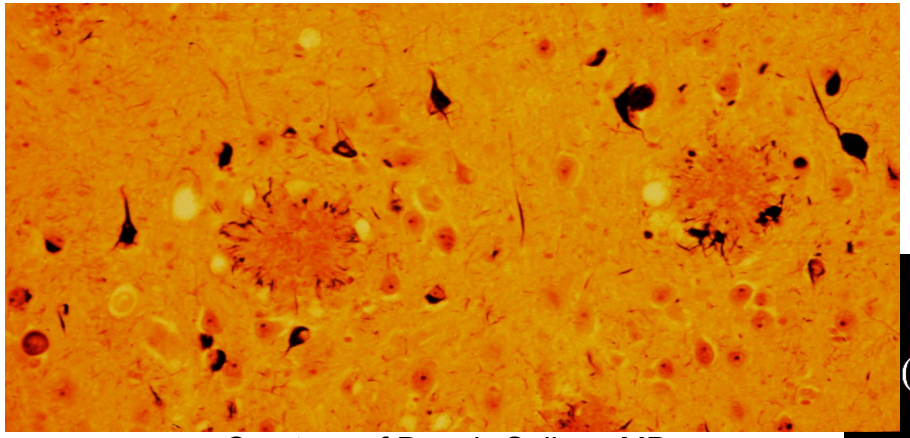
The continuum of Alzheimer's disease



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FDA Draft Guidance

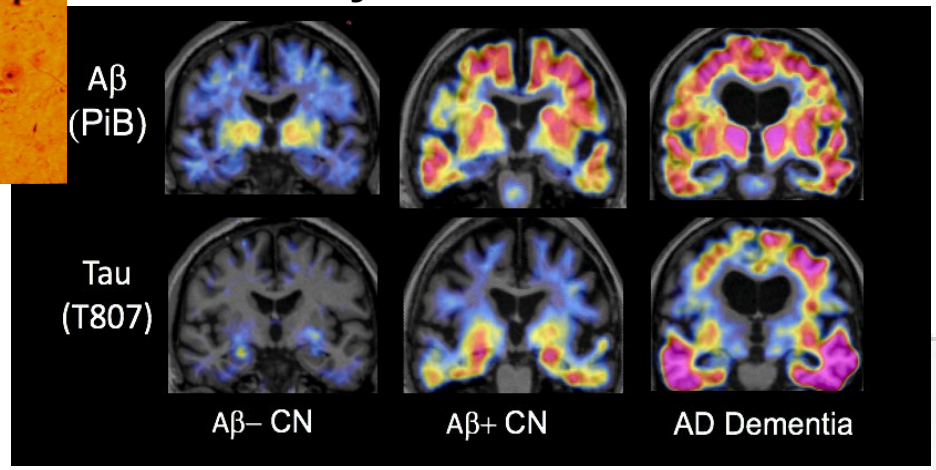
Detecting Alzheimer's Disease During Life

Amyloid (Aβ) Plaques and Tau Tangles



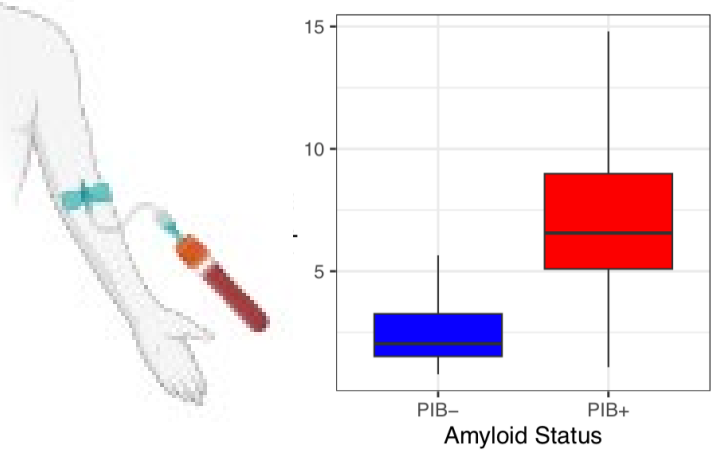
Courtesy of Dennis Selkoe, MD

Amyloid and Tau PET



Sperling, Mormino, Johnson *Neuron* 2014

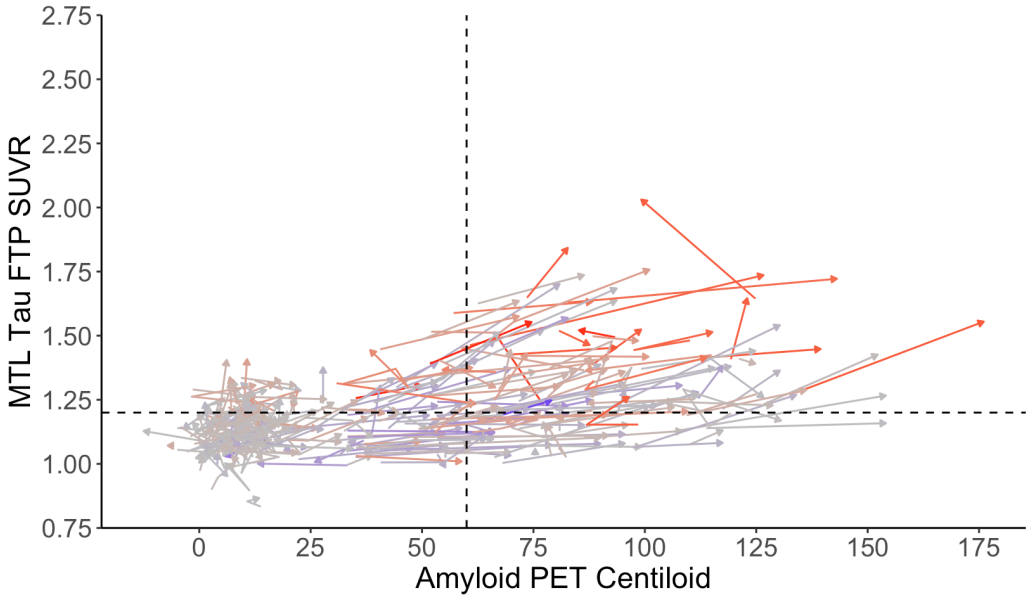
Blood Test



Yang HS et al
Nature Comm In press

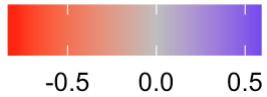
Association of Amyloid and Tau Thresholds with Cognitive Decline in Preclinical AD Preventing the “Ca-Tau-Strophe”

MTL Tau



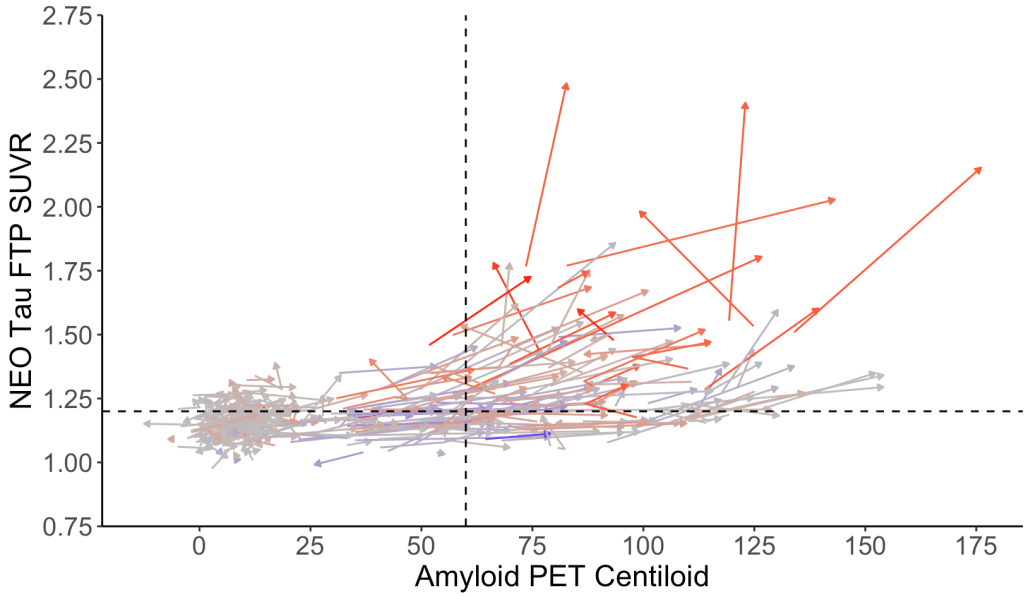
A4 Pbo= 135
HABS = 281

PACC slope



Keith Johnson

Neocortical Tau



	CL ≤ 60 Mean PACC slope	CL > 60 Mean PACC slope
MTL tau > 1.2	-0.026 (n=76)	-0.25 (n=62)
MTL tau < 1.2	-0.0069 (n=229)	-0.0021 (n=38)
T-test results	t = 4.1, p-value <0.0001	t = 4.9, p-value <0.0001

