Early diagnosis and prevention of Alzheimer's disease

NASDAQ: ACIU | KOL Webinar, April 2023

AC Immune

Version: 17.04.2023

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Agenda

Introduction	**Gary Waanders, PhD, MBA** Head of Investor Relations and Communications, AC Immune
Strategy and pipeline overview	**Andrea Pfeifer, PhD** Chief Executive Officer, AC Immune
CSF and blood biomarkers for diagnosis and triage of Alzheimer's	**Kaj Blennow, MD, PhD** Clinical Neurochemistry Lab at Sahlgrenska University Hospital in Gothenburg
Amyloid imaging for accurate diagnosis and targeted therapy to prevent Alzheimer's	**Giovanni Frisoni, MD** Department of Psychiatry of the Faculty of Medicine, University of Geneva
The need for Precision Medicine and neuroimaging to diagnose and treat earlier	**Marie Kosco-Vilbois, PhD** Chief Scientific Officer, AC Immune
Clinical vaccine programs	**Johannes Streffer, MD** Chief Medical Officer, AC Immune
Q&A and closing remarks	**Andrea Pfeifer, PhD** Chief Executive Officer, AC Immune

(1) Alpha-synuclein; (2) Neurodegenerative diseases; Positron emission tomography

Strategy and pipeline overview

Andrea Pfeifer, PhD, Chief Executive Officer

AC Immune

AC Immune at a glance

Pioneering new ways to treat neurodegenerative diseases

Broad, diverse pipeline – 16 programs
1 Phase 3 program and 5 in Phase 2

Key differentiation: Precision Medicine
Integrates therapeutics and diagnostics

Multiple global partnerships
>CHF 3 billion in potential milestones

Clinically validated technology platforms
Best-in-class small molecules and biologics

Strong Balance sheet
Funded into Q3 2024

- Based in Lausanne, Switzerland
- ~150 employees
- Listed September 2016 (NASDAQ: ACIU)
- 83.6 million shares outstanding[1]
- Cash of CHF 122.6 million[2] (~USD 132.5 million)

(1) As of December 31, 2022; excluding treasury shares; (2) As of December 31, 2022

Successfully treating neurodegeneration requires precision medicine

From a mono- to a multi-target combination approach informed by cutting edge diagnostics

Imaging: AC Immune's Unique Tracers

- **Positron Emission Tomography**

→

- Tau
- a-syn[1]
- TDP-43[2]

Biofluids

- **Blood / Serum**
- **Cerebrospinal Fluid**

→

- a-syn
- TDP-43

Future Technologies

In collaboration:

- **Digital Health Technologies & Wearable Devices**

Treating the

right proteinopathies,

in the right patient,

at the right time

- Non-invasive diagnostics are critical for accurate patient selection and treatment to improve clinical outcomes
- Early and comprehensive diagnosis may eventually lead to disease prevention and combination therapy

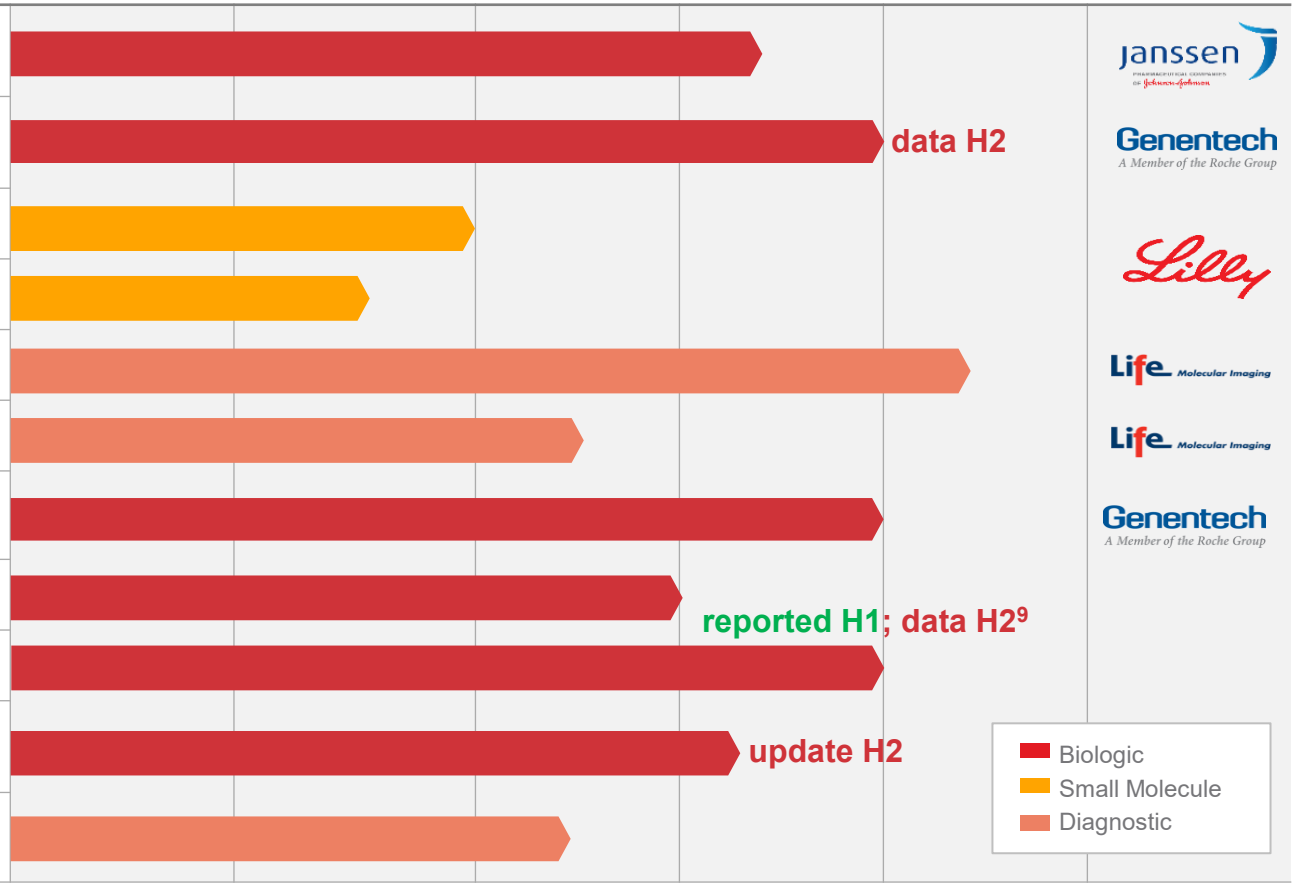
(1) alpha-synuclein; (2) TAR DNA-binding protein 43;

Broad and robust pipeline in neurodegenerative diseases

Driven by validated proprietary technology platforms for sustained growth

Clinical Stage Programs

TARGET	PRODUCT CANDIDATE	INDICATION	PARTNER
Tau	**ACI-35.030** *(anti-pTau vaccine)*	AD[1] treatment	Janssen
	Semorinemab *(anti-Tau antibody)*	AD treatment *(mild-to-moderate)*[2]	Genentech
	Morphomer® Tau aggregation inhibitor	Rare Tauopathies	Lilly
		AD treatment	
	Tau-PET[3] tracer	AD diagnostic	Life Molecular Imaging
		PSP[4] diagnostic	Life Molecular Imaging
Abeta	**Crenezumab** *(anti-Abeta antibody)*	AD prevention[5]	Genentech
	ACI-24.060 *(anti-Abeta vaccine)*	AD treatment (*Down syndrome*[6])	
		AD treatment	
a-syn[7]	**ACI-7104.056** *(anti-a-syn vaccine)*	PD[8], a-synucleinopathies	
	a-syn-PET tracer	a-synucleinopathies (e.g. MSA[10])	



(1) Alzheimer's disease; (2) Open label extension study is ongoing; (3) Positron emission tomography; (4) Progressive supranuclear palsy; (5) Prevention trial API-ADAD in Colombia; (6) Down syndrome-related Alzheimer's disease; (7) alpha-synuclein; (8) Parkinson's disease; (9) Refers to expected readouts from a Phase 1b/2 trial of an optimized formulation of ACI-24 (ACI-26.060) in patients with AD and patients with Down syndrome; (10) Multiple system atrophy

AC Immune

Key milestones for value creation in 2023

Multiple clinical readouts for wholly-owned vaccines

✓ Achieved
● Clinical readouts
○ Other development events

Vaccines		H1	H2	
ACI-24.060	Abeta	○		Initiation of Down syndrome cohort of Phase 1b/2 ABATE study
		○		IND submission to enable expansion of ABATE study to U.S.
		✓	●	**Two interim analyses in AD[1] – safety, immunogenicity**
			●	**Interim analysis in Down syndrome – safety, immunogenicity**
ACI-35.030	Tau		○	Further development with initiation of next trial in AD and **milestone payment**
ACI-7104	a-syn[2]		●	**Phase 2 VACSYN study in PD update**
Monoclonal antibodies				
Semorinemab	Tau		●	**Phase 2 Lauriet Trial Open Label Extension results**
Monoclonal antibody	TDP-43		○	Candidate into preclinical development (tox)
Diagnostics				
a-syn[2]-PET[3] tracer	a-syn		○	Next clinical candidate declaration for PD[4]
TDP-43-PET tracer	TDP-43	○		Clinical candidate declaration

(1) Alzheimer's disease; (2) Alpha-synuclein; (3) Positron emission tomography; (4) Parkinson's disease; (5) TAR DNA-binding protein 43

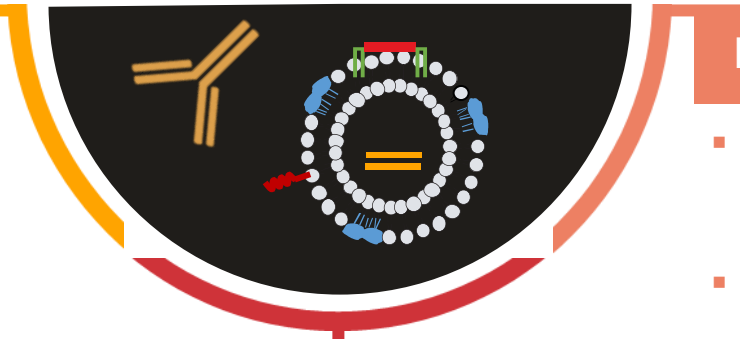
Vaccines as a new class of treatment for neurodegenerative disease

AC Immune vaccines: Potential for profound social and economic impact

Treatment

High efficacy with:

- Multiple epitope targeting
- Long-lasting immune response
- Steady titers
- Favorable safety and tolerability
- Convenient, annual dosing



Prevention

- Vaccination is the best strategy to preserve function and quality of life
- Cost-effective and global application

Maintenance

- Use as maintenance therapy after monoclonal anti-Abeta antibodies
- Convenient, annual dosing to maintain low plaque levels

- Goal: Global vaccines for neurodegenerative diseases

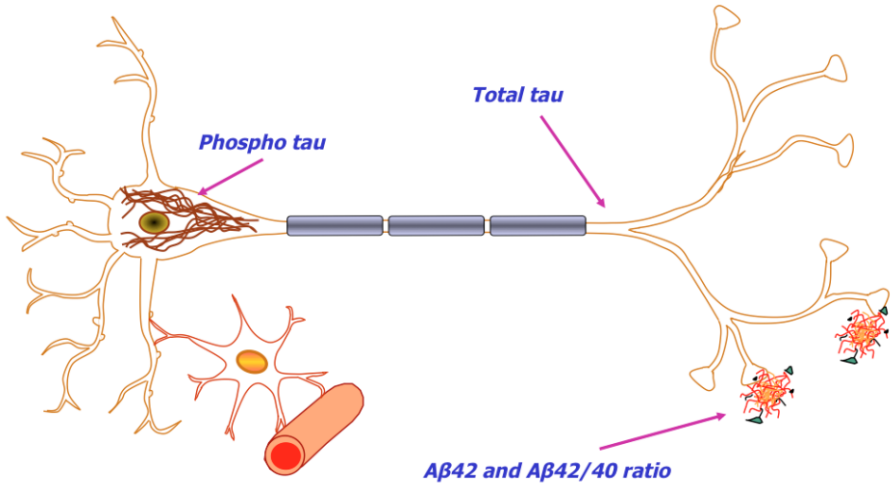
AC Immune: Pioneering science and precision medicine

