Leveraging Data and Analytic Approaches in ADNI for Enhanced Clinical Trial Participant Selection and Characterization

Jeffrey L. Dage, PhD
Indiana University School of Medicine
Senior Research Professor of Neurology
Senior Research Professor of Medical & Molecular Genetics
Primary Member, Stark Neurosciences Research Institute

https://medicine.iu.edu/faculty-labs/dage

Disclosures of Interest

Jeffrey L. Dage, PhD Indiana University School of Medicine

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- Indiana Alzheimer's Disease Research Center (IADRC) P30AG072976
- National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) U24AG021886
- IU/JAX/PITT MODEL-AD Center U54AG054345
- IUSM Alzheimer's Disease Drug Discovery (Treat-AD) Center U54AG065181
- Centrally-linked Longitudinal Peripheral Biomarkers of AD in Multi-ethnic Populations (CLEAR-AD) U19AG074879
- Epidemiological and Genetic Investigations of Blood-Based Biomarkers for Alzheimer's Disease in the Multiethnic, Washington Heights, Inwood, Columbia Aging Project (WHICAP) R01AG072474

CTSI Funding

2023-Effects of Ship1 inhibitor, TAD000032, on interstitial brain levels of AD biomarkers

Institutional Funding

Neurology, Stark Neuroscience Research Institute

Consultancies/Advisory

- Genotix Biotechnologies Inc
- Karuna Therapeutics
- AlzPath Inc
- Gates Ventures
- ADDF
- AbbVie
- Prevail Therapeutics
- Eisai co ltd
- Voyager Therapeutics
- Monument Biosciences

Industry Support

- Roche Diagnostics *Title: Longitudinal Early-onset AD Study (LEADS)/RD005665
- Lilly Research Award Title: Discovery of blood-based biomarkers of Lewy body pathology

Speakers Bureau

Eli Lilly and Company

Clinical Trials

Past Lilly Neuroscience Trials (2014-2020)

Roche Diagnostics - RD006263

Patents

Compounds and methods targeting human tau

Prevention of axonal damage using antibody binding to amyloid beta 1-42

-I am a minor shareholder of Eli Lilly and Company. I have stock or equity as founder of Monument biosciences, advisor to AlzPath Inc, and advisor to Genotix biotechnologies.
-All financial relationships have been mitigated

Clinical Trial Use of Biomarkers – Gaps/Barriers

Interpretation of and comparison with competitor data

Pre-Clinical - Phase 1

Barriers in Discovery

- Sample type and volume
- Accessible platform
- Cost and throughput
- Range
- Effect size
- Assay performance and validation

Early POC

Barriers in Development

- Effect size
- Sources of variation
- Relationship with common measures
- Cost and throughput
- Accessible platform
- Assay performance and validation

Personalized Medicine

Or

End point

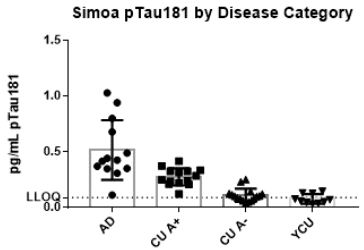
Barriers preventing Use

- Cut points
- PPV and NPV
- Risks
- Sources of variation in real world
- Relationship with clinical measures
- Accessible platform
- Cost
- Change management

The Many Uses of Plasma P-tau

A marker of Alzheimer's Disease Neuropathological Change used for:

Clinical Trial Enrollment, Associations with Pathology, Diagnosis, Prognosis, Risk Screening, pharmacodynamics

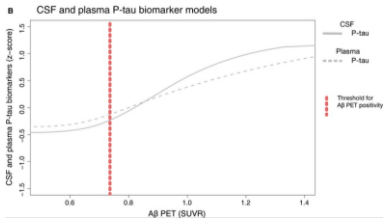


2018

Mielke et al., Alz Dem

P-TAU181 IS ASSOCIATED WITH AMYLOID AND TAU PET

2018

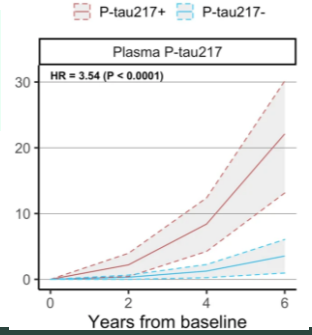


2019

Thijssen et al., Nat Med
Janelidze et al., Nat Med
Palmqvist et al., JAMA

Diagnostic Value of P-tau181 and superiority of P-tau217 established

2020

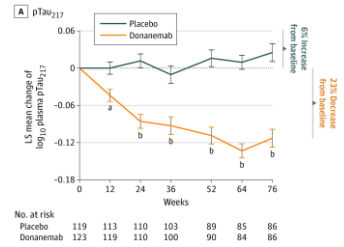


2021a

Mattsson-Carlgren et al., EMBO Mol MEd

Independent effects of plaque and tangle density on plasma P-tau217

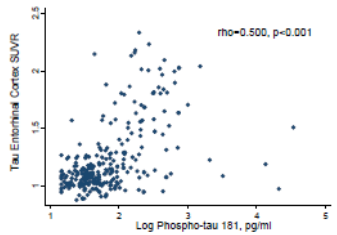
2021b



2022

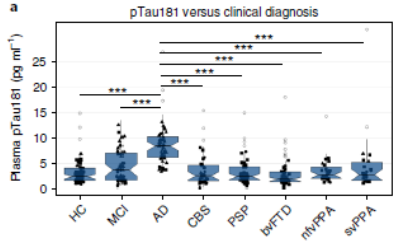
Biomarker Discovery Study-LZAT

PLASMA P-TAU181 IS ASSOCIATED WITH AMYLOID PET AND DIAGNOSIS



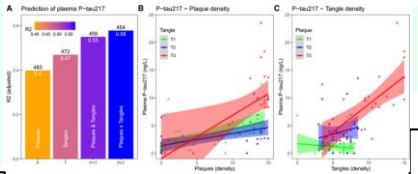
Palmqvist et al., EMBO Mol Med

Relative trajectories of P-tau217 in CSF and Plasma



Cullen et al., Nat Commun
Palmqvist et al., Nat MED
Pereira et al., Brain

Prognosis and Risk screening with P-tau217



Pontecorvo et al., JAMA Neurol

Demonstrated pharmacodynamic response to anti-amyloid therapy

Pharmacodynamic use of P-tau Biomarkers

P-tau217 levels increase at a rate of about 7% every six months in a mild and moderate clinical AD population but changes are variable between subjects