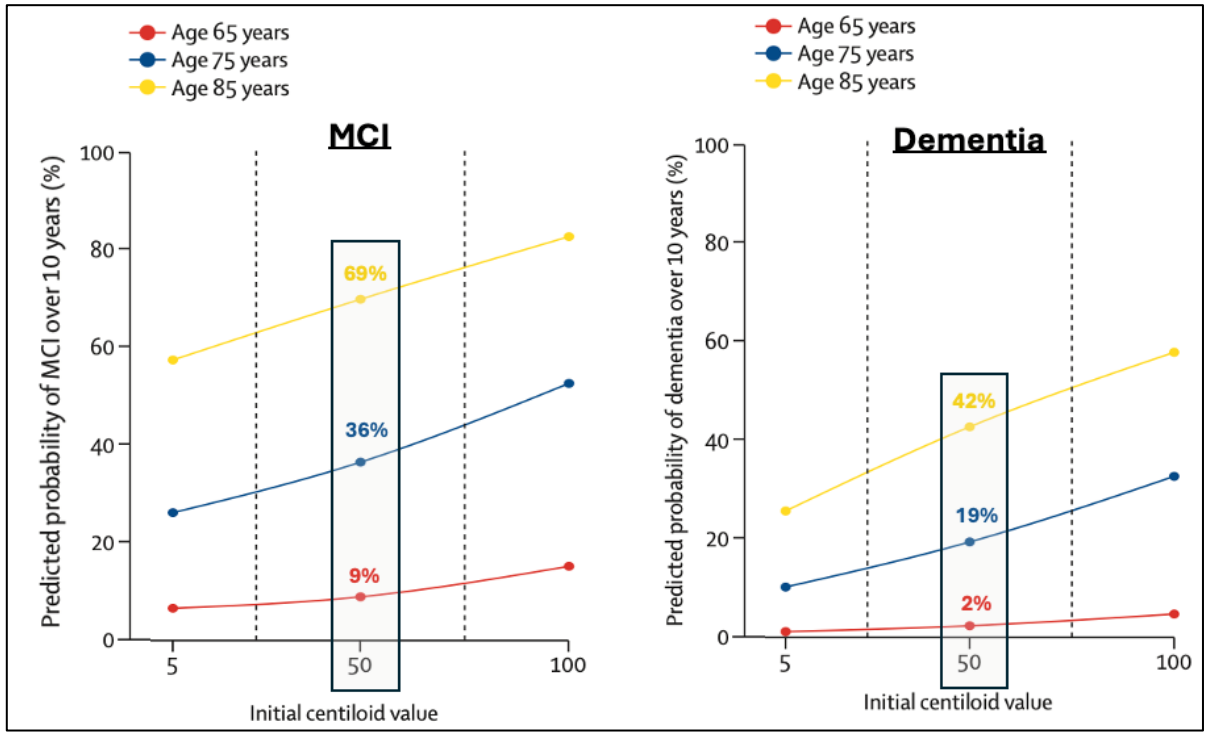
Alzheimer Tau Platform Combination Trial Starting 2026!

	CL ≤ 60 Mean PACC slope	CL > 60 Mean PACC slope
NEO tau > 1.2	-0.028 (n=76)	-0.22 (n=64)
NEO tau < 1.2	-0.0021 (n=229)	-0.0043 (n=36)
T-test results	t = 2.1, p-value = 0.039	t = 3.3, p-value = 0.001

Lifetime and 10-year absolute risk of cognitive impairment in relation to amyloid PET severity: a retrospective, longitudinal cohort study

Lancet Neurol 2025; 24: 1016–25

Clifford R Jack Jr, Mingzhao Hu, Heather J Wiste, David S Knopman, Prashanthi Vemuri, Jonathan Graff-Radford, Val J Lowe, Maria Vassilaki, Petrice M Cogswell, Christopher G Schwarz, Alicia Algeciras-Schimnich, Ronald C Petersen, Terry M Therneau