Shifting the treatment paradigm for neurodegenerative disease towards precision medicine and disease prevention

CSF and blood biomarkers for diagnosis and triage of Alzheimer's disease

Kaj Blennow, MD, PhD, Professor and Academic Chair in Neurochemistry (University of Gothenburg), Head of the Clinical Neurochemistry Lab (Sahlgrenska University Hospital in Gothenburg)

The Alzheimer ATN CSF biomarkers are highly clinically validated



Articles

CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

Bob Olsson, Ronald Lautner, Ulf Andreasson, Annika Öhrfelt, Erik Portelius, Maria Bjerke, Mikko Hölttä, Christoffer Rosén, Caroline Olsson, Gabrielle Strobel, Elizabeth Wu, Kelly Dakin, Max Petzold, Kaj Blennow, Henrik Zetterberg

ALZFORUM
NETWORKING FOR A CURE

AlzBiomarker database Version 3.0
With data from 487 papers
Cross-disease biomarker data

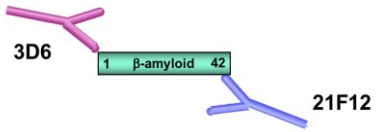
ORIGINAL CONTRIBUTION

Cerebrospinal Fluid β-Amyloid(1-42) in Alzheimer Disease

Differences Between Early- and Late-Onset Alzheimer Disease and Stability During the Course of Disease

Niels Andreasen, MD; Camilla Hesse; Pia Davidsson, PhD; Lennart Minthon, MD, PhD; Anders Wallin, MD, PhD; Bengt Winblad, MD, PhD; Hugo Vanderstichele, PhD; Eugeen Vanmechelen, PhD; Kaj Blennow, MD, PhD

Arch Neurol 1999

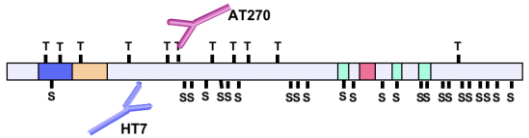


ELSEVIER

Neuroscience Letters

Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization

E. Vanmechelen[a,*], H. Vanderstichele[a], P. Davidsson[b], E. Van Kerschaver[a], B. Van Der Perre[a], M. Sjögren[c], N. Andreasen[d], K. Blennow[b,c]

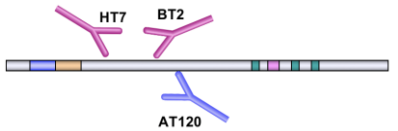


tau Protein in Cerebrospinal Fluid

A Biochemical Marker for Axonal Degeneration in Alzheimer Disease?

K. BLENNOW,*,[1] A. WALLIN,[2] H. ÅGREN,[2] C. SPENGER,[3] J. SIEGFRIED,[4] AND E. VANMECHELEN[5]

Mol Chem Neuropathol 1995



CSF Aβ42
➔ **Brain amyloid deposition**
• **Reduction to 55 % in AD**

• 210 studies
• 24.900 AD patients and controls

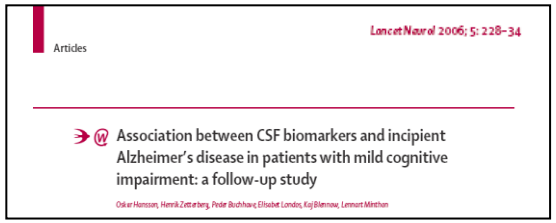
CSF P-tau181
➔ **Tau phosphorylation / pathology**
• **187 % increase in AD**

• 153 studies
• 19.600 AD patients and controls

CSF T-tau
➔ **Intensity of neurodegeneration**
• **248 % increase in AD**

•238 studies
• 27.400 AD patients and controls

How do the core AD CSF biomarkers work in prodromal / preclinical AD ?

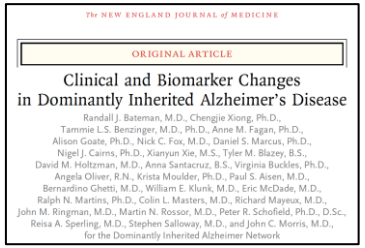

Lancet Neurol 2006; 5: 228–34

Articles

Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study

Oskar Hansson, Henrik Zetterberg, Peder Buchhave, Elisabet Londos, Kaj Blennow, Lennart Minthon

BioFinder study on MCI (n=134) and controls (n=37)
4-7 years clinical follow-up

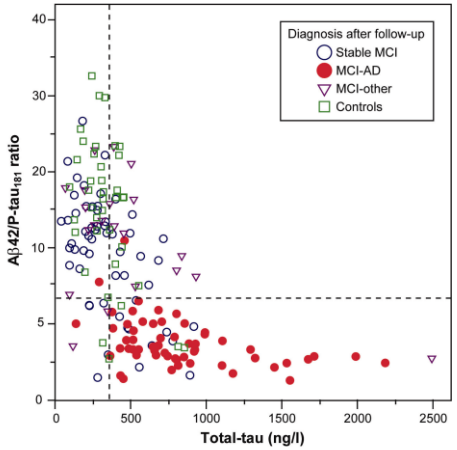

The NEW ENGLAND JOURNAL of MEDICINE

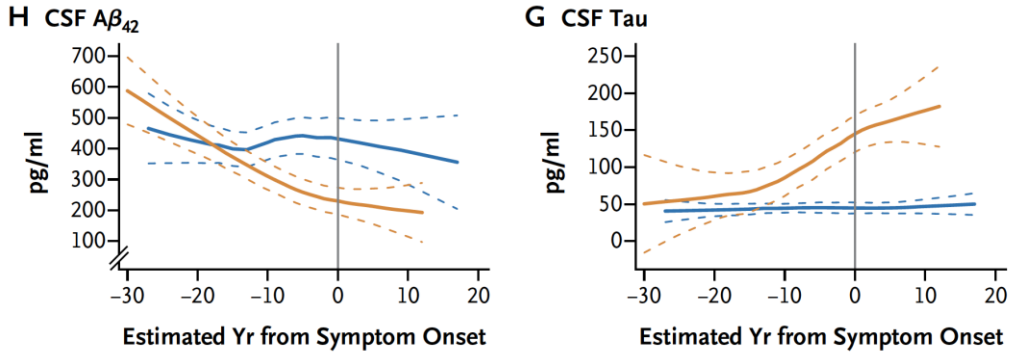
ORIGINAL ARTICLE

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

DIAN longitudinal study:
data on 128 carriers (n=88) and non-carriers (n=40)





Performance in the MCI stage:

Sensitivity	for MCI-AD	95%
Specificity	for MCI-stable/other	87 %

CSF Aβ42 decrease >15 years before and
CSF tau increase >10 years before expected symptom onset

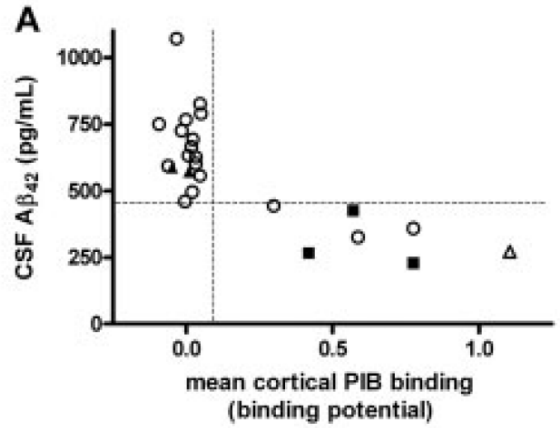
➔ The core AD CSF biomarkers show high diagnostic performance also in the MCI stage,

➔ The CSF AD biomarkers change in the preclinical phase; Aβ42 before tau

Does CSF Aβ42 reflect brain amyloidosis ?

Inverse Relation between In Vivo Amyloid Imaging Load and Cerebrospinal Fluid $A\beta_{42}$ in Humans

Anne M. Fagan, PhD,[1–3] Mark A. Mintun, MD,[2,4] Robert H. Mach, PhD,[2,4] Sang-Yoon Lee, PhD,[4] Carmen S. Dence, MS,[4] Aarti R. Shah, MS,[1,2] Gina N. LaRossa, BS,[4] Michael L. Spinner, MA,[1,3] William E. Klunk, MD, PhD,[5] Chester A. Mathis, PhD,[6] Steven T. DeKosky, MD,[7] John C. Morris, MD,[1,2,8] and David M. Holtzman, MD[1–3,9]



➔ CSF Aβ42 is associated with brain amyloidosis

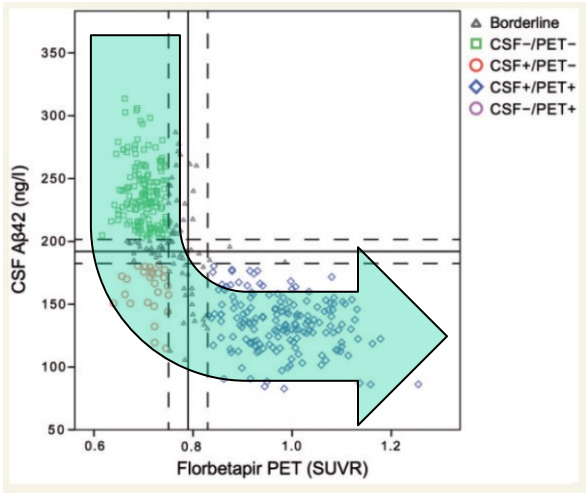
➔ Verified in many subsequent studies

Brain Advance Access published March 2, 2016
BRAIN
A JOURNAL OF NEUROLOGY

Cerebrospinal fluid analysis detects cerebral amyloid-β accumulation earlier than positron emission tomography

Sebastian Palmqvist[1,2] Niklas Mattsson[1,3] and Oskar Hansson[1,3] for the Alzheimer's Disease Neuroimaging Initiative*

- ADNI data for CSF Aβ42 vs. amyloid PET
- Follow-up amyloid PET after 2 years



- Longitudinal PET data (2 years):
  CSF+ but PET- cases will accumulate amyloid, similar to PET+ cases

➔ CSF Aβ42 is associated with brain amyloidosis

➔ CSF Aβ42 is a more sensitive / earlier biomarker than amyloid PET

What does CSF tau proteins stand for ?