Understanding Longitudinal Changes in P-tau217, Concentration pg/mL in Preparation for Interpretation as PD biomarker					
TrT	**Study**	**N**	**52 Week Change P-tau pg/mL**	**SD ChP-tau pg/mL**	**95%CI**
PL	LZAM	187	0.065	0.223	(0.032-0.097)
PL	LZAN	241	0.083	0.271	(0.048-0.117)
TrT	**Study**	**N**	**80 Week Change P-tau pg/mL**	**SD ChP-tau pg/mL**	**95%CI**
PL	LZAM	175	0.082	0.245	(0.046-0.119)
PL	LZAN	191	0.100	0.269	(0.062-0.138)

- Predicted effect size (AD vs Healthy volunteers) = 3
- Using a simple two sided t-test, sample size to detect -33% change from BL with 0.9 power = 35/group

P-tau217 Levels from Stored Sampled Collected During a Phase 1b Study where an Amyloid Reduction is Observed

Donanemab, (LY3002813), is a humanized IgG1 antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in brain amyloid plaques.

I5T-MC-AACD (NCT02624778) Phase 1b:

A Single- and Multiple-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Intravenous Doses of LY3002813 in Patients With Mild Cognitive Impairment Due to Alzheimer‘s Disease or Mild to Moderate Alzheimer’s Disease
(Last patient visit, 5 Nov 2019)

Objective: Safety, tolerability, PK, PD (florbetapir PET), and immunogenicity.

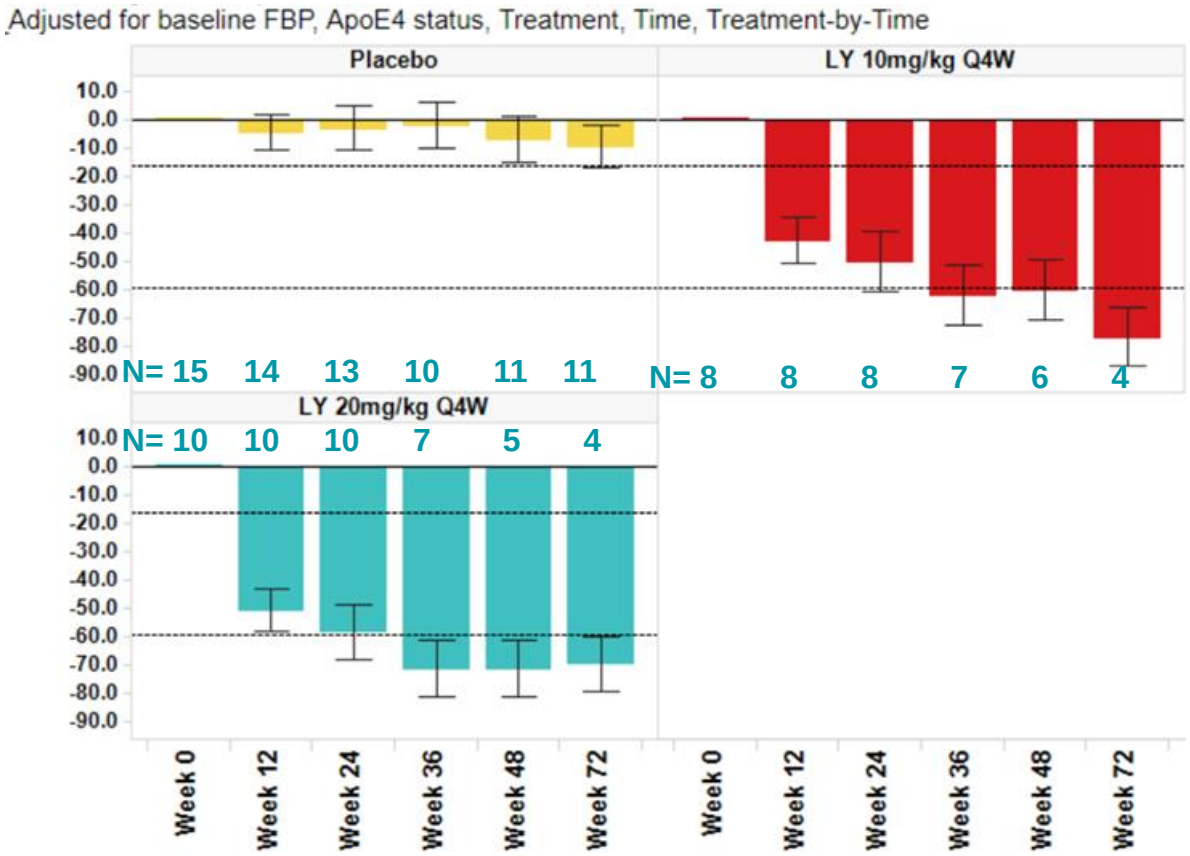
Study Population: Florbetapir-positive prodromal-moderate AD

- NIA-AA research diagnostic criteria [2, 3]
- Age ≥ 50 years
- FCSRT ≤ 27 free recall, CDR 0.5-2, MMSE 16-30
- Excluded for history/evidence of macrohemorrhage or >4 microhemorrhages on MRI