nature medicine

Article

https://doi.org/10.1038/s41591-026-04206-y

Predicting onset of symptomatic Alzheimer's disease with plasma p-tau217 clocks

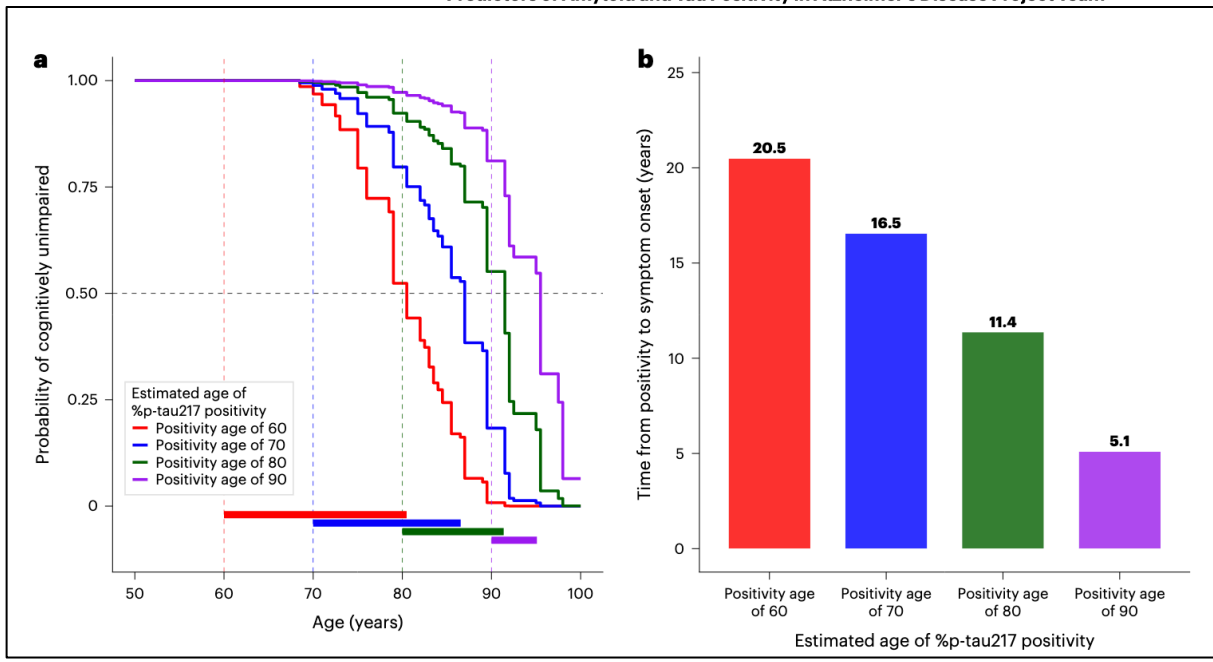
Received: 6 July 2025

Accepted: 31 December 2025

Published online: 19 February 2026

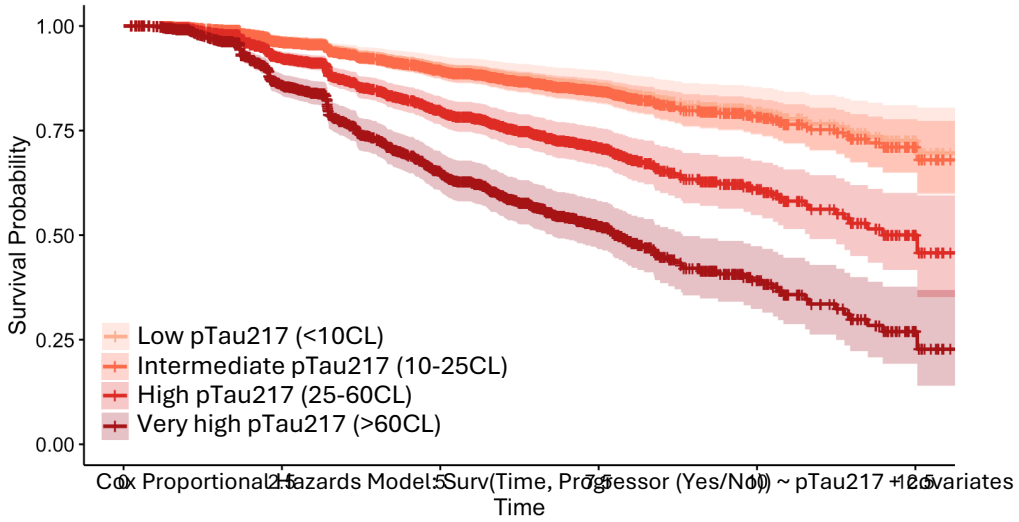
Check for updates

Kellen K. Petersen[1], Marta Milà-Alomà[2,3], Yan Li[1], Lianlian Du[4,5,6,7], Chengjie Xiong[8,9], Duygu Tosun[2,3], Benjamin Saef[1], Ziad S. Saad[10], Lei Du-Cuny[11], Janaky Coomaraswamy[12], Yulia Mordashova[11], Carrie E. Rubel[13], Emily A. Meyers[14], Leslie M. Shaw[15], Jeffrey L. Dage[16,17], Nicholas J. Ashton[18,19,20], Henrik Zetterberg[18,21,22,23,24,25], Kyle Ferber[13], Gallen Triana-Baltzer[10], Michael Baratta[12], Erin G. Rosenbaugh[26], Carlos Cruchaga[8,27,28,29], Eric McDade[1,8], David M. Holtzman[1,8,29], John C. Morris[1,8], J. Martin Sabandal[26], Randall J. Bateman[1,8,29,30], Anthony W. Bannon[31], William Z. Potter, Suzanne E. Schindler[1,8,29] ✉, Alzheimer's Disease Neuroimaging Initiative (ADNI)* & On behalf of the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Plasma Aβ and Phosphorylated Tau as Predictors of Amyloid and Tau Positivity in Alzheimer's Disease Project Team*

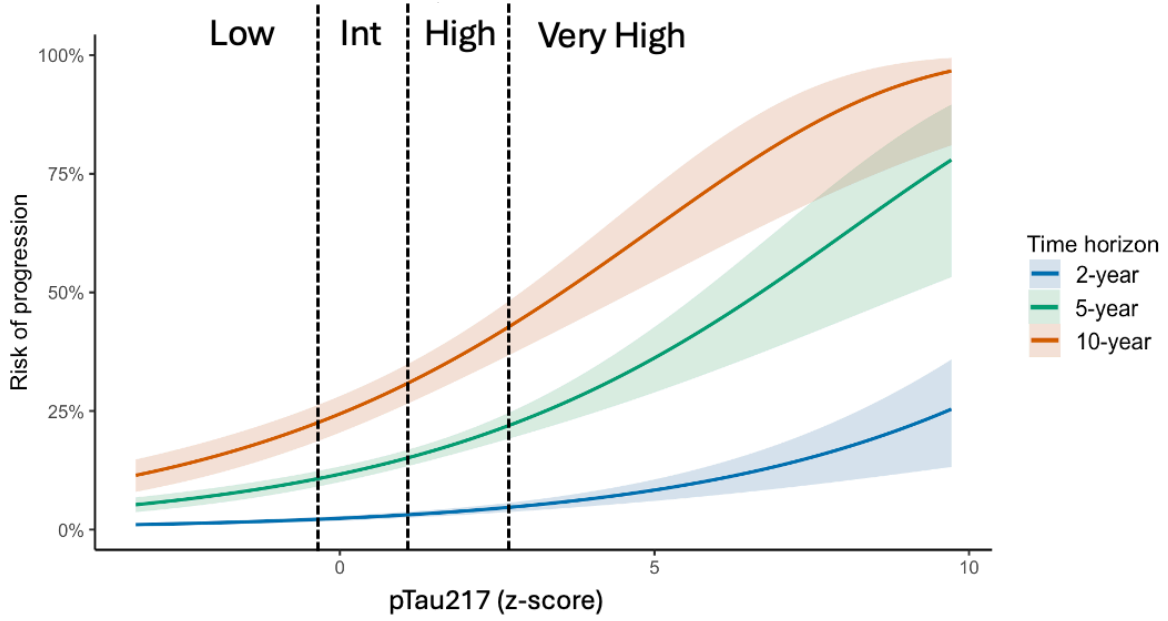


One SD increase in pTau217 is associated with 38% risk of progression to cognitive impairment

Harmonized data across cognitively unimpaired individuals (N=2705) from 6 cohorts



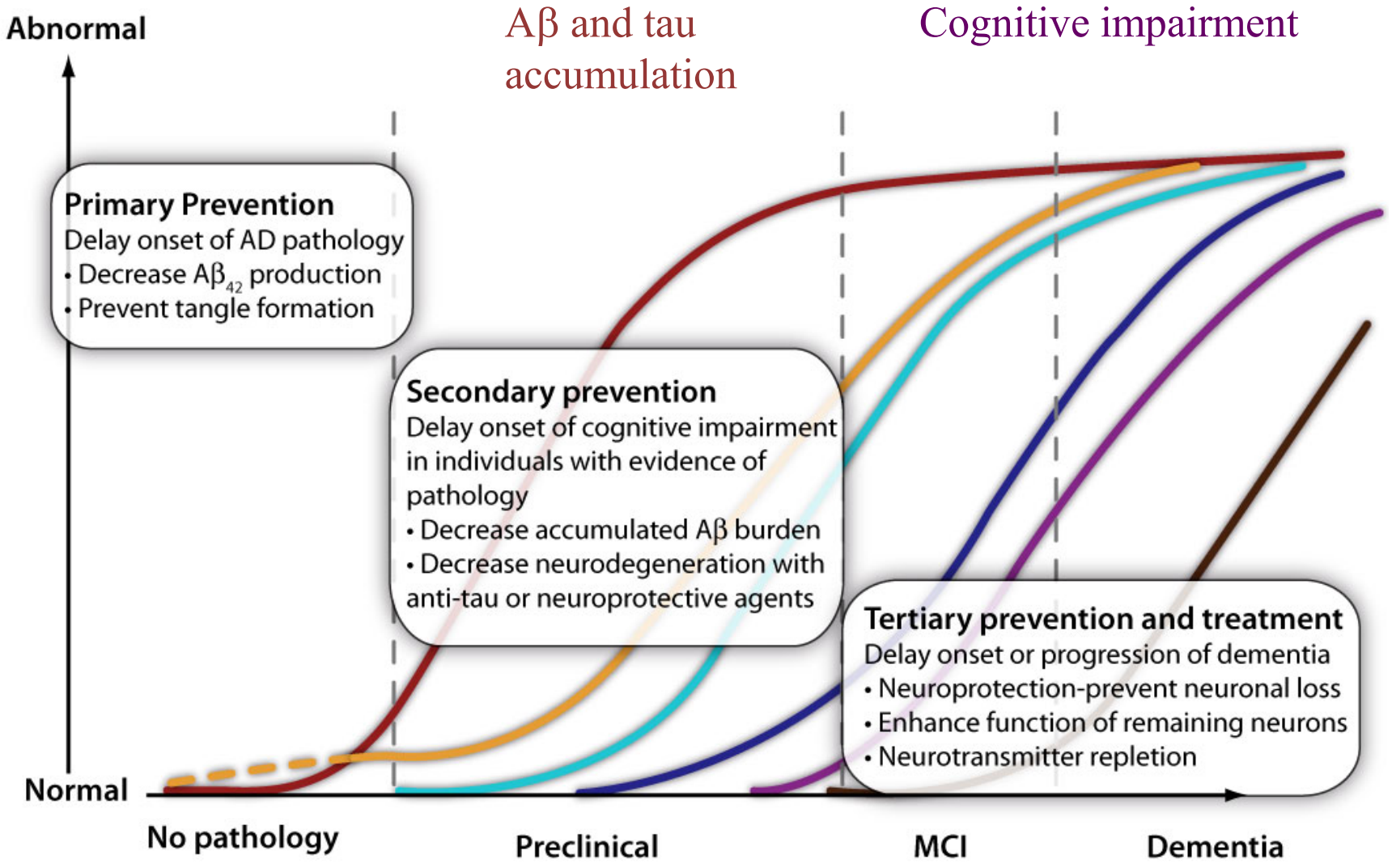
Variable	Estimate	95%CI	*p*
pTau217$_{continuous}$	**1.38**	**[1.31, 1.44]**	**<0.0001**
Age	**1.38**	**[1.23, 1.54]**	**<0.0001**
Female	**0.63**	**[0.53, 0.76]**	**<0.0001**
*APOE*ε4+	1.16	[0.97, 1.39]	0.11
Education	**0.82**	**[0.75, 0.90]**	**<0.0001**



pTau217	Low (n=516)	Int (n=1089)	High (n=594)	Very High (n=506)
2-year	2%	2%	4%	8%
5-year	10%	11%	20%	35%
10-year	21%	22%	39%	63%