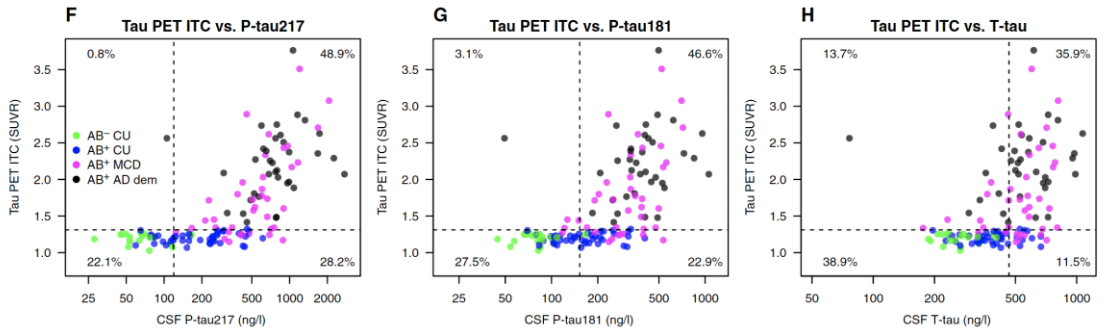
SCIENCE ADVANCES | RESEARCH ARTICLE
Sci. Adv. 2020; 6 : eaaz2387
NEUROSCIENCE

Aβ deposition is associated with increases in soluble and phosphorylated tau that precede a positive Tau PET in Alzheimer's disease

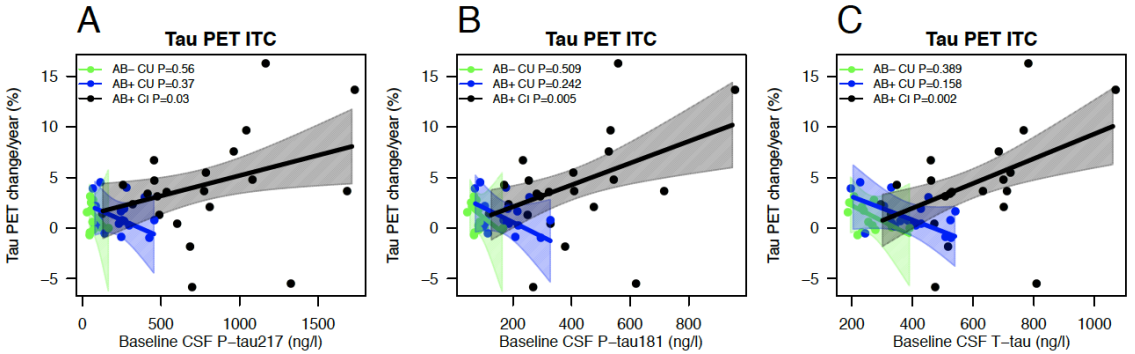
Niklas Mattsson-Carlgren[1,2,3]*, Emelie Andersson[1], Shorena Janelidze[1], Rik Ossenkoppele[1,4], Philip Insel[1], Olof Strandberg[1], Henrik Zetterberg[5,6,7,8], Howard J. Rosen[9], Gil Rabinovici[9], Xiyun Chai[10], Kaj Blennow[5,6], Jeffrey L. Dage[10], Erik Stomrud[1], Ruben Smith[1,2], Sebastian Palmqvist[1,2], Oskar Hansson[1,11]*

Large clinical cohort (BioFinder) with tauPET (n= 131)

$A\beta^-$ CU	$A\beta^+$ CU	$A\beta^+$ mild cognitive deficits	$A\beta^+$ AD dementia
18	40	38	35



CSF P-tau and T-tau increase with more severe tau pathology

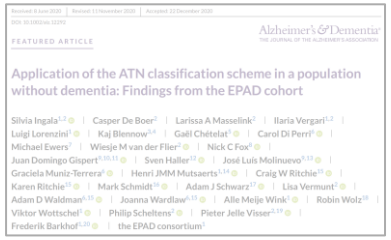


Higher CSF P-tau and T-tau predicts future rate of tau deposition (assessed by tau PET)

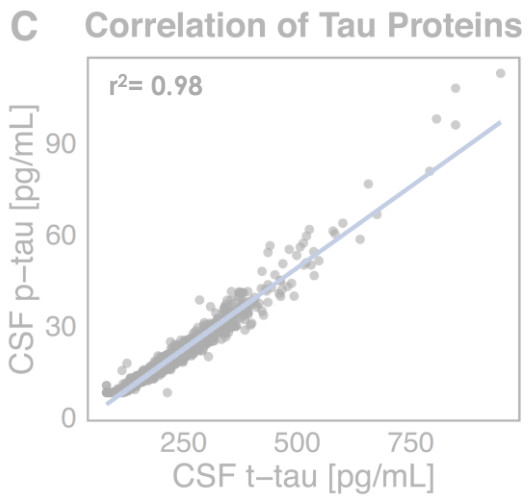
In cohorts of CU elderly people and patients within the AD continuum,

➔ CSF P-tau variants and T-tau increases with severity of tau pathology but also predict future rate of tau deposition by PET

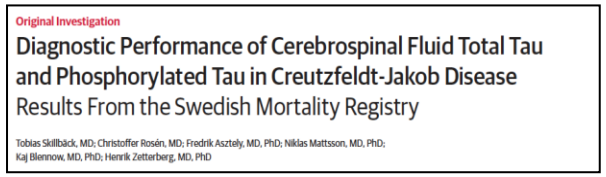
So is then CSF P-tau and T-tau “more of the same” ?



EPAD cohort n = 1188



- Tight correlation CSF P-tau to T-tau along the AD continuum
- The same ratio P-tau/T-tau in CU, MCI and AD dementia



JAMA Neurol 2014;71:476-483

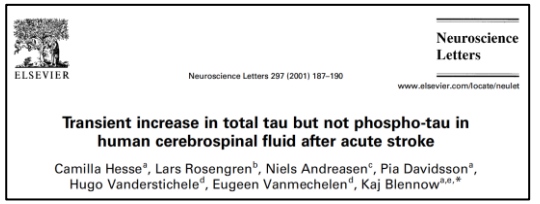
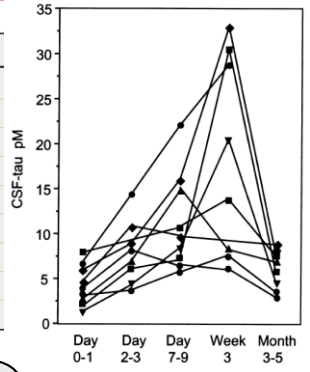
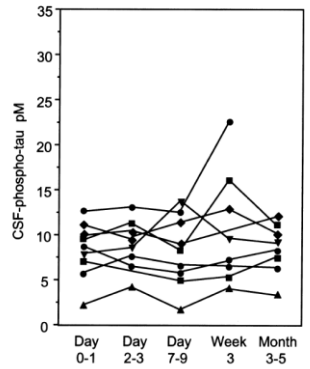


Table 1. Demographic Characteristics

Characteristic	CJD	Non-CJD
T-tau level, ng/L		
Mean (SD)	9794 (19 994)	594 (676)
Median (IQR)	4300 (2200-9960)	490 (310-730)
P-tau level, ng/L		
Mean (SD)	61 (31)	73 (40)
Median (IQR)	59 (38-73)	64 (45-91)
T-tau to P-tau ratio		
Mean (SD)	155 (280)	8.4 (7.8)
Median (IQR)	101 (34-170)	7.3 (6.2-8.6)





Creutzfeldt-Jakob disease

- ➔ 30-fold increase in CSF T-tau (2.5 fold increase in AD)
- ➔ No change in CSF P-tau

Acute stroke

- ➔ several fold increase in CSF T-tau (depending on infarct size)
- ➔ No change in CSF P-tau

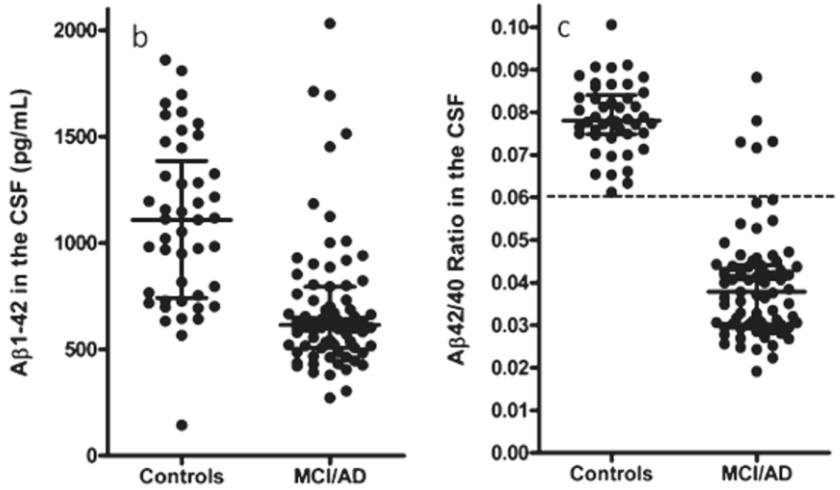
- ➔ Although CSF P-tau and T-tau correlate in AD continuum cohorts, they are not the same
- ➔ CSF T-tau reflects intensity of neurodegeneration and severity of acute neuronal injury

The Aβ 42/40 ratio improves diagnostic performance compared to Aβ42 alone

Journal of Alzheimer's Disease 43 (2015) 183–191
DOI 10.3233/JAD-140771
IOS Press

Amyloid-β 42/40 Cerebrospinal Fluid Concentration Ratio in the Diagnostics of Alzheimer's Disease: Validation of Two Novel Assays

Piotr Lewczuk*, Natalia Lelental, Philipp Spitzer, Juan Manuel Maler and Johannes Kornhuber
Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen, and Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany

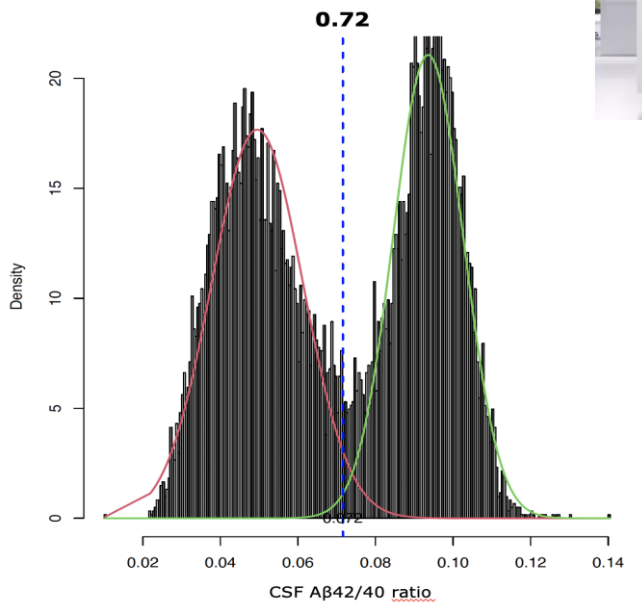


➔Aβ 42/40 ratio compensates for
differences in "total" brain Aβ production ?
differences in "total" Aβ secretion to CSF/blood ?
pre-analytical confounders ?

FDA approved Lumipulse tests for CSF Aβ42 and Aβ40

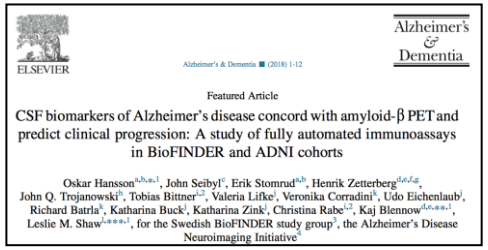
- Consecutive unselected patients in clinical routine
- 12012 samples during 3 years
- Analyses 2 times per week using different lots of reagents and calibrators

Lumipulse G1200



➔ 50% lowering in CSF Aβ42/40 ratio
➔ very distinct bimodal distribution of values
➔ stable cut-off over time

FDA approved cobas Elecsys CSF biomarkers – concordance with amyloid PET



ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-12

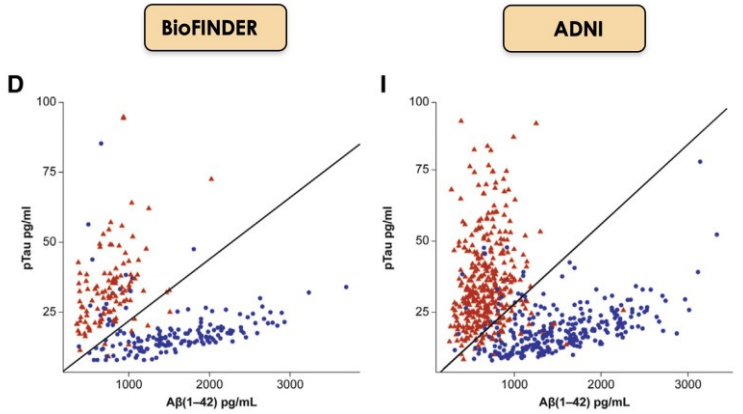
Alzheimer's & Dementia

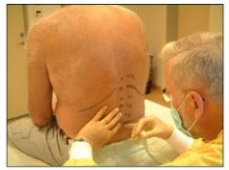
Featured Article

CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts

Oskar Hansson[a,b,*,1], John Seibyl[c], Erik Stomrud[a,b], Henrik Zetterberg[d,e,f,g], John Q. Trojanowski[h], Tobias Bittner[i,2], Valeria Lifke[i], Veronika Corradini[i], Udo Eichenlaub[i], Richard Batrla[k], Katharina Buck[i], Katharina Zink[i], Christina Rabe[i,2], Kaj Blennow[d,e,*,1], Leslie M. Shaw[h,*,1], for the Swedish BioFINDER study group[3], the Alzheimer's Disease Neuroimaging Initiative[4]