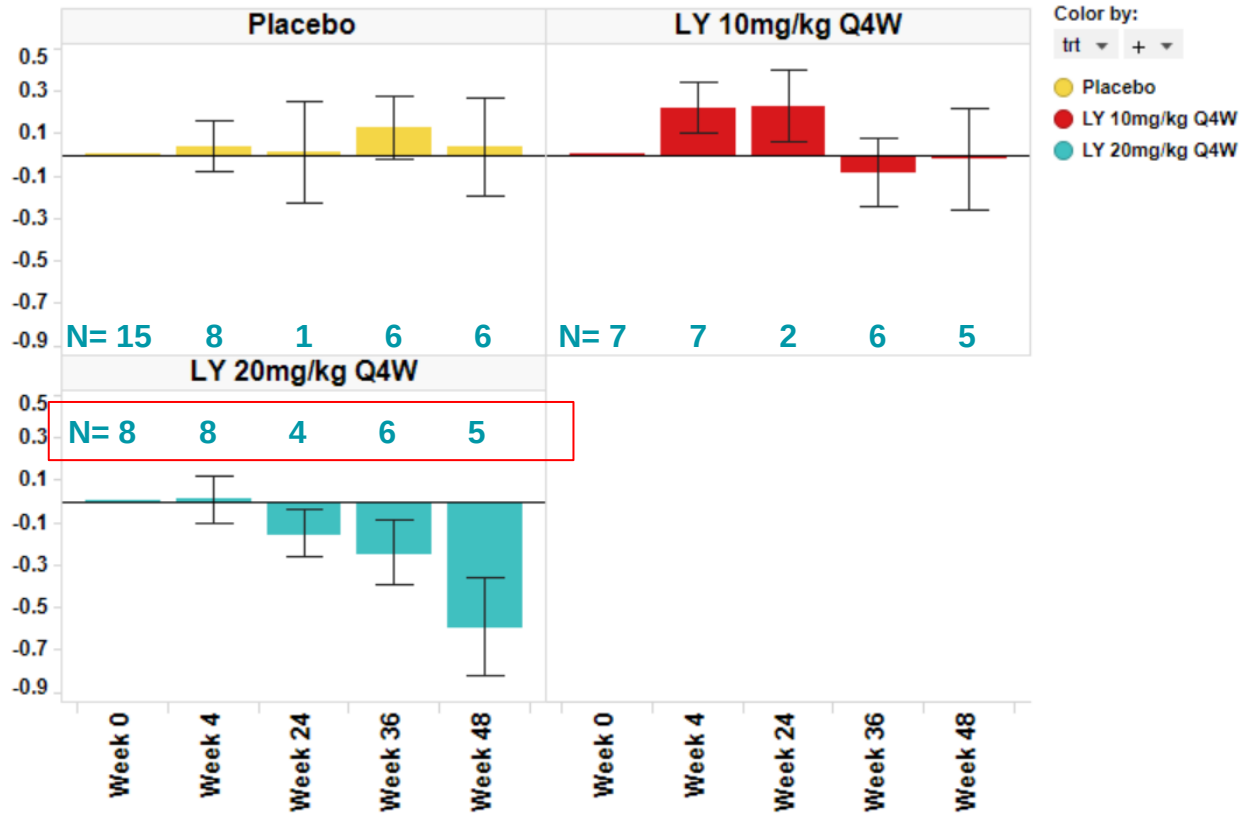
With a Significant Reduction in Amyloid there is an Observed Dose and Time Related PD Effect on Plasma P-tau217 Levels