Buckley R et al: Under Review
https://medrxiv.org/cgi/content/short/2026.02.06.26345770v1

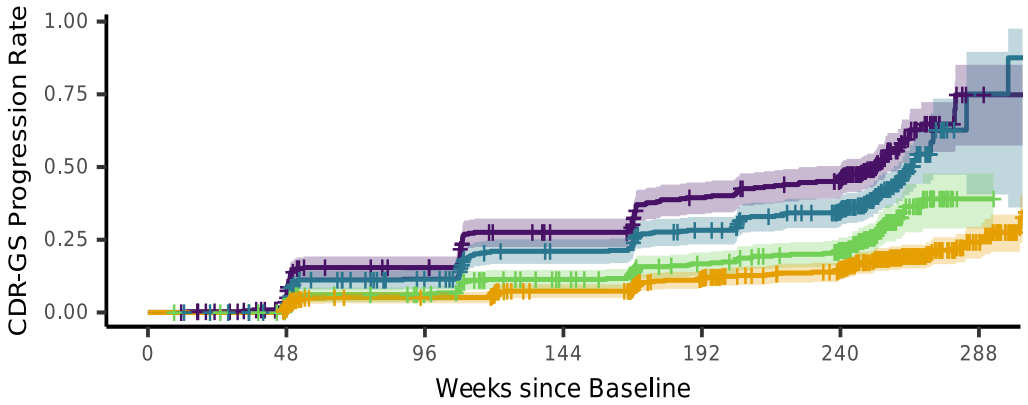
Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease



Sperling, Jack, Aisen *Science Trans Med* 2011

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

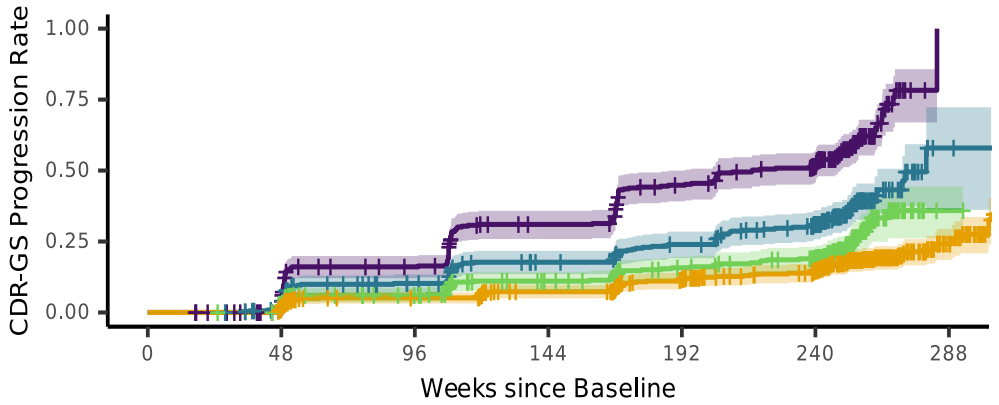
Baseline Amyloid PET



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

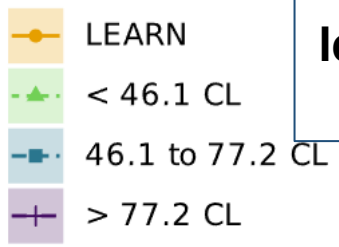
Baseline Plasma P-tau 217

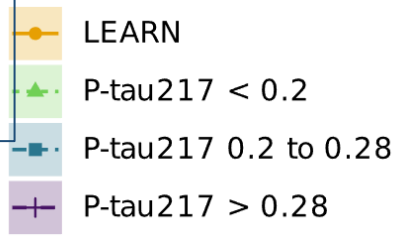


Number at risk

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	273	243	202	1
LEARN	506	492	442	399	334	282	72