Cohorts: BioFINDER (n= 277) and ADNI (n=646)

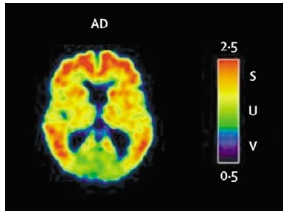




cobas Elecsys methods for CSF Aβ42 and pTau181

versus

Amyloid PET visual read pos/neg (3 raters)

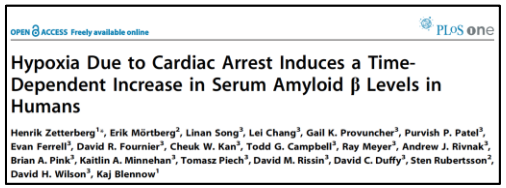


Concordance figures:	visual amyloid PET vs. CSF pTau/Aβ42	OPA = 90 %
	Inter-rater PET agreement	OPA = 90%
	Visual vs. SUVR PET agreement	OPA = 90-91%

➔ CSF biomarkers and amyloid PET can be used interchangeably for inclusion purposes or diagnostics

Blood-based assays – the holy grail for AD biomarkers

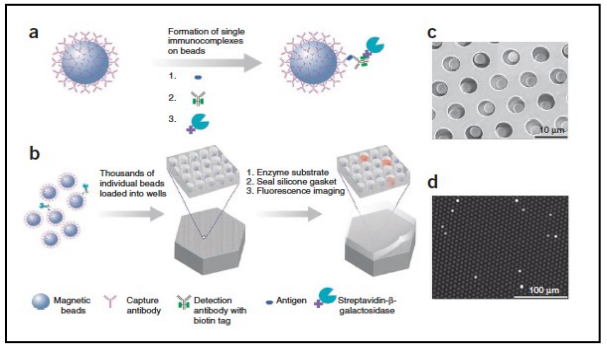
2011: Single molecule array (Simoa) for plasma Aβ



OPEN ACCESS Freely available online — PLoS one

Hypoxia Due to Cardiac Arrest Induces a Time-Dependent Increase in Serum Amyloid β Levels in Humans

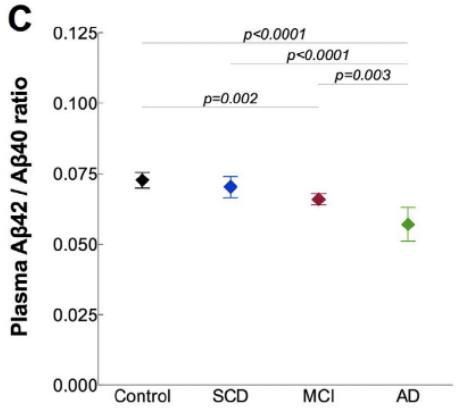
Henrik Zetterberg[1*], Erik Mörtberg[2], Linan Song[3], Lei Chang[3], Gail K. Provuncher[3], Purvish P. Patel[3], Evan Ferrell[3], David R. Fournier[3], Cheuk W. Kan[3], Todd G. Campbell[3], Ray Meyer[3], Andrew J. Rivnak[3], Brian A. Pink[3], Kaitlin A. Minnehan[3], Tomasz Piech[3], David M. Rissin[3], David C. Duffy[3], Sten Rubertsson[2], David H. Wilson[3], Kaj Blennow[1]



Plasma Aβ42/40 by Simoa in BIOFINDER (n= 719)

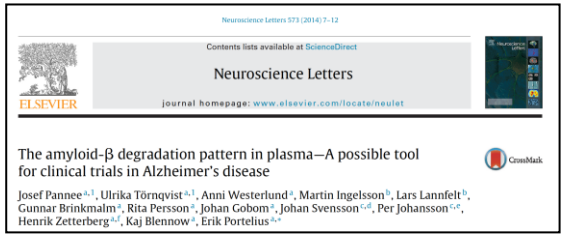
SCIENTIFIC REPORTS

OPEN Plasma β-amyloid in Alzheimer's disease and vascular disease



➔ Significant, but minor, decrease in plasma Aβ42/40 ratio in MCI (10%) and AD dementia (22%)

2014: Immunoprecipitation – mass spectrometry (LC-MS) SRM method for plasma Aβ42 and Aβ40



Neuroscience Letters 573 (2014) 7–12

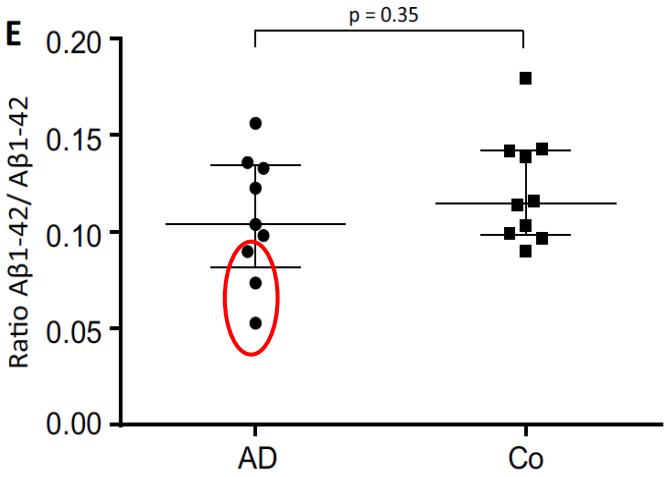
Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

The amyloid-β degradation pattern in plasma—A possible tool for clinical trials in Alzheimer's disease

Josef Pannee[a,1], Ulrika Törnqvist[a,1], Anni Westerlund[a], Martin Ingelsson[b], Lars Lannfelt[b], Gunnar Brinkmalm[a], Rita Persson[a], Johan Gobom[a], Johan Svensson[c,d], Per Johansson[c,e], Henrik Zetterberg[a,f], Kaj Blennow[a], Erik Portelius[a,*]



➔ Minor (10%) decrease in plasma Aβ42/40 ratio in AD

➔ Too small pilot cohort to evaluate clinical utility

Several assays for plasma Aβ ratio show good associations with brain amyloidosis

Research

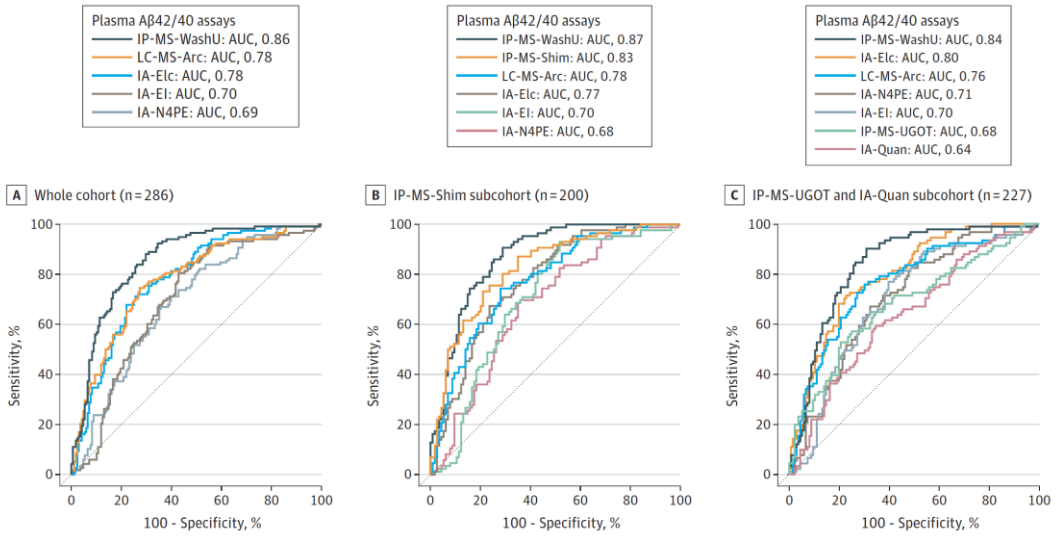
JAMA Neurology | Original Investigation

Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease

Shorena Janelidze, PhD; Charlotte E. Teunissen, PhD; Henrik Zetterberg, MD, PhD; José Antonio Allué, PhD; Leticia Sarasa, PhD; Udo Eichenlaub, PhD; Tobias Bittner, PhD; Vitaliy Ovod, MSs; Inge M. W. Verberk, MSs; Kenji Toba, MD, PhD; Akinori Nakamura, MD, PhD; Randall J. Bateman, MD, PhD; Kaj Blennow, MD, PhD; Oskar Hansson, MD, PhD

IP – MS Washington University (IP-MS-WashU)
Antibody-free LC-MS Araclon (LC-MS-Arc)
IP-MALDI Shimadzu (IP-MS-Shim)
IP-MS Gothenburg (IP-MS-UGOT)

Elecsys immunoassay Roche Diag (IA-Elc)
ELISA Euroimmun (IA-EI)
Simoa ADx and Quanterix (IA-N4PE)
Simoa Quanterix (IA-Quan)



	Aβ negative (n = 168)[a]	Aβ positive (n = 118)[a]

Table 1. Characteristics of Study Participants in BioFINDER

Characteristic	Fold change
CSF Aβ42/40	- 56 %
Plasma Aβ42/40	
IP-MS-WashU	- 8 %
LC-MS-Arc	- 11 %
IA-Elc	- 9 %
IA-EI	- 9 %
IA-N4PE	- 12 %

➔ **Plasma Aβ ratio gives high AUCs for brain amyloidosis, especially the WashU IP-MS method**

➔ **Biomarker fold change is low – independently of assay used**

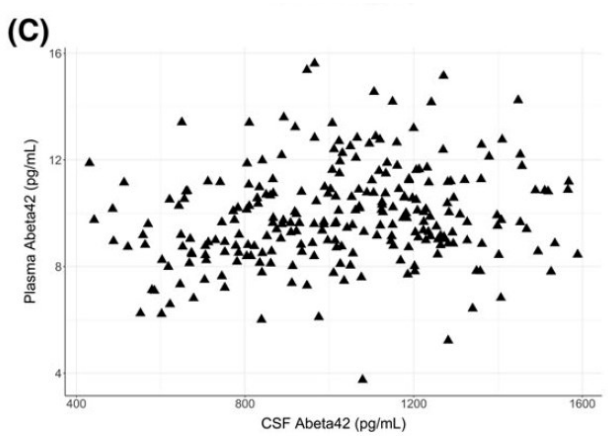
Why is plasma Aβ ratio only marginally reduced (when CSF shows marked change)?