Unpublished

Amyloid PET change from BL

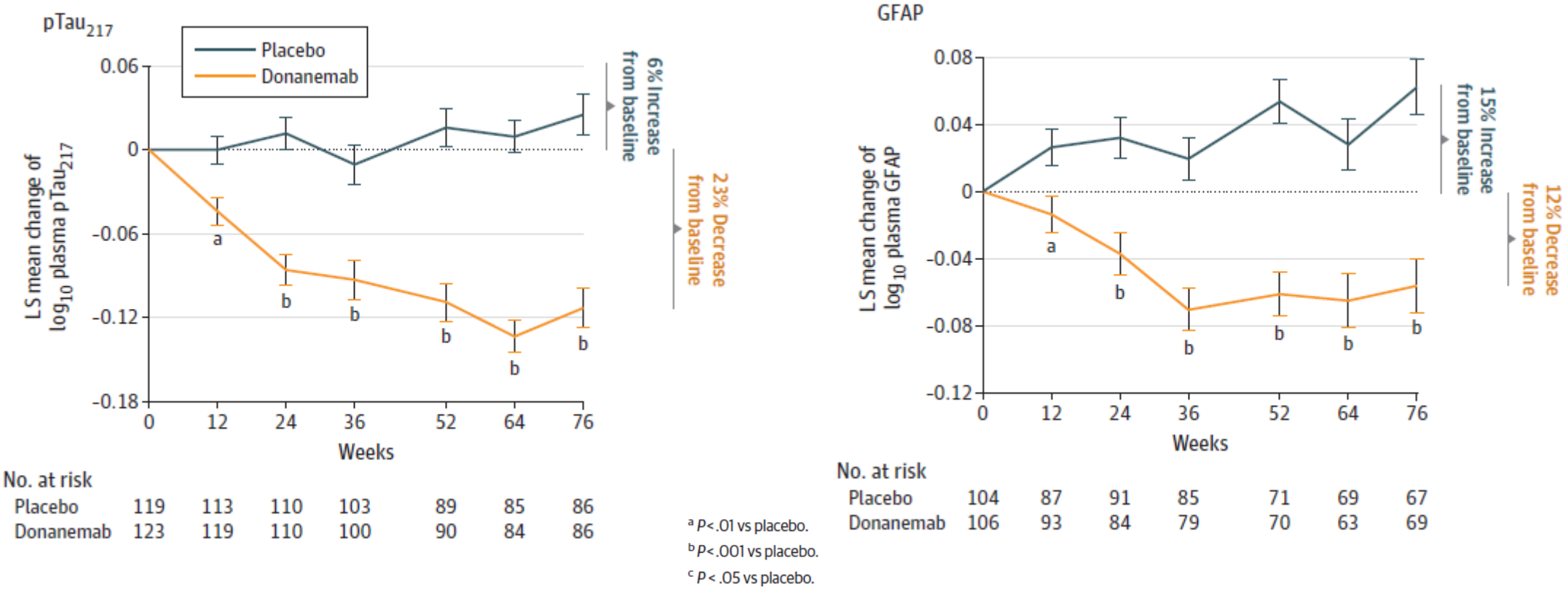


Log (P-tau217) change from BL



p-value - vs placebo: 0.868 0.566 0.091 0.062

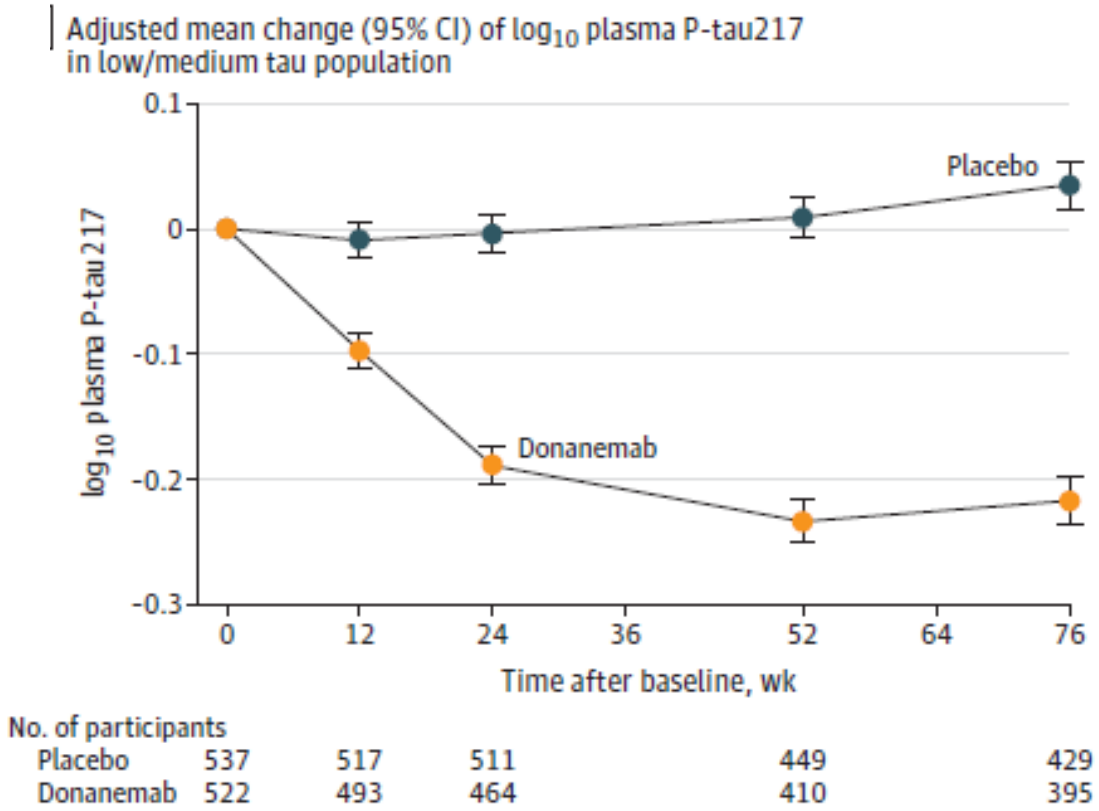
Pharmacodynamic Change in Blood Biomarkers with Amyloid Removal - Donanemab (Phase 2 Study)

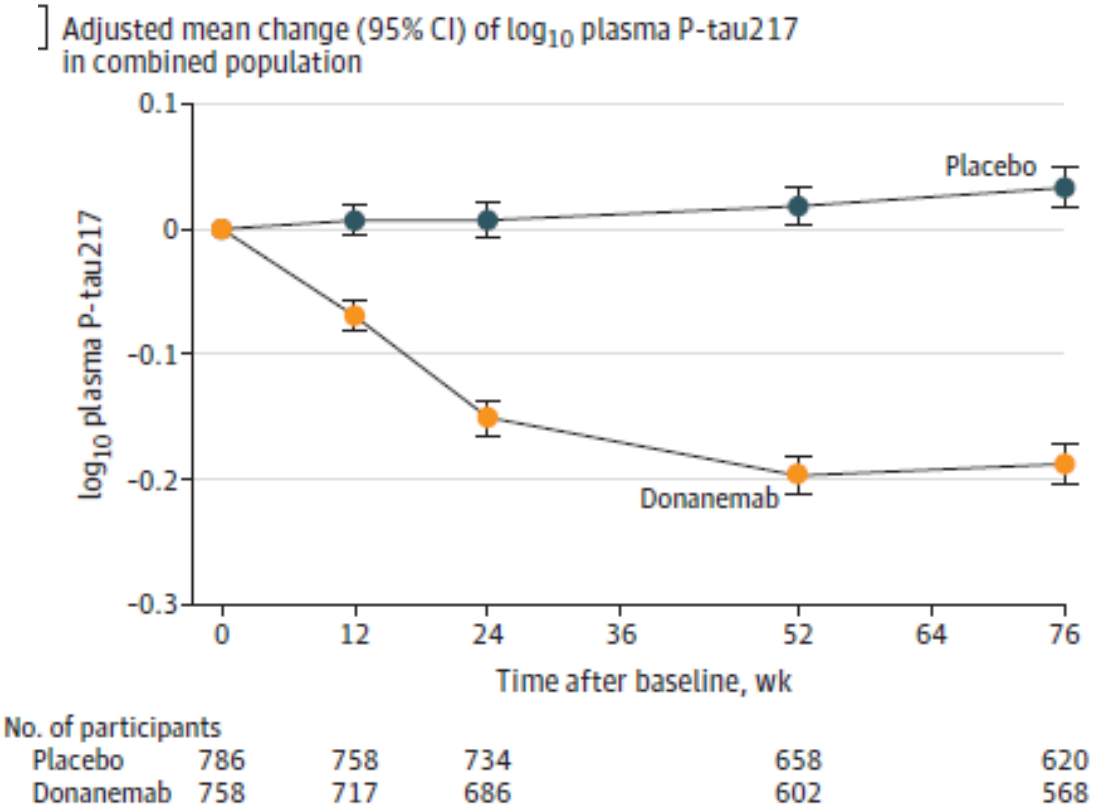


[a] $P<.01$ vs placebo.
[b] $P<.001$ vs placebo.
[c] $P<.05$ vs placebo.