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

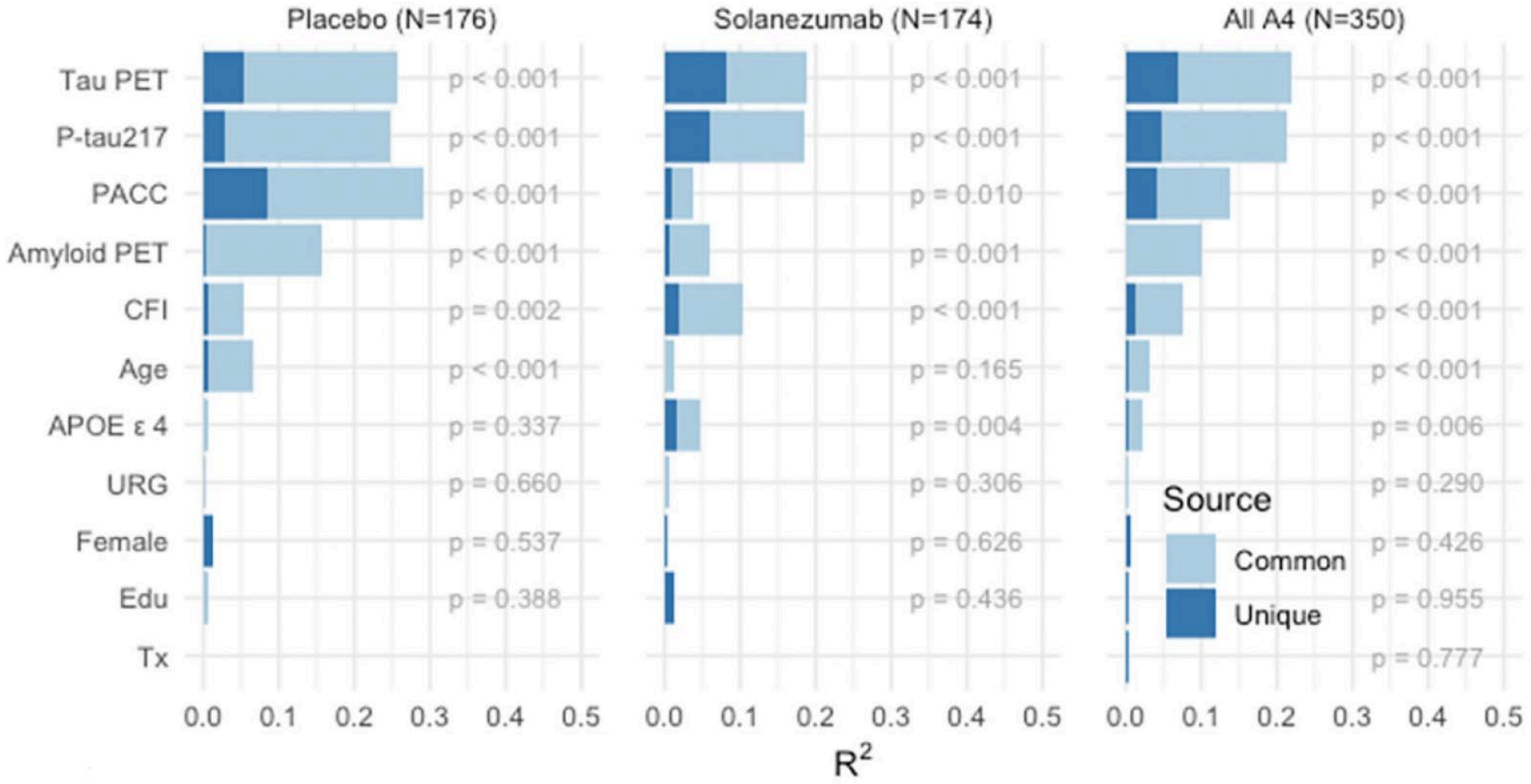




The A4 Study
NOW IS THE TIME

Sperling R et al *JPAD* 2024

Predictors of Cognitive Decline – Tau PET Substudy

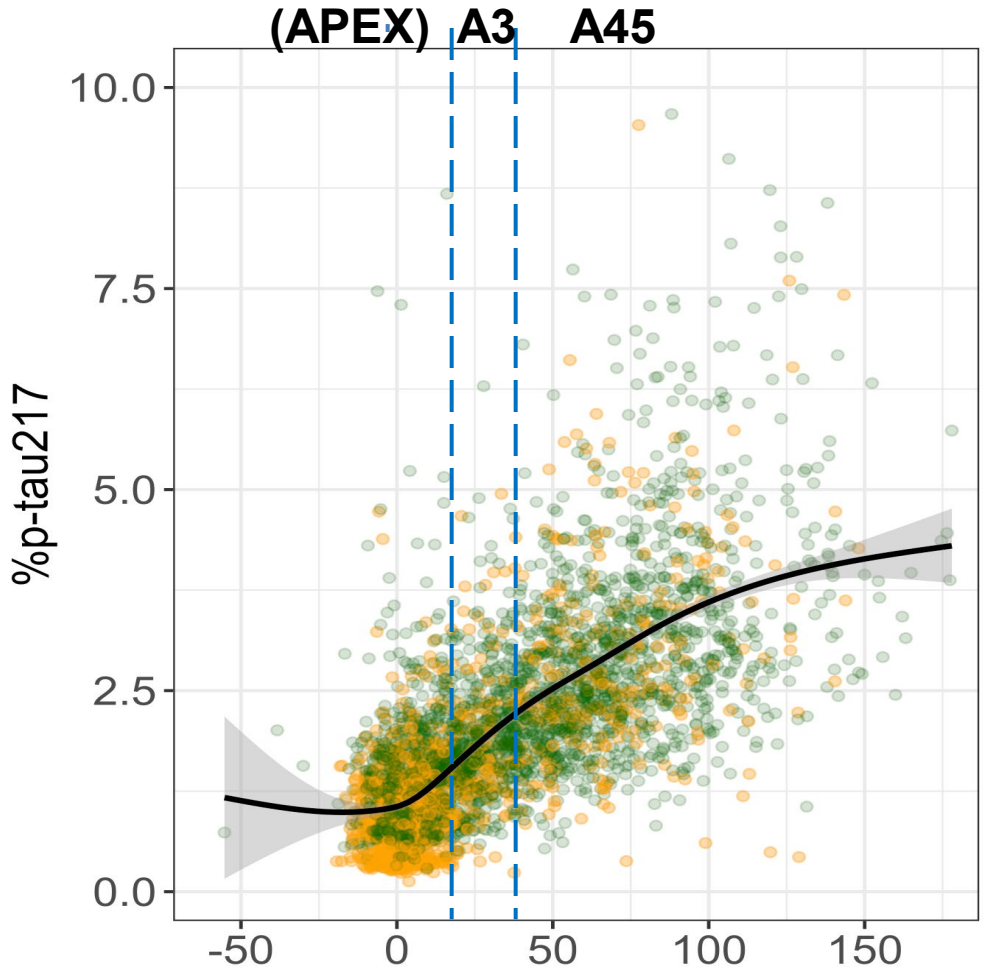


The A4 Study
NOW IS THE TIME

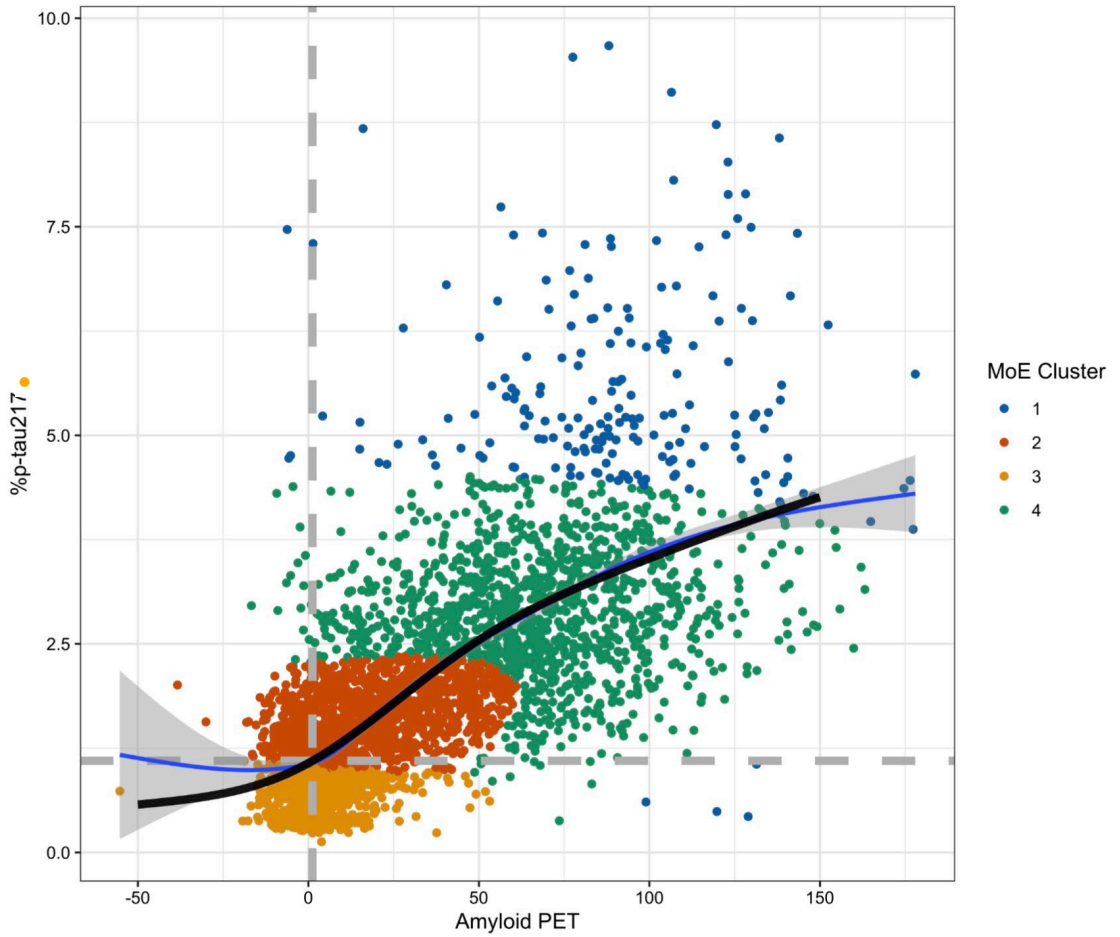
Sperling R et al JPAD 2024

Association of plasma %p-tau217 with Amyloid PET (N=3811)