RESEARCH ARTICLE

Plasma Amyloid as Prescreener for the Earliest Alzheimer Pathological Changes

Inge M. W. Verberk, MSc,[1,2,3] Rosalinde E. Slot, MD,[1,2] Sander C. J. Verfaillie, PhD,[1,2,4] Hans Heijst, BSc,[1,3] Niels D. Prins, MD, PhD,[1,2] Bart N. M. van Berckel, MD, PhD,[1,4] Philip Scheltens, MD, PhD,[1,2] Charlotte E. Teunissen, PhD,[1,3a] and Wiesje M. van der Flier, PhD[1,2,5a]

Plasma vs. CSF Aβ42 (Simoa)



ARTICLE CLASS OF EVIDENCE

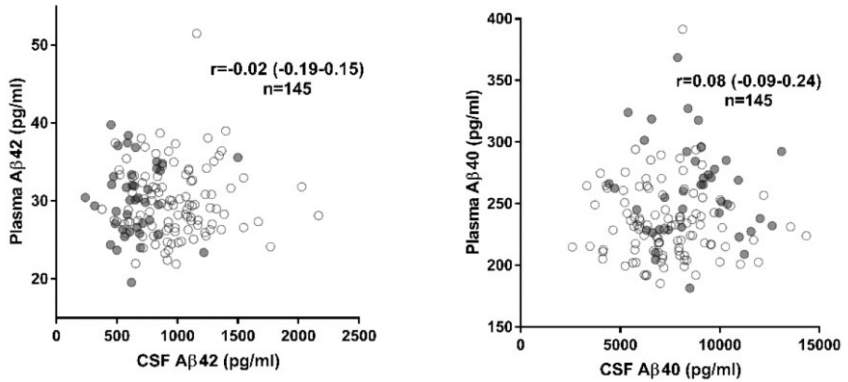
High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis

Suzanne E. Schindler, MD, PhD, James G. Bollinger, PhD, Vitaliy Ovod, MS, Kwasi G. Mawuenyega, PhD, Yan Li, PhD, Brian A. Gordon, PhD, David M. Holtzman, MD, John C. Morris, MD, Tammie L.S. Benzinger, MD, PhD, Chengjie Xiong, PhD, Anne M. Fagan, PhD, and Randall J. Bateman, MD

Correspondence
Dr. Bateman
batemanr@wustl.edu

Neurology® 2019;93:e1647-e1659. doi:10.1212/WNL.0000000000008081

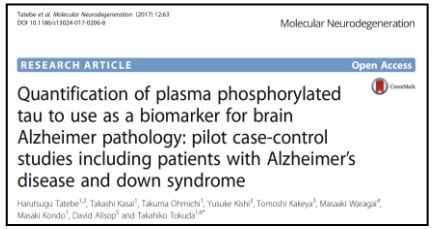
Plasma vs. CSF Aβ42 and Aβ40 (IP Mass spec)



➔ Plasma and CSF levels of Aβ42 or Aβ40 do not correlate, *regardless* of analytical technique used

➔ Biomarker (not assay) problem, suggesting that only a minor portion of plasma Aβ comes from the brain

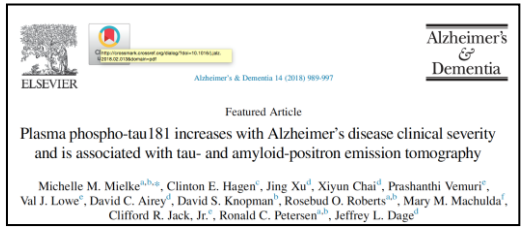
Plasma p-tau – how it started



Molecular Neurodegeneration

RESEARCH ARTICLE Open Access

Quantification of plasma phosphorylated tau to use as a biomarker for brain Alzheimer pathology: pilot case-control studies including patients with Alzheimer's disease and down syndrome



ELSEVIER

Alzheimer's & Dementia

Featured Article

Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography

Michelle M. Mielke, Clinton E. Hagen, Jing Xu, Xiyun Chai, Prashanthi Vemuri, Val J. Lowe, David C. Airey, David S. Knopman, Rosebud O. Roberts, Mary M. Machulda, Clifford R. Jack, Jr., Ronald C. Petersen, Jeffrey L. Dage

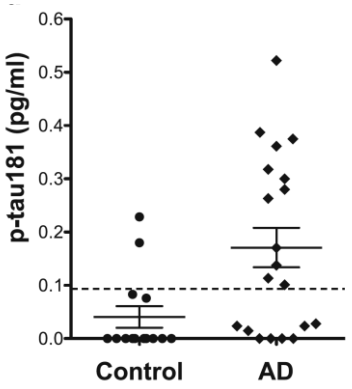
Plasma p-tau181 measured by AT270-modified version of Simoa T-tau

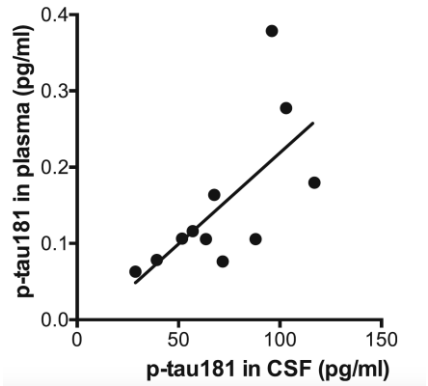
Cohort: 15 controls, 20 AD dementia

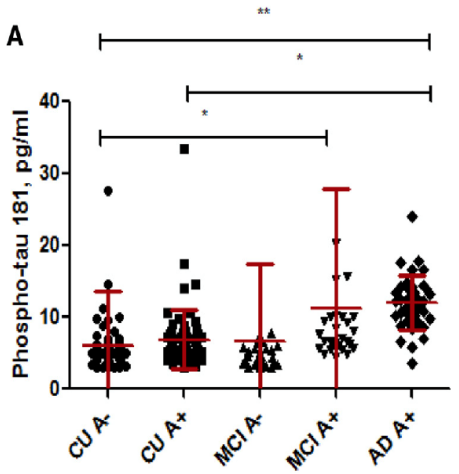
Plasma p-tau181 (AT270) – MSD

Mayo cohort: 172 CU, 57 MCI, 40 AD dementia

Stratification by amyloid PET







AUC 0.80 for amyloid PET+

P-tau181 correlates with tauPET in A+ CU and MCI/AD cases

➔ **Very promising results for plasma P-tau181 a blood biomarker for AD, correlating with CSF P-tau181 levels and associated with amyloid and tau PET measures of AD pathology**

The three current plasma P-tau biomarkers in AD

Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts

Plasma p-tau181
UGOT Simoa method (now Quanterix)
BioFinder cohort, 763 cases

JAMA | Original Investigation

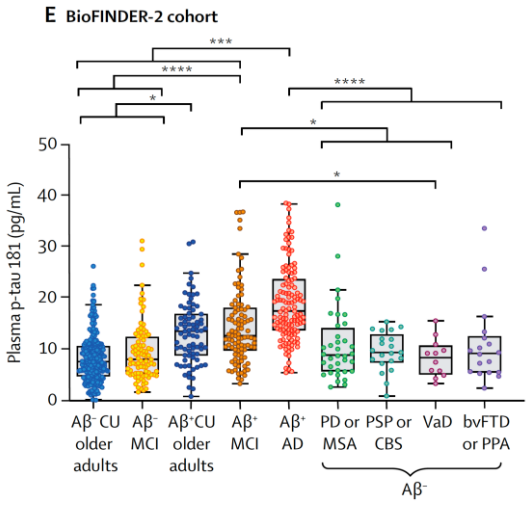
Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders

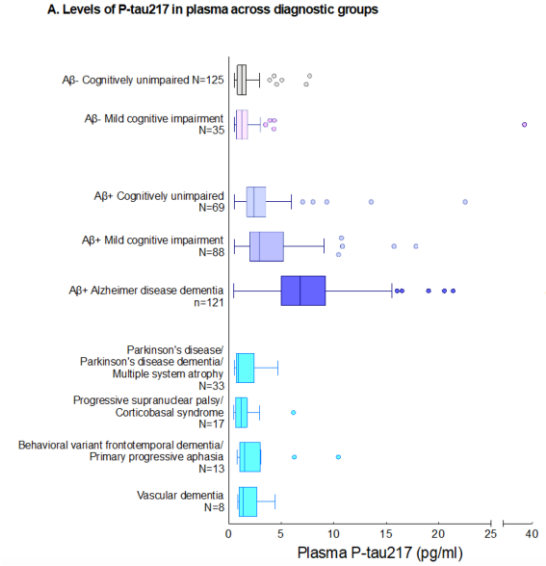
Plasma p-tau217
Lilly MSD method
BioFinder cohort, 738 cases

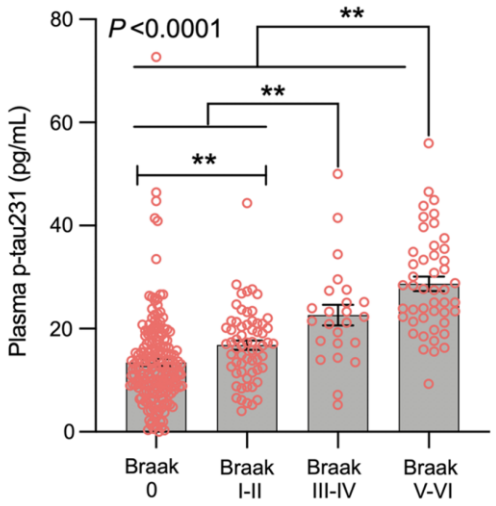
ORIGINAL PAPER

Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology

Plasma p-tau231
UGOT Simoa method
TRIAD cohort, 313 cases







- ➔ **P-tau 181 and 217 and 231 biomarkers are increased in AD dementia and Aβ+ MCI and also in Aβ+ CU P-tau 217 has the largest fold change**
- ➔ **Plasma P-tau does not change in other tauopathies or dementias**
- ➔ **Plasma P-tau increases with more severe tau pathology**

Comparing P-tau biomarkers - plasma P-tau217 and P-tau181

Lancet Neurol 2021; 20: 739–52

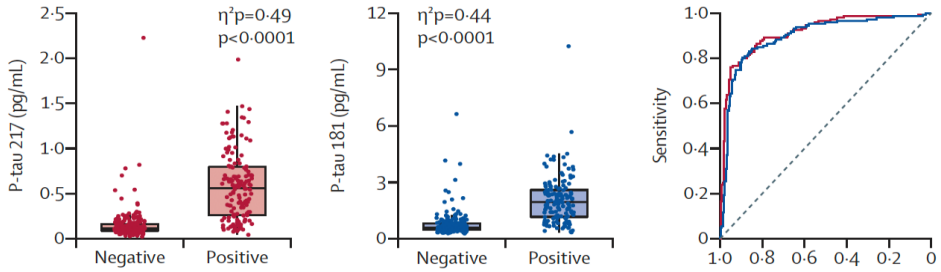
Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study

Elisabeth H Thijssen*, Renaud La Joie*, Amelia Strom, Corrina Fonseca, Leonardo Iaccarino, Amy Wolf, Salvatore Spina, Isabel E Allen, Yann Cobigo, Hilary Heuer, Lauren VandeVrede, Nicholas K Proctor, Argentina Lario Lago, Suzanne Baker, Rajeev Sivasankaran, Agnieszka Kieloch, Arvind Kinhikar, Lili Yu, Marie-Anne Valentin, Andreas Jeromin, Henrik Zetterberg, Oskar Hansson, Niklas Mattsson-Carlgren, Danielle Graham, Kaj Blennow, Joel H Kramer, Lea T Grinberg, William W Seeley, Howard Rosen, Bradley F Boeve, Bruce L Miller, Charlotte E Teunissen, Gil D Rabinovici, Julio C Rojas, Jeffrey L Dage, Adam L Boxer, on behalf of the Advancing Research and Treatment for Frontotemporal Lobar Degeneration investigators†

Clinical cohort of AD and FTD spectrum patients and controls
360 with amyloid PET and 230 with tau PET

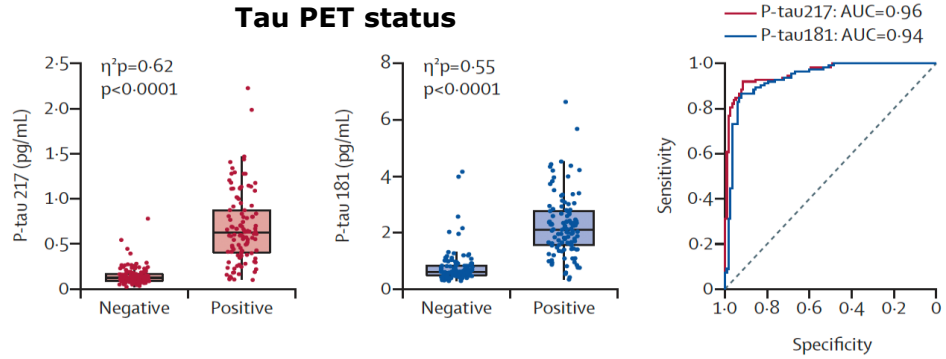
Plasma P-tau181 and P-tau217 measured using identical MSD assays that *only differed* in p-tau epitope specificity

Amyloid PET status



Amyloid PET pos vs. neg
Fold change P-tau217 3.9
P-tau181 2.5

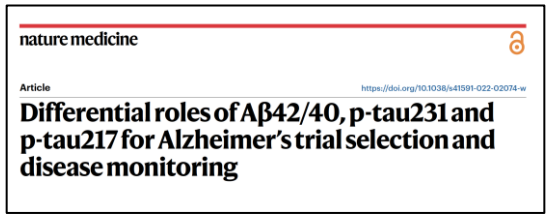
Tau PET status



Tau PET pos vs. neg
Fold change P-tau217 4.5
P-tau181 2.5

➔ **P-tau181 and P-tau217 have similar accuracy to identify brain amyloidosis and tau pathology**
➔ **Fold change is higher for P-tau217 (verified in many studies)**