Pontecorvo MJ, Lu M, Burnham SC, et al. Association of Donanemab Treatment With Exploratory Plasma Biomarkers in Early Symptomatic Alzheimer Disease: A Secondary Analysis of the TRAILBLAZER-ALZ Randomized Clinical Trial. JAMA Neurol. Oct 17 2022;doi:10.1001/jamaneurol.2022.3392

Replication of PD effect of Donanemab (Phase 3 Study)





Sims et al., JAMA August 8, 2023 Volume 330, Number 6

Alzheimer's Disease biomarkers help enable drug discovery

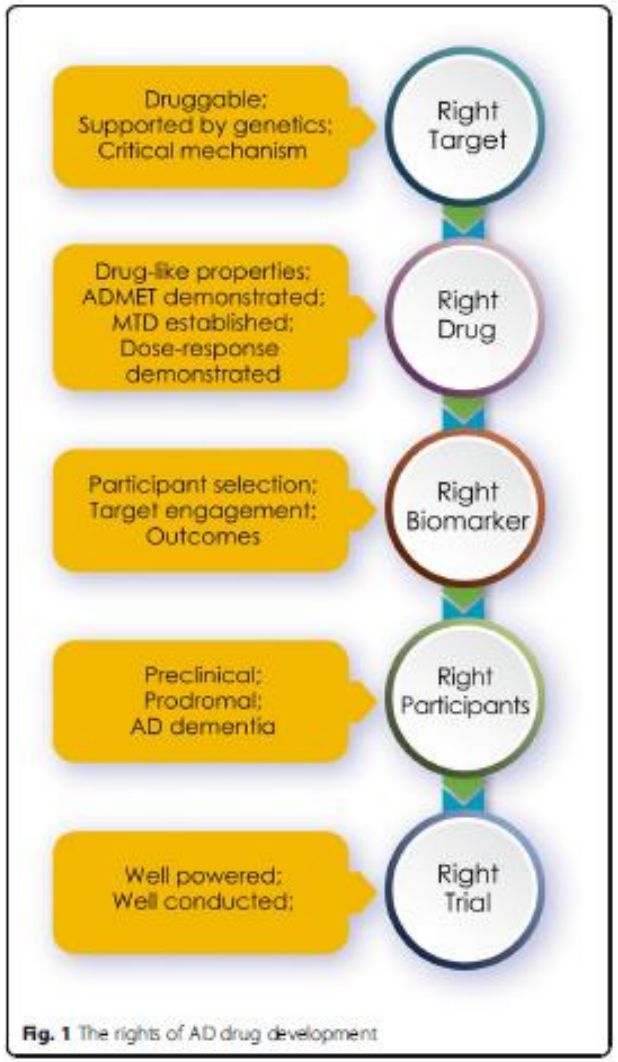


Fig. 1 The rights of AD drug development

REVIEW Open Access

The "rights" of precision drug development for Alzheimer's disease

Jeffrey Cummings[1*], Howard H. Feldman[2] and Philip Scheltens[3]

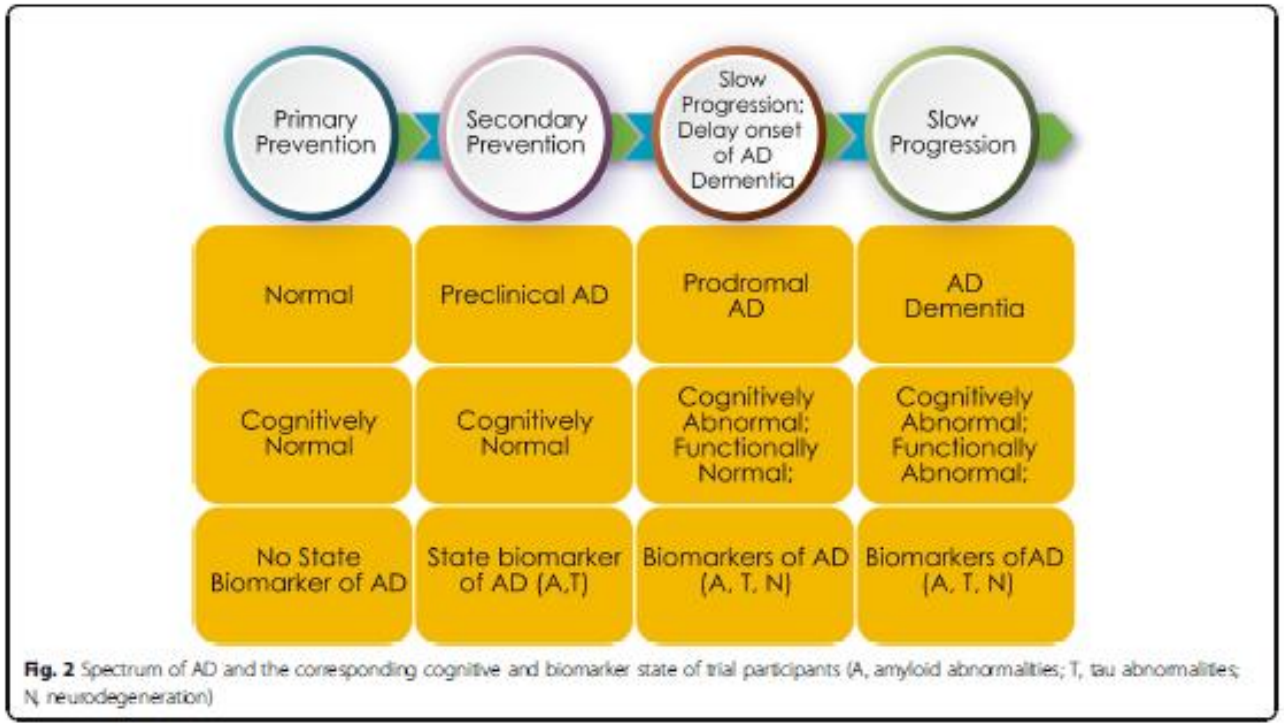


Fig. 2 Spectrum of AD and the corresponding cognitive and biomarker state of trial participants (A, amyloid abnormalities; T, tau abnormalities; N, neurodegeneration)