Amyloid PET; N=3811; ρ=.743



Mixture of Experts Modeling

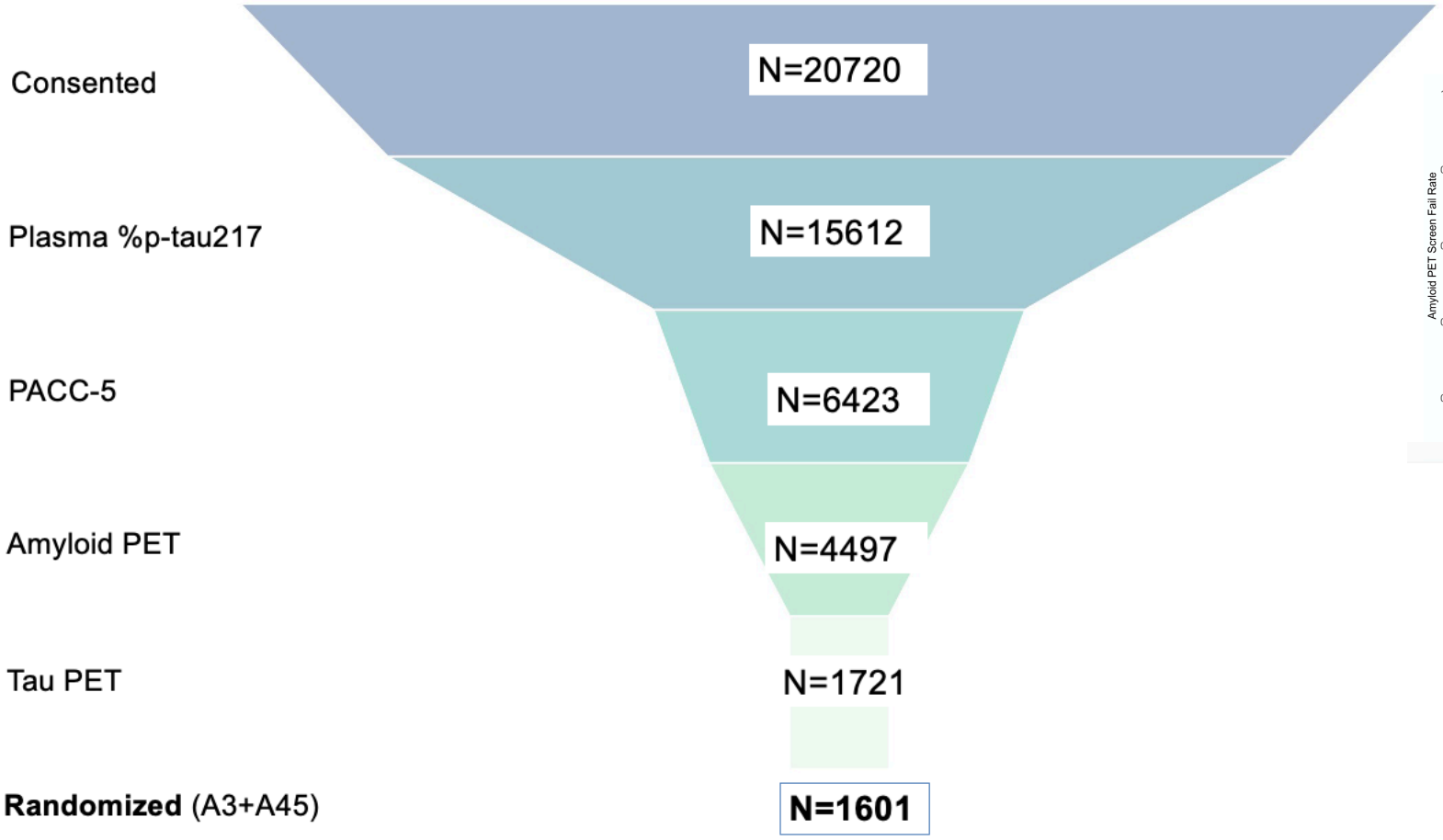


Screening cohort:

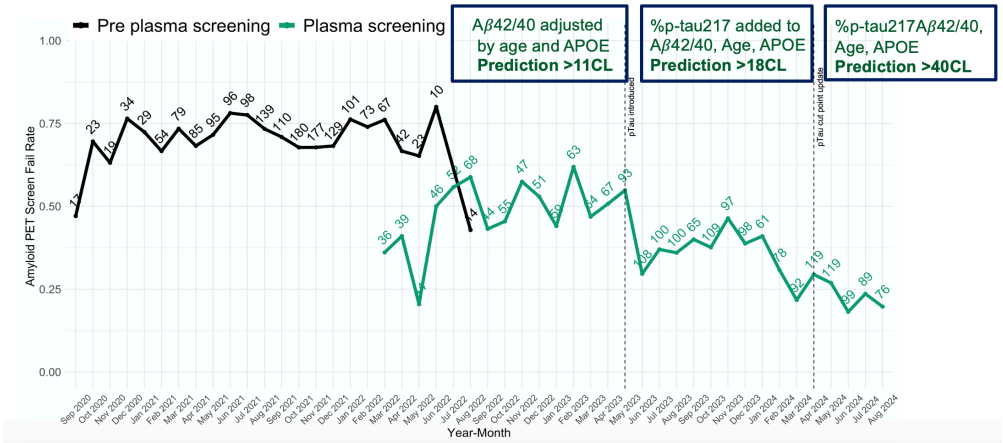
● Pre-plasma screening ● Post-plasma screening

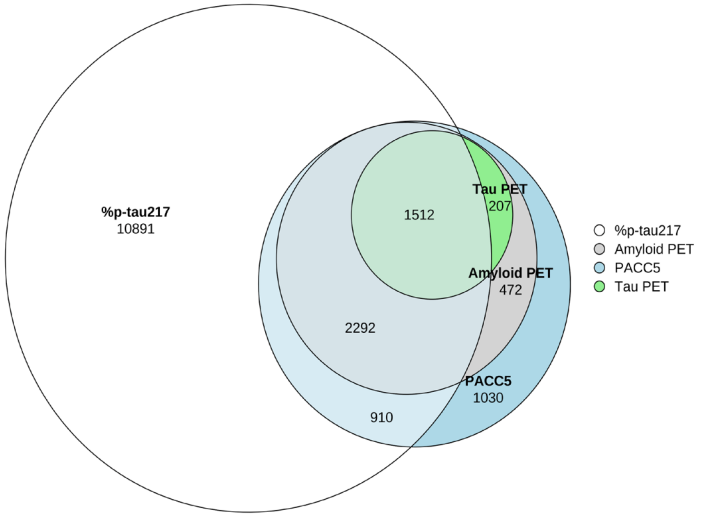
Oliver Langford/Mike Donohue
ACTC/ATRI Biostats

AHEAD 3-45 Study Screening Data



Plasma screening introduced
In Year 2 of AHEAD Enrollment



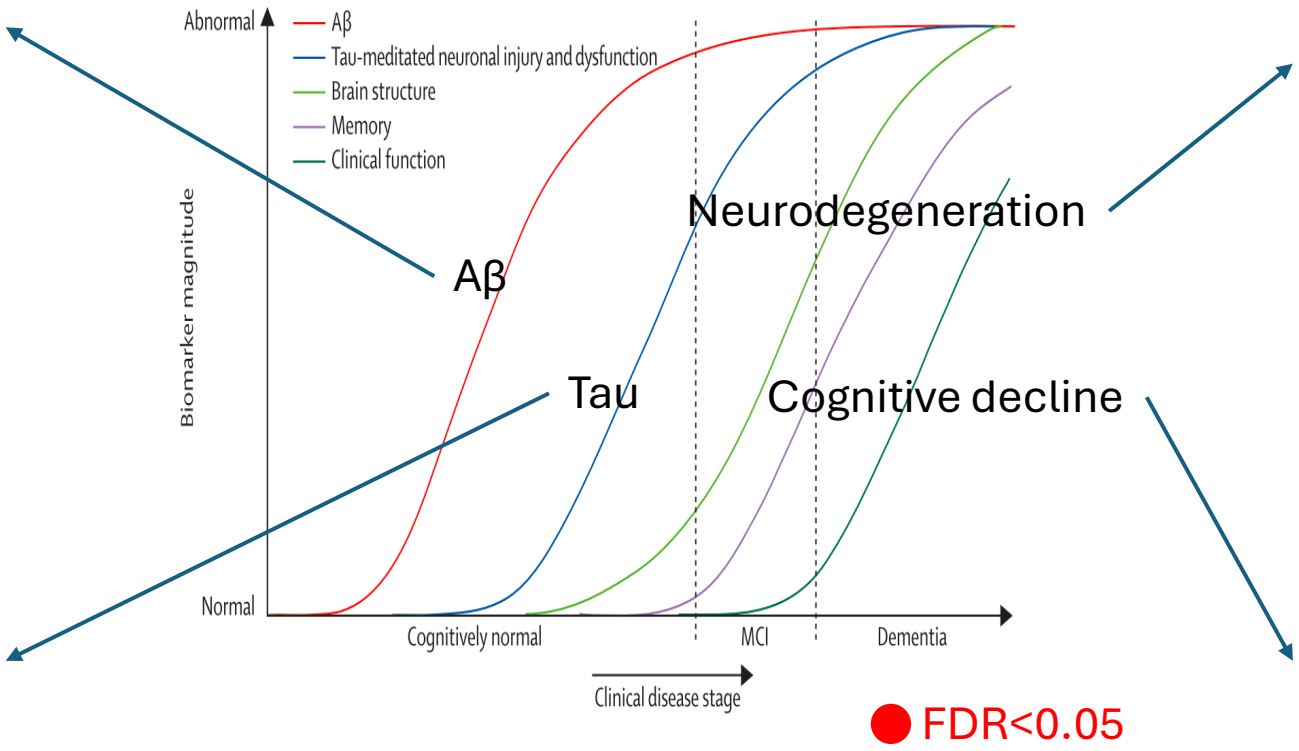


Targeted Plasma Proteomics (NULISA) Prediction of Longitudinal Change – Harvard Aging Brain Study