Detailed comparison of plasma P-tau181, 217 and 231 – BioFinder


nature medicine

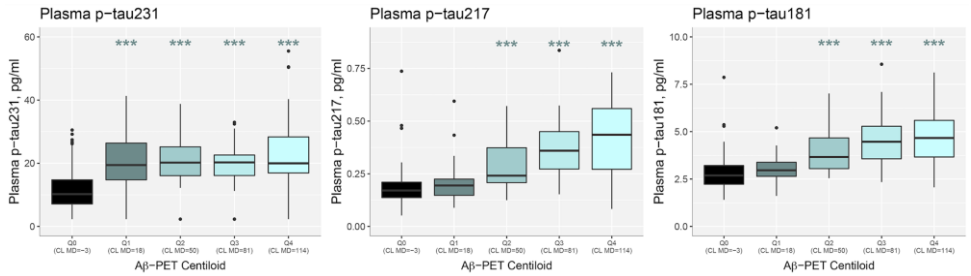
Article

https://doi.org/10.1038/s41591-022-02074-w

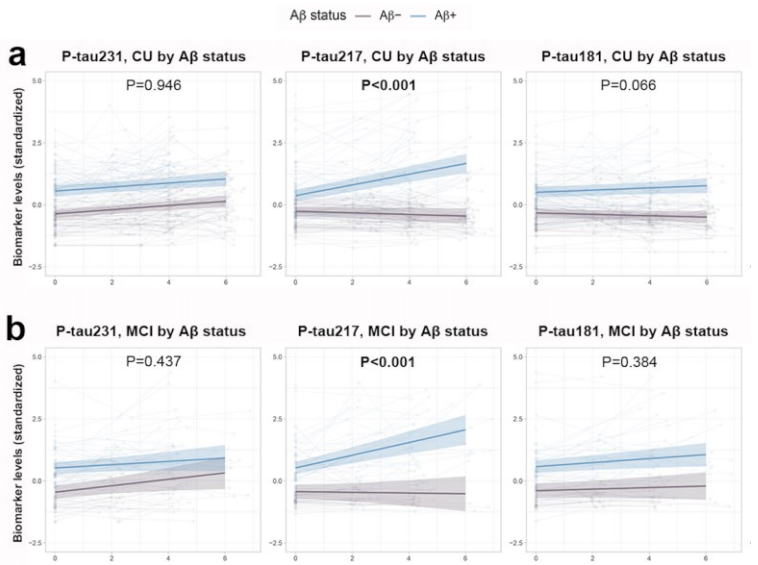
Differential roles of Aβ42/40, p-tau231 and p-tau217 for Alzheimer's trial selection and disease monitoring

Ashton N, …., Blennow K, Hansson O.

BioFinder 1 cross-sectional cohort, n= 575 (388 CU, 187 MCI)
longitudinal cohort n= 242 (147 CU, 95 MCI)



Plasma P-tau231 is more changed (than 217 or 181) at lower thresholds of amyloid pathology



Longitudinally, P-tau217 shows an amyloid-associated increases over 4-6 years, in both CU and MCI stages

➔ **Plasma P-tau231 seems to be earlier (more responsive to minor amyloid pathology)**
➔ **P-tau217 to better track disease progression (higher fold change with more severe disease)**

Plasma P-tau probability score – a two-step screening workflow

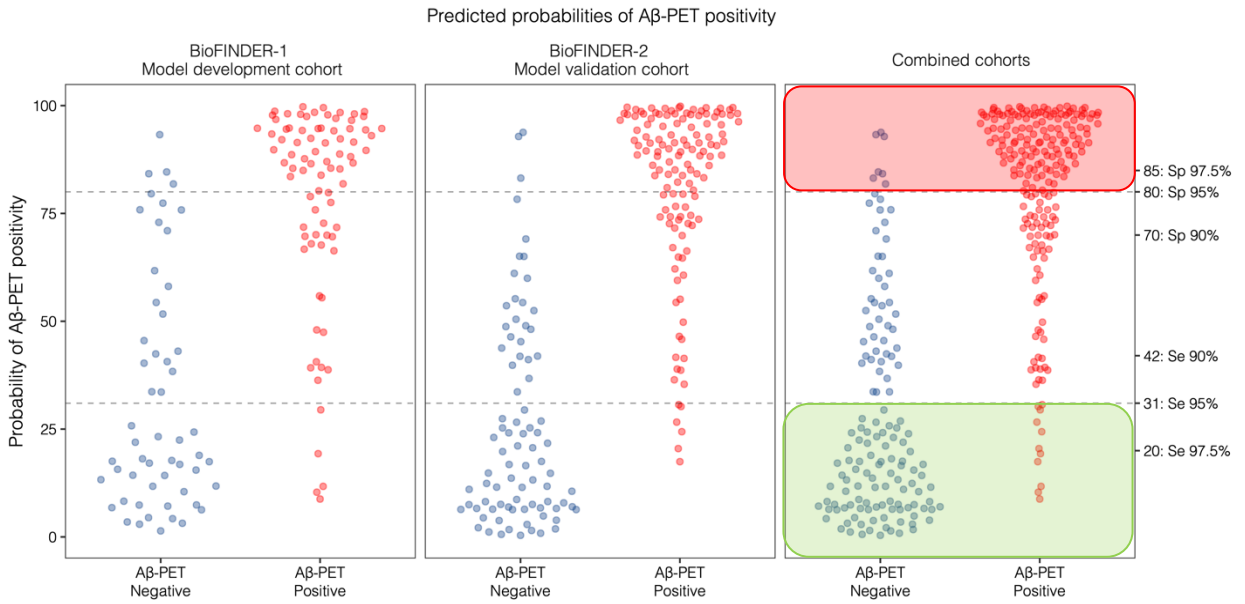
Logistic regression model to predict Aβ-PET positivity:

plasma p-tau217, age, *APOE* ε4

Development cohort BioFinder-1 n=136 MCI patients
Validation cohort BioFinder-2 n=212 MCI patients

Plasma P-tau217 performance for Aβ-PET positivity (single cut-off):

Development cohort ➔ Sens 78.0 % Spec 81.5 %
Validation cohort ➔ Sens 87.6 % Spec 83.1 %



➔ High probability

➔ Intermediate group

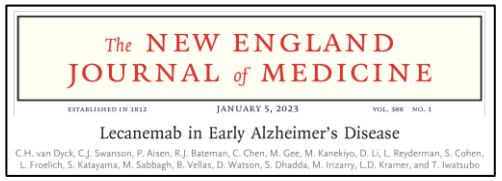
➔ Low risk group

More stringent cut-offs ➔ more accurate prediction of risk for brain amyloidosis at the expense of a larger intermediate risk group

Reduction in # of CSF / PET tests goes from 86% ➔ 73% ➔ 61%

Brum, Blennow, Hansson

Plasma P-tau to monitor downstream treatment effects of Aβ immunotherapy


The NEW ENGLAND JOURNAL of MEDICINE

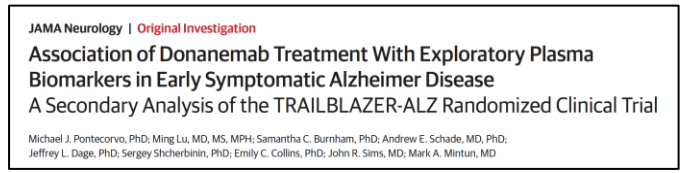
ESTABLISHED IN 1812 JANUARY 5, 2023 VOL. 388 NO. 1

Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

Lecanemab Phase III trial

Aβ protofibril antibody


JAMA Neurology | Original Investigation

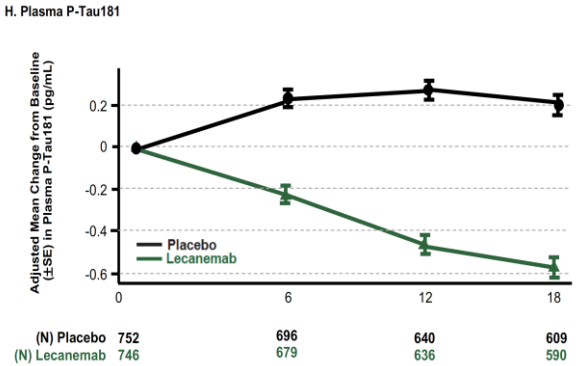
Association of Donanemab Treatment With Exploratory Plasma Biomarkers in Early Symptomatic Alzheimer Disease

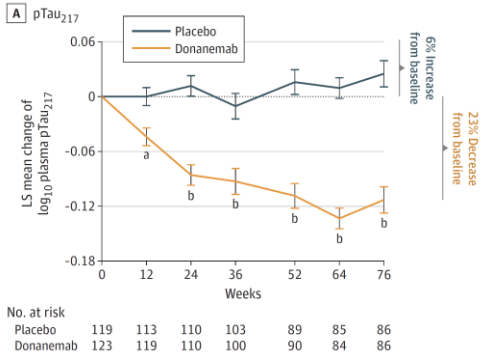
A Secondary Analysis of the TRAILBLAZER-ALZ Randomized Clinical Trial

Michael J. Pontecorvo, PhD; Ming Lu, MD, MS, MPH; Samantha C. Burnham, PhD; Andrew E. Schade, MD, PhD; Jeffrey L. Dage, PhD; Sergey Shcherbinin, PhD; Emily C. Collins, PhD; John R. Sims, MD; Mark A. Mintun, MD

Donanemab Phase II trial

Pyroglutamate-Aβ antibody





➔ **Reduction in plasma pTau181 from month 6 and on**

➔ **Reduction in plasma pTau217 (23%) from week 12 and on**

Table 2 Clinical performance of the six P-tau assays

	AD dementia	Controls	
	Median [IQR]	Median [IQR]	Fold change
P-tau181 Eli Lilly	11.1 [10.4–13.6]	6.1 [5.1–7.4]	1.8
P-tau181 ADx	37.6 [28.8–48.6]	13.2 [10.3–17.6]	2.9
P-tau181 Quanterix	3.4 [2.7–4.1]	1.6 [1.4–2.2]	2.0
P-tau217 Eli Lilly	0.7 [0.6–0.9]	0.17 [0.14–0.2]	4.1
P-tau231 ADx	7.3 [5.6–9.1]	5.5 [4.5–6.9]	1.3
P-tau231 Gothenburg	15.3 [13.9–19.8]	10.3 [8.9–11.9]	1.5

Bayoumy *et al.*
Alzheimer's Research & Therapy (2021) 13:198

Fold change of P-tau217 in AD is 4.1 (increase to 410 % of controls)

Plasma P-tau217 drops 23% from baseline level with donanemab

Will continued treatment (how long) take P-tau217 down to normal levels?

Will P-tau217 creep back up with discontinuation of treatment?

➔ **Can plasma P-tau be used to monitor Aβ immunotherapy in the clinic ?**

The future of AD blood biomarkers

Current clinical trials on biomarker performance are from highly specialized research centers

- defined patient cohorts and samples analyzed in one batch where optimal parameters can be determined

Clinical validation with prospective studies for real-world application

- "real-life" patient populations (range of pathologies including AD and other dementias; co-morbidities)

AND

- "clinical routine-like" lab analyses (pre-set fixed parameters; daily/weekly analyses; different reagent batches)

Data also needed on differences or interferences in relation to:

- age-dependency; ethnicity; comorbidities; drug interactions

Future clinical use of blood biomarkers will likely depend on:

- Performance and robustness of biomarker algorithms (e.g. P-tau + ApoE4) as well as logistics and economics

Thanks for listening !