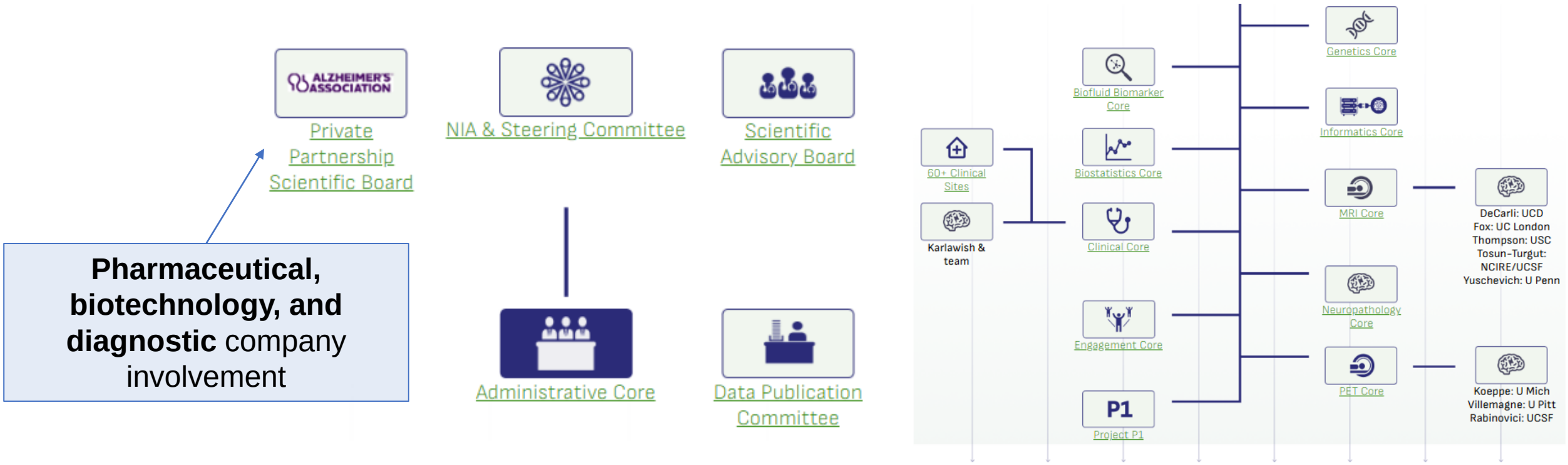
Alzheimer's Disease Neuroimaging Initiative

ADNI

The overall goal of the ADNI is to optimize and validate biomarkers for clinical trials while sharing all data and biofluid samples with the global scientific community

2004 - TBD PI: Dr. Michael W. Weiner

Public-private partnership - NIA, FNIH, Alzheimer's Association, and dozens of companies



Public-Private Partnership Scientific Board (PPSB)

The PPSB carries over four working groups from previous incarnations of ADNI that parallel key focus areas of the ADNI Core.

They are:

1. ADNI PPSB **Biofluid Biomarkers** Work Group.
2. ADNI PPSB **Clinical Endpoints** Work Group.
3. ADNI PPSB **PET Endpoints** Working Group.
4. ADNI PPSB **Diversity, Inclusion & Equity** Work Group.

ADNI Alzheimer's Disease Neuroimaging Initiative

Phases of ADNI

The ADNI study began in 2004 and has been continuously collecting data across the various phases of the study. ADNI4 is the current study phase (2022-2027).

	ADNI 1	ADNI GO	ADNI 2	ADNI 3	ADNI 4
	2004 – 2010	2009 – 2011	2011 – 2016	2016-2022	2022 and beyond
Primary Goal	Develop biomarkers as outcome measures for clinical trials	Examine biomarkers in earlier stages of disease	Develop biomarkers as predictors of cognitive decline, and as outcome measures	Study the use of tau PET and functional imaging techniques in clinical trails	Improve representation of historically underrepresented groups in AD research
Funding	$40 million federal (NIA), $27 million industry and foundation	$24 million American Recovery Act funds	$40 million federal (NIA), $27 million industry and foundation	$40 million federal (NIA), up to $20 million industry and foundation	$147 million federal (NIA)
Duration	5 years/October 2004	2 years/September 2009	5 years/September 2011	5 years/September 2016	5 years/September 2022
Cohort	200 elderly controls 400 MCI 200 AD	Existing ADNI1 + 200 early MCI	Existing ADNI1 and ADNI Go 150 elderly controls 100 elderly MCI 150 late MCI 150 AD	Existing ADNI1,ADNI Go, ADNI2 + 133 elderly controls 151 MCI 87 AD	Existing ADNI 1, ADNI-GO, ADNI-2, ADNI-3 + 200 elderly controls, 200 MCI, 100 AD/DEM
	Learn More	Learn More	Learn More	Learn More	Learn More

https://adni.loni.usc.edu/about/

Utilization of Public Private Partnerships and Observational Research Studies

Biotech/Pharma Focus

- **Pre-Clinical (Phase 1)**
- **Early POC (Phase 1b/2)**
- **End point (Phase 3) Personalized Medicine**