Aβ Accumulation

Hippocampal Volume

Baseline Plasma → **Longitudinal** Biomarker and Cognition

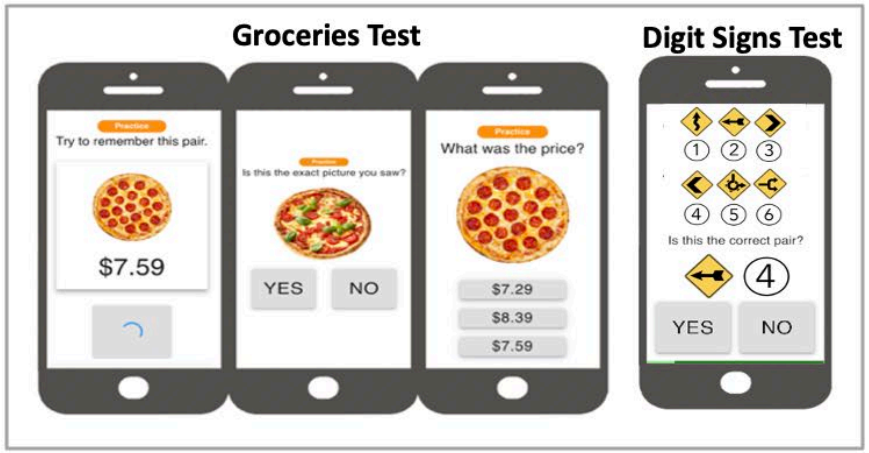


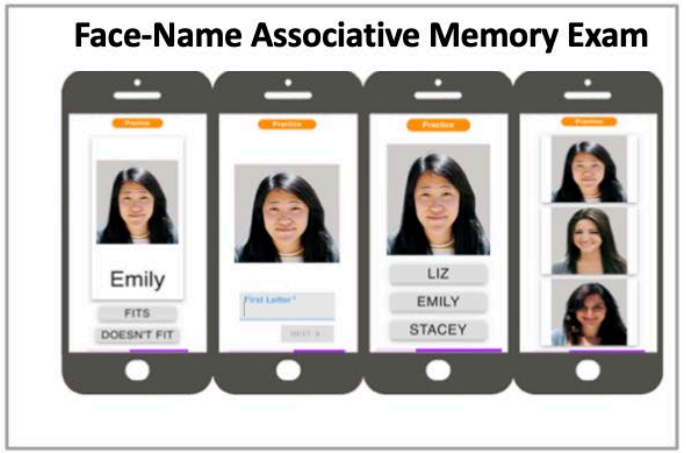
Inf Temporal Tau

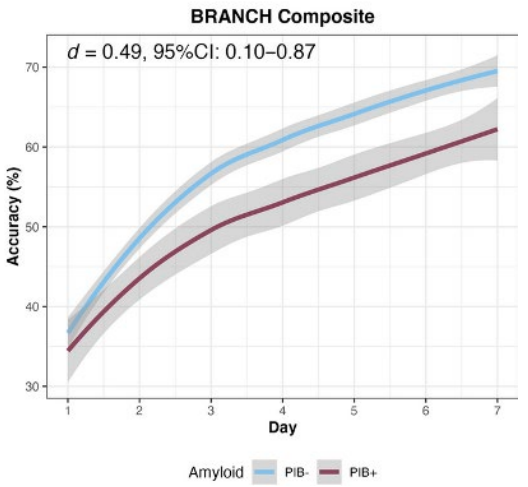
Cognition (PACC5)

Harvard Aging Brain Study Data Yang HS et al. In preparation

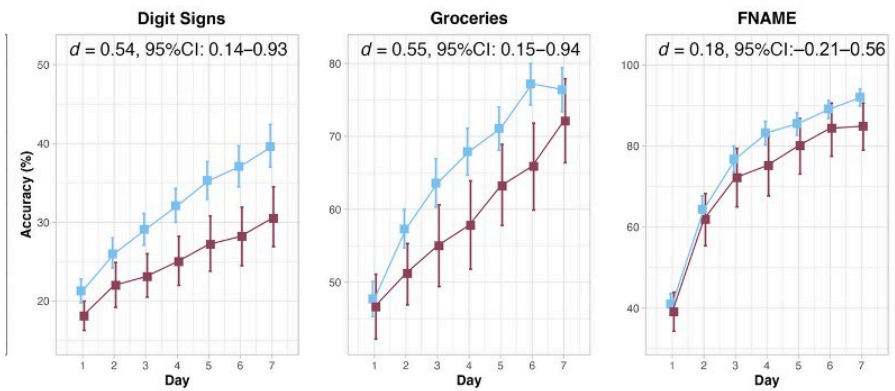
Digital Multi-Day BRANCH Learning Curves Diminished Learning in Preclinical AD





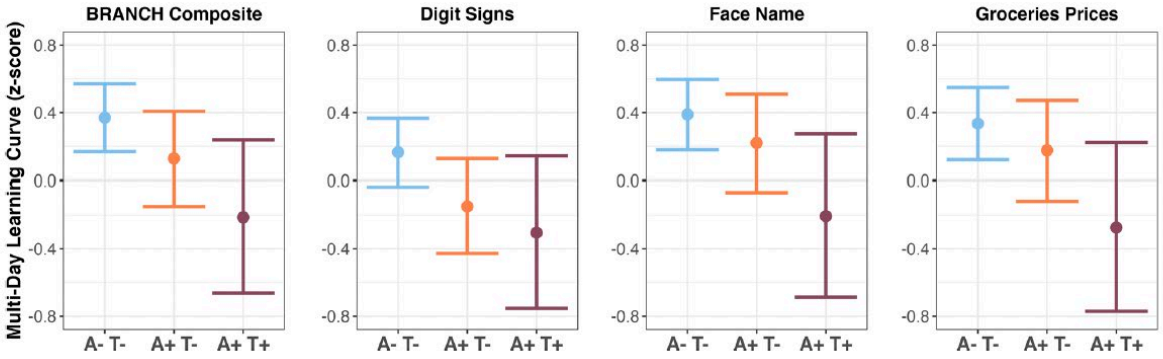


Amyloid Status



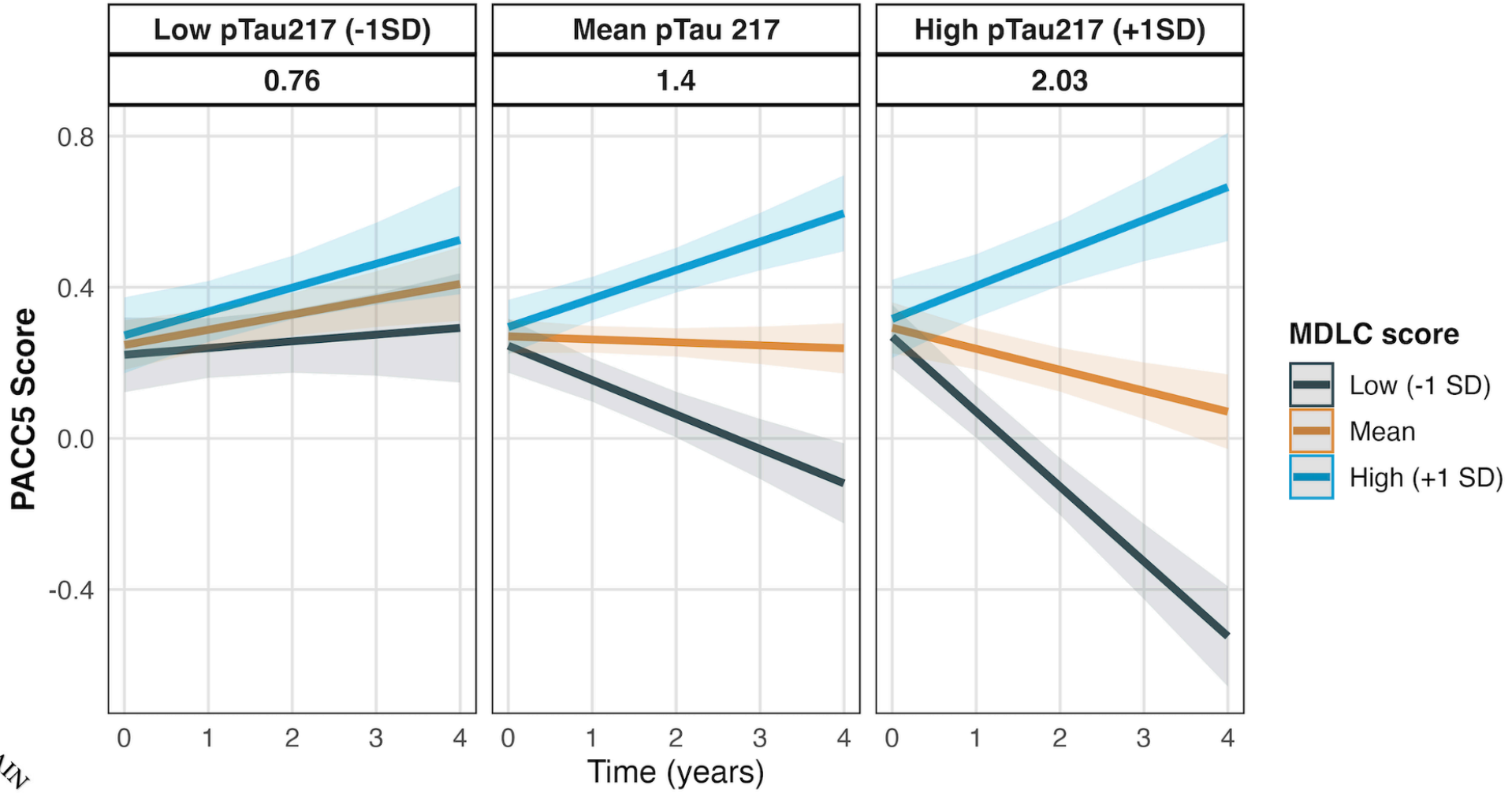
Papp K et al *Annals of Neurology* 2024

Amyloid and Tau Status



Jutten R et al *npj Digital Medicine* 2025

Digital Multi-Day BRANCH Learning Curves Adds to Plasma Biomarker Prediction of Cognitive Decline