Amyloid imaging for accurate diagnosis and targeted therapy to prevent Alzheimer's disease

Giovanni Frisoni, MD, Professor of Clinical Neuroscience (University of Geneva),
Director of the Memory Clinic at Geneva University Hospital

UNIVERSITÉ DE GENÈVE

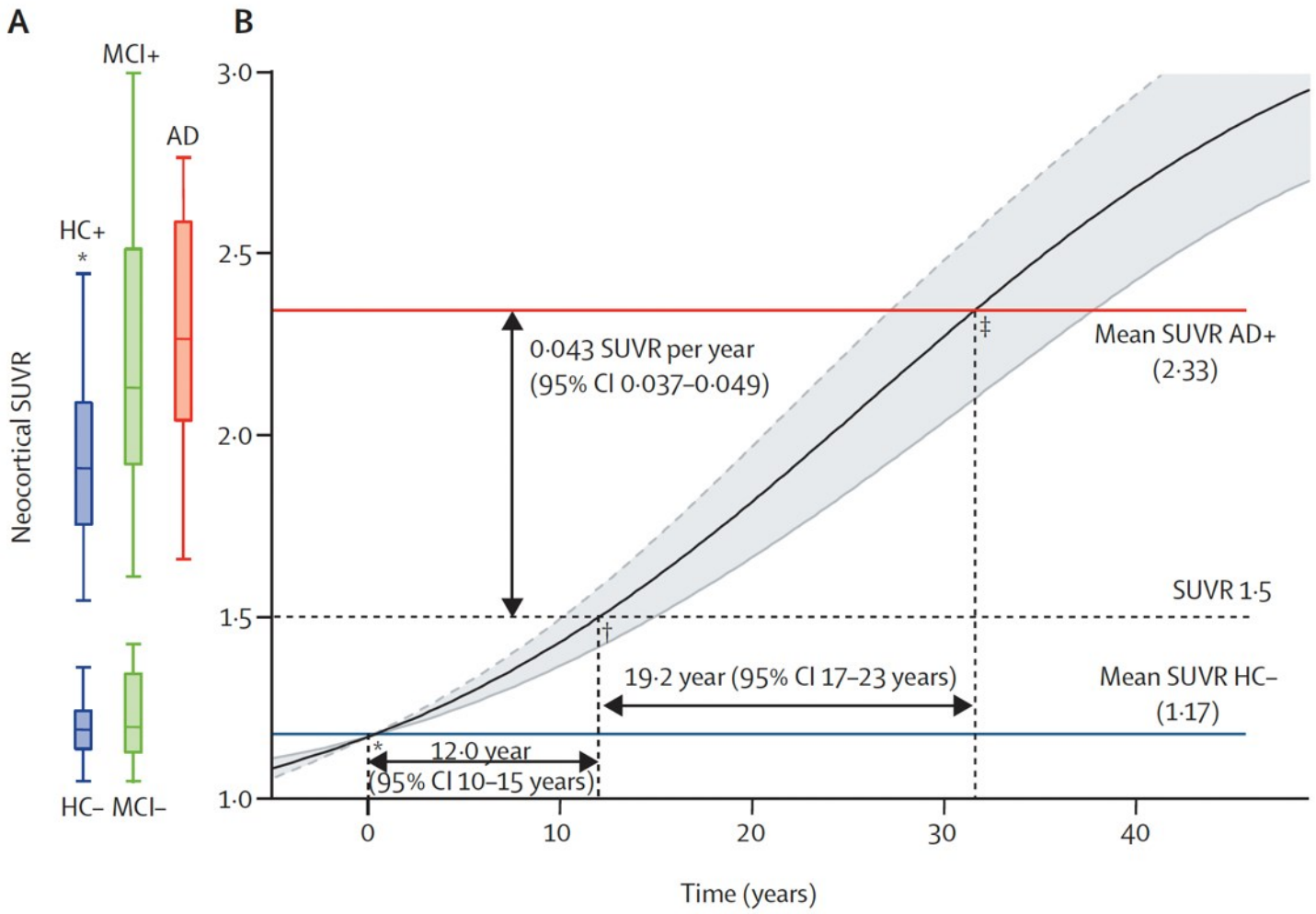
HUG Hôpitaux Universitaires Genève

Where human amyloid research started for real:

11C-labelled tracers for research
18F-labelled tracers in the clinic

Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study with 11C-PIB

Lancet Neurol 2013; 12: 357–67

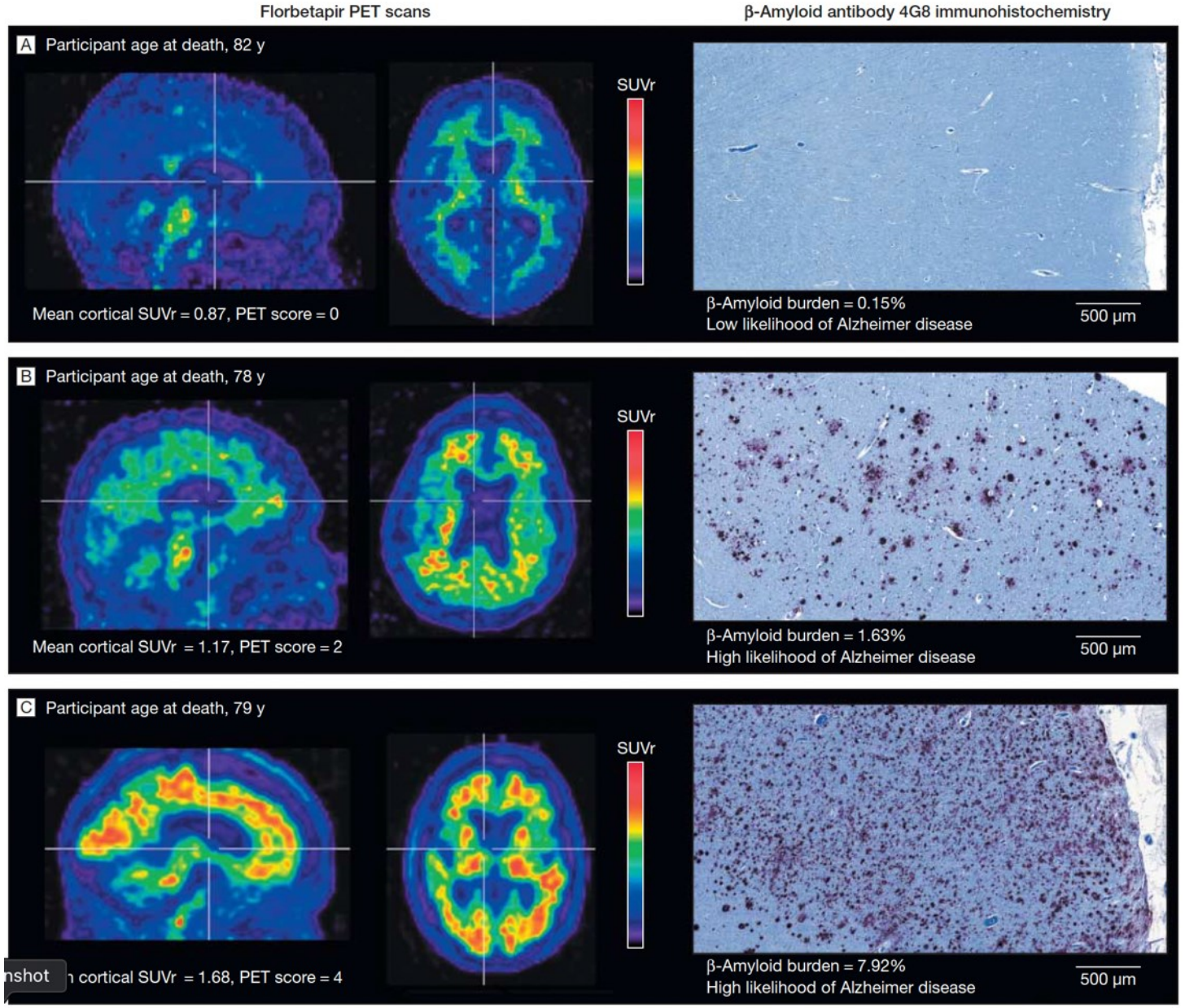


18F-labeled amyloid PET tracers

No / sparse

Moderate

Frequent



Clark CM et al., JAMA, 2011

Amyloid PET in the clinic

Where does amyloid PET stand in its pathway to validation?

	Phase 1: preclinical exploratory studies; PA	Phase 2: clinical assay development for Alzheimer's disease pathology					Phase 3: retrospective studies using longitudinal data available in repositories						Phase 4: prospective diagnostic accuracy studies					Phase 5: disease burden reduction studies; PA
		PA	SA1	SA2	SA3	SA4	PA1	PA2	SA1	SA2	SA3	SA4	PA	SA1	SA2	SA3	SA4	
MRI medial temporal atrophy*	Full	Full	Part	Full	Full	Full	Full	PE	Part	Part	Part	NA	NE	NE	NE	NE	NE	NE
^{18}F-fluorodeoxy-glucose PET	Full	Full	Full	Full	Full	Part	Full	Part	PE	Part	Part	PE	NE	PE	NE	PE	NE	NE
^{11}C-PiB and fluorinated tracers for amyloid PET†	Full	Full	Part	Full	Part	Part	Full	Part	NE	Part	Part	PE	NE	NE	NE	NE	NE	NE
CSF measures (Aβ42 or Aβ42:Aβ40 or total tau and hyperphosphorylated tau)	Full	Full	PE	Full	Part	Part	Full	Part	Part	Part	Part	PE	PE	NE	NE	NE	NE	NE

PA=primary aim. SA=secondary aim. Full=Phase fully achieved (no need to collect further evidence). Part=Phase partly achieved (studies available but replication or completion is required). PE=only preliminary evidence available. NA=not applicable. NE=no evidence available. PiB=Pittsburgh compound. Aβ=fibrillar β-amyloid. *Assessments represent the least developed level between visual and volumetric medial temporal atrophy. †Using tracers such as florbetapir, flutemetamol, or florbetaben.

Table 4: State of completion of biomarkers development in Alzheimer's disease for the five phases in the strategic roadmap

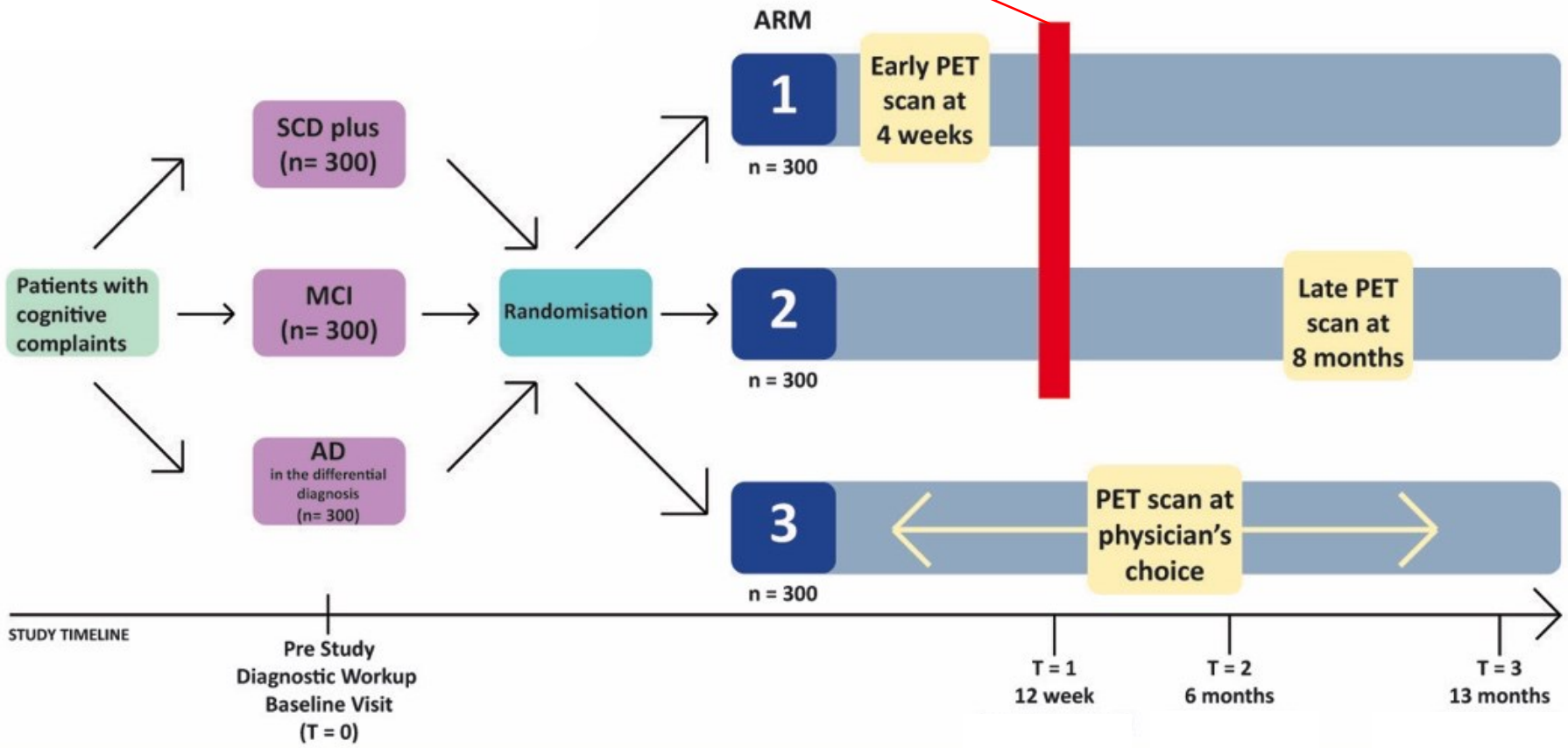
Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers

Lancet Neurol 2017; 16: 661–76

Giovanni B Frisoni, Marina Boccardi, Frederik Barkhof, Kaj Blennow, Stefano Cappa, Konstantinos Chiotis, Jean-Francois Démonet, Valentina Garibotto, Panteleimon Giannakopoulos, Anton Gietl, Oskar Hansson, Karl Herholz, Clifford R Jack Jr, Flavio Nobili, Agneta Nordberg, Heather M Snyder, Mara Ten Kate, Andrea Varrone, Emiliano Albanese, Stefanie Becker, Patrick Bossuyt, Maria C Carrillo, Chiara Cerami, Bruno Dubois, Valentina Gallo, Ezio Giacobini, Gabriel Gold, Samia Hurst, Anders Lönneborg, Karl-Olof Lovblad, Niklas Mattsson, José-Luis Molinuevo, Andreas U Monsch, Urs Mosimann, Alessandro Padovani, Agnese Picco, Corinna Porteri, Osman Ratib, Laure Saint-Aubert, Charles Scerri, Philip Scheltens, Jonathan M Schott, Ida Sonni, Stefan Teipel, Paolo Vineis, Pieter Jelle Visser, Yutaka Yasui, Bengt Winblad

IMI2 AMYPAD
A randomised study to validate amyloid PET in the clinic

Primary Endpoint: Difference in the proportion of patients with an etiologic diagnosis with ≥90% confidence.

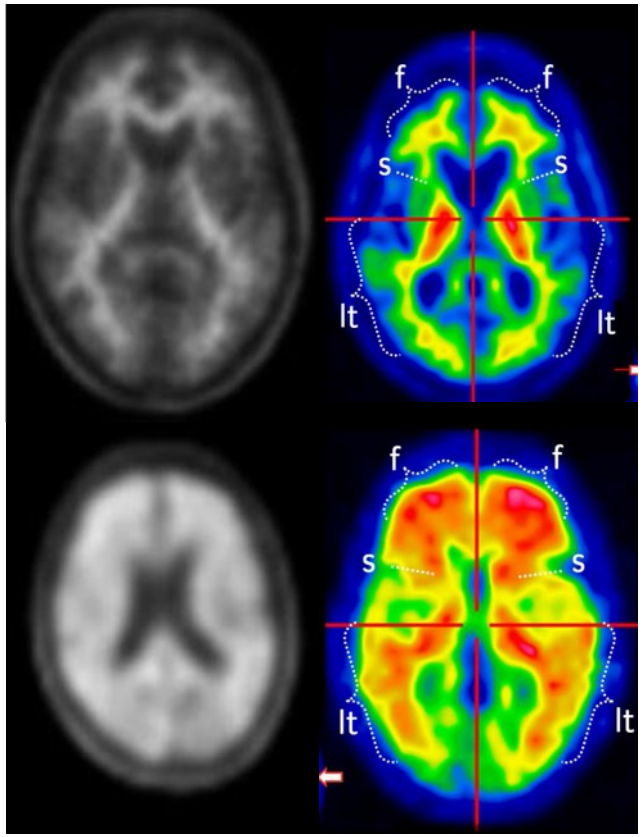


Secondary endpoints

Diagnosis and Confidence	Patient Management	Health Economic Outcomes	Imaging Assessment
Time to communicate etiological Dx	N. of patients randomized to AD clinical trials	Impact of patient reported outcomes	Estimate amyloid deposition over 18 months
Changes in etiological Dx over time	Change in Management Plan	Cost of diagnostic WU to high conf. Dx	Stand. methods of image quantitation
Changes of likelihood that ss are due to AD		Differences of use of medical resources	
Changes over time in utilization of amyloid PET imaging in Free Choice Arm		N. of subject discharged by memory clinic after exclusion of AD	

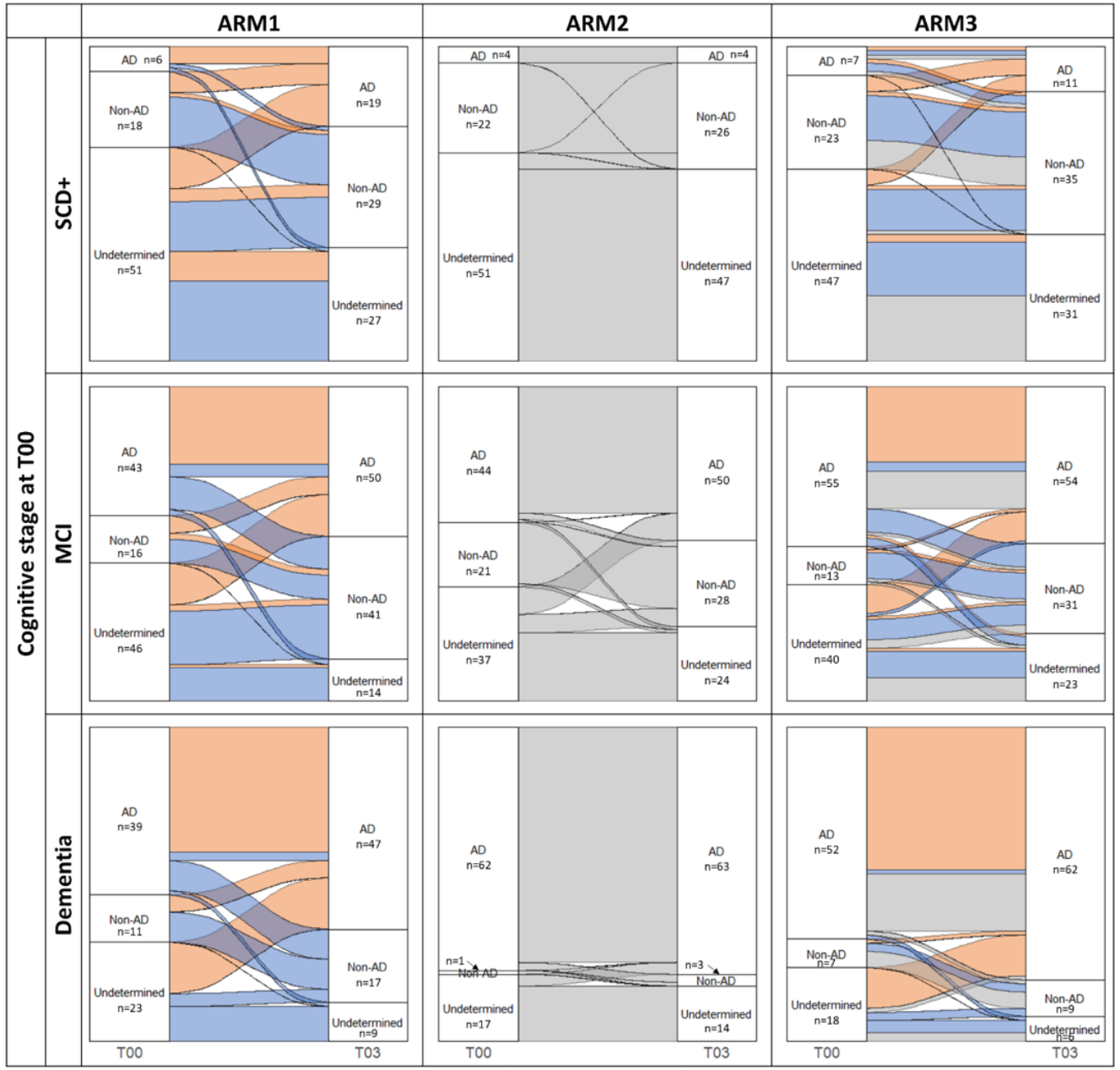
AMYPAD: Collaborative research centres

Neuraceq
UCL, London
CHU Toulouse
Cologne
VuMC, Amsterdam



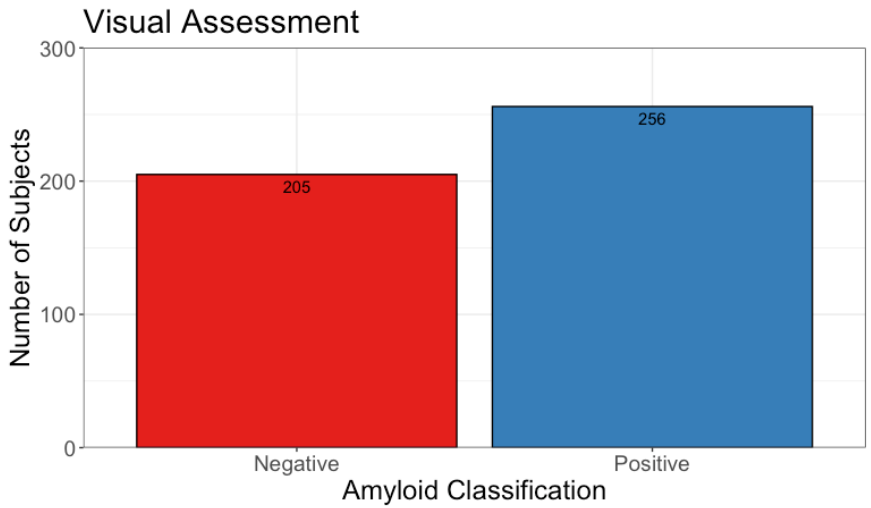
Vizamyl
HUG Geneva
Karolinska
Barcelona Beta
Edinburgh (flute IMP)

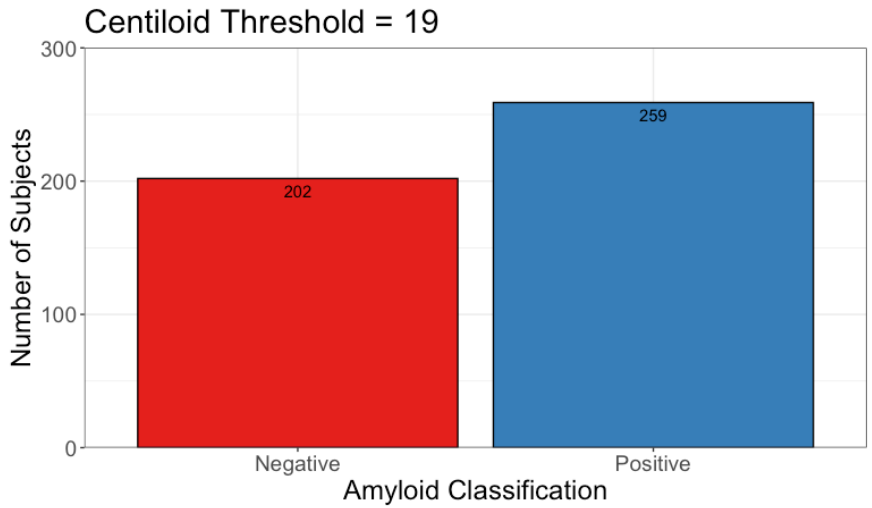
Amyloid PET changes diagnostic assignment



Altomare et al., JAMA Neurol 