Need
Understand and stay current on scientific advancements in disease area

Limited Resources
Time
Budget
Expertise

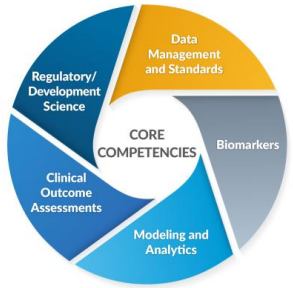
Benefits of Precompetitive Research

- Shared financial burden
- Consensus experimental plan
- Biosample availability
- Prespecified end points
- Practical applications
- Regulatory body input and/or information transfer
- Unbiased analysis and results

Overview of C-Path

Overview of C-Path

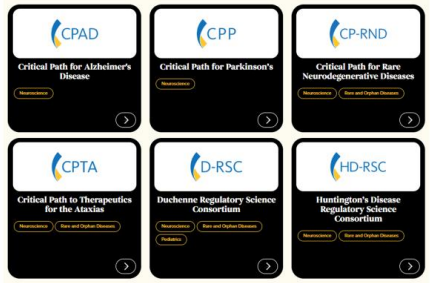
Critical Path Institute (C-Path) is a nonprofit organization dedicated to improving and streamlining the process of drug development. We achieve tangible, actionable results by fostering collaboration between industry executives and scientists, academic researchers, regulators, and patient groups.



CRITICAL PATH INSTITUTE

Neuroscience

C-Path's Neuroscience Program unites regulators, pharmaceutical and biotech companies, academics, and patient advocates to advance drug development and create better treatments for people living with Parkinson's, Alzheimer's, and rare neurodegenerative diseases.



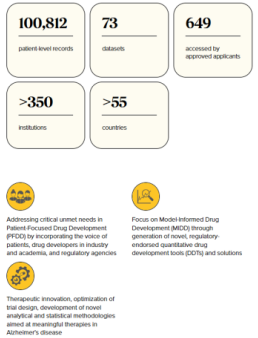
Critical Path for Alzheimer's Disease

CPAD

The (CPAD) program accelerates the development of Alzheimer's treatments by establishing public-private partnerships and fostering collaboration between industry, regulators, and academia. It works on refining biomarkers, clinical trial designs, and data standards to enhance regulatory processes and clinical endpoints. CPAD aims to create more effective therapies and drive faster approval for Alzheimer's treatments.

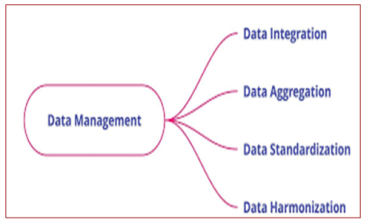
CPAD Working Groups:

- **Tau-PET Harmonization Working Group**: Develops standardized scales for tau protein quantification across imaging techniques, ensuring consistency in evaluating Alzheimer's.
- **Tau-PET Surrogacy Working Group**: Investigates tau PET imaging as a surrogate endpoint for predicting clinical benefits and supporting accelerated drug approvals.
- **Quantitative Modeling Working Group**: Builds disease progression models using patient-level data to optimize trial design, patient selection, and endpoint identification.



(CPAD): Regulatory Successes

Accelerated Drug Development:	FDA Endorsement of Novel Endpoints:	Guidance on Surrogate Endpoints:	Harmonization of Data Standards:	Support for Accelerated Approval Pathways:
•CPAD developed tools that streamline FDA assessments, **enabling faster approval processes for Alzheimer's treatments.**	•CPAD's work on new biomarkers and trial designs has led to FDA acceptance of more reliable endpoints for Alzheimer's trials, **expediting therapy identification.**	•CPAD's advancement of surrogate markers like tau and amyloid PET imaging is helping the FDA assess treatments before clinical benefits, **such as memory improvement, are evident.**	•CPAD has unified clinical trial data standards, ensuring consistency and comparability across studies, **which aids in regulatory review**.	•By providing reliable disease progression measures, CPAD has facilitated the use of the FDA's accelerated approval pathway for Alzheimer's drugs, **speeding up reviews for conditions with unmet needs.**



Overview of FNIH Biomarkers Consortium

The FNIH Biomarkers Consortium is a public-private biomedical research partnership led by the Foundation for the National Institutes of Health (FNIH).

Mission: To accelerate the development of biomarkers that support new drug development, enhance disease detection, and improve patient outcomes.

Goal: Facilitate collaboration among public, private, academic, and nonprofit sectors to validate biomarkers and qualify them for regulatory use.

FNIH
Foundation for the National Institutes of Health

NIH National Institutes of Health
Turning Discovery Into Health

FDA

FNIH Biomarkers Consortium

Who Are Our Partners?

Collaborative Network: The Biomarkers Consortium partners include a mix of pharmaceutical companies, government agencies, academic institutions, and nonprofit organizations.

Pharmaceuticals: Many of the major pharmaceutical companies
Many of the major diagnostic companies

Governmental and Regulatory: FDA, NIH

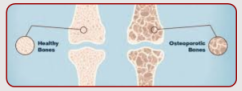
Academic & Research Institutions: Universities contributing to biomarker discovery

Nonprofit & Patient Advocacy: Organizations supporting patient-centered research

The FNIH Biomarkers Consortium's Key Achievements:

Cardiovascular Disease & RA: Blood biomarkers developed to predict cardiovascular risk in RA patients.

Alzheimer's Disease: Advanced imaging tools and blood-based screening tests.



Osteoporosis: FDA-approved biomarkers for clinical trial endpoints.

Digital Health: Engaged patients in shaping digital health measures.