Kim H et al *Alz & Dementia (In press)*

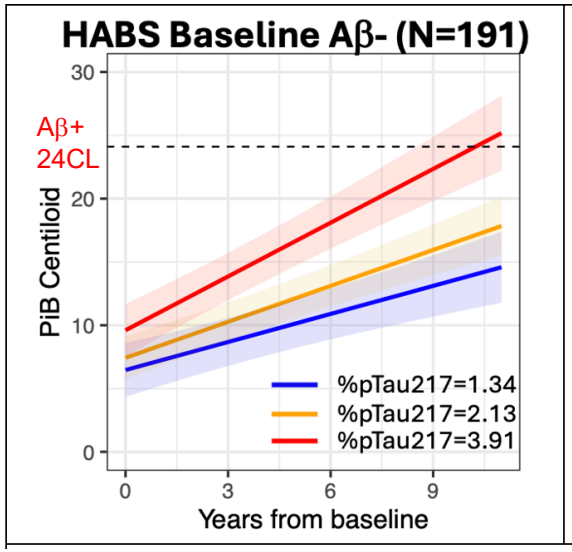
HARVARD AGING BRAIN

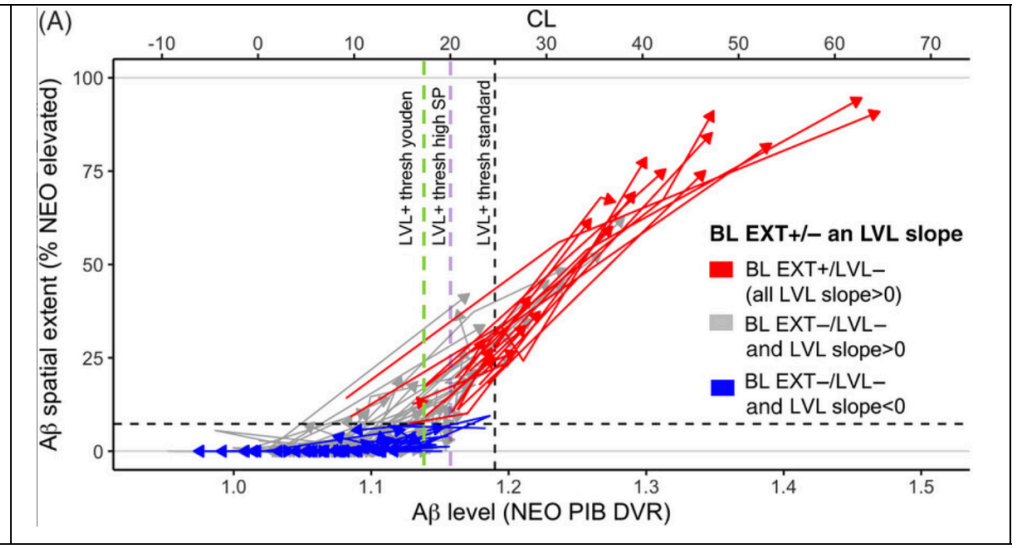
Massachusetts General Hospital ~ Harvard Medical School ~ Brigham and Women's Hospital

Predicting Future "Amyloid Positivity"
Preliminary Data from Harvard Aging Brain Study and LEARN Study

HARVARD AGING BRAIN

Massachusetts General Hospital ~ Harvard Medical School ~ Brigham and Women's Hospital

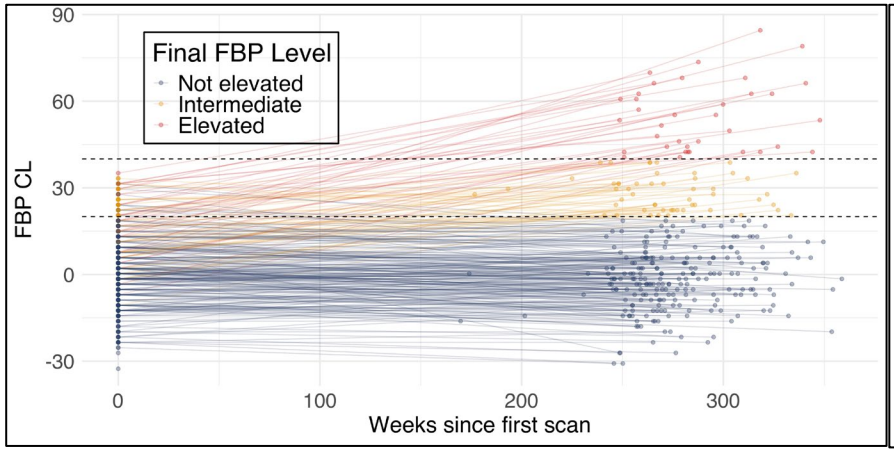


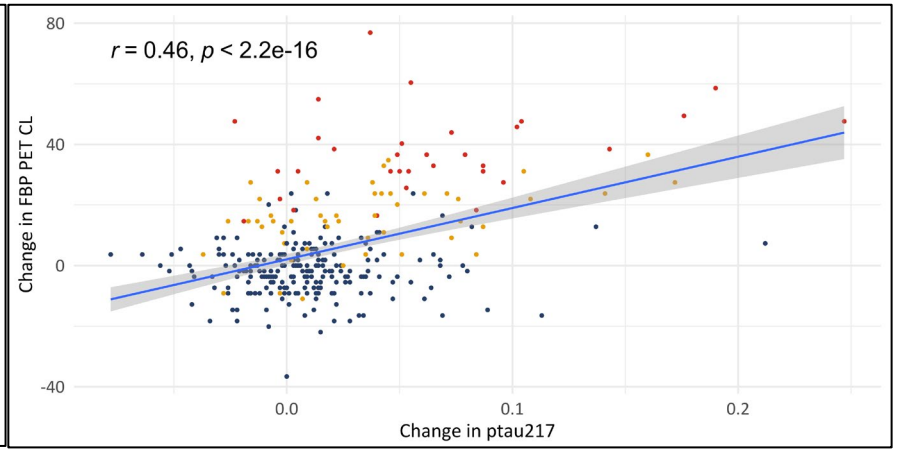


Yang HS et al *Nature Comm (In press)*

Farrell M et al *Alz & Dementia* 2024

LEARN





Summary and Remaining Challenges

- Convergent evidence that higher baseline amyloid and tau is predictive of faster decline and clinical progression
  - Biomarkers already used to select participants for prevention trials
- Still unexplained variance, heterogeneity in rates of decline
  - Need markers of neural reserve, vascular and metabolic processes
  - Need synaptic markers – are we making the brain work better? Digital cognitive testing may help
- More longitudinal data needed in clinical trials to model therapeutic response and time lags
  - Not clear that fluid (soluble forms) biomarkers are changing in parallel with imaging (aggregated forms) outcomes

Acknowledgments

- Keith Johnson and colleagues from Harvard Aging Brain Study
- Paul Aisen and ATRI/ACTC Clinical Trial Teams
- AHEAD Teams at Eisai, A4 Teams at Eli Lilly
- Clinical trial site investigators and staff
- Most of all - the research participants and their study partners!

- Data available:
  - –Harvard Aging Brain Study: https://habs.mgh.harvard.edu/
  - –A4 Study/LEARN: https://www.a4studydata.org/
  - –AHEAD 3-45 Study (screening): https://www.aheadstudydata.org/