Head-to-head evaluation of leading blood tests for amyloid pathology

Objective

A workgroup put together by the **FNIH Biomarker Consortium** sought to compare leading commercial assays for Aβ42/Aβ40 and pTau

Project Design

- Plasma samples were provided by the **ADNI biorepository** and shipped to the relevant laboratories for analysis
- A statistical team including academia and industry analysts implemented a **pre-specified plan**; analysts from different groups replicated the key analyses
- Published results

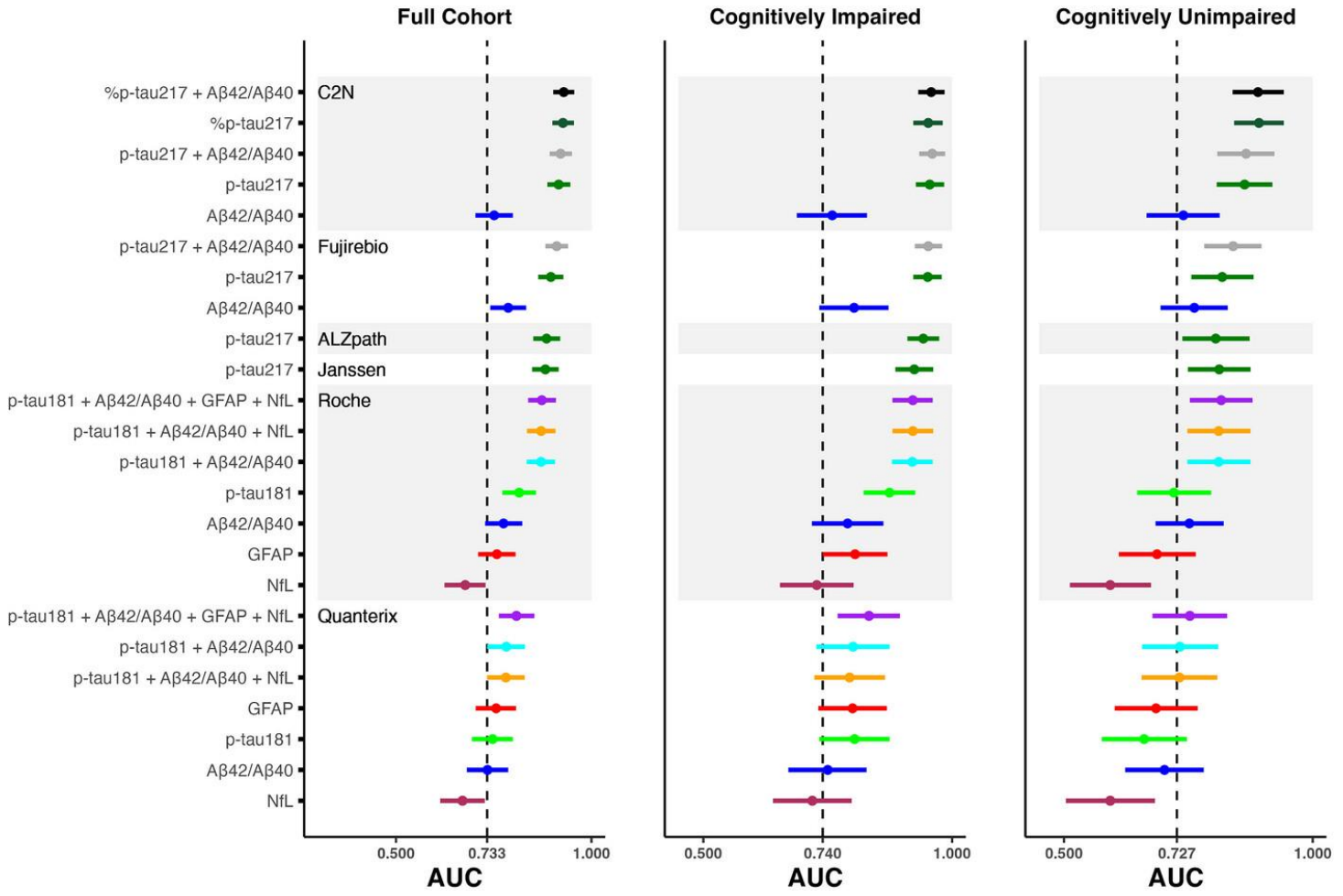
Schindler SE, Petersen KK, Saef B, Tosun D, Shaw LM, Zetterberg H, Dage JL, Ferber K, Triana-Baltzer G, Du-Cuny L, Li Y, Coomaraswamy J, Baratta M, Mordashova Y, Saad ZS, Raunig DL, Ashton NJ, Meyers EA, Rubel CE, Rosenbaugh EG, Bannon AW, Potter WZ; Alzheimer's Disease Neuroimaging Initiative (ADNI) 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. Head-to-head comparison of leading blood tests for Alzheimer's disease pathology. Alzheimers Dement. 2024 Nov;20(11):8074-8096. doi: 10.1002/alz.14315. Epub 2024 Oct 12. Erratum in: Alzheimers Dement. 2024 Dec 30. doi: 10.1002/alz.14494. PMID: 39394841; PMCID: PMC11567821.

Case Study: Type and Impact of FNIH Biomarker Consortium Research

Case Study Alzheimer's Disease

- **Goal:** Validate and compare plasma biomarkers for treatment development
- **Impact:** Enables use in clinical trial enrichment

Classification accuracies of individual and combined plasma biomarker measures for key outcomes in the full cohort.



Alzheimers Dement. 2024 Oct 12. doi: 10.1002/alz.14315. Online ahead of print.

Conclusions

- Integration of plasma P-tau217 into clinical trials represents a promising approach to improving participant selection, monitoring disease progression, and evaluating therapeutic responses.
- The rapid advancement across the field would not have been achieved without the use ADNI data and samples
- The collective efforts of researchers, industry partners, and regulatory bodies through public-private partnerships (FNIH Biomarkers Consortium, and CPAD) has been crucial in advancing AD treatment and achieving better patient outcomes.
- This presentation underscores the value for ongoing support, innovation, and collaboration in biomarker research to drive the future of AD therapeutics.

https://medicine.iu.edu/faculty-labs/dage

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Kelley Faber - NCRAD

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Roche Diagnostics - RD005665
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WHICAP -R01AG072474
CLEAR-AD – U19 AG074879
ADACC – U24AG082930
IBDS (Tau) - R01AG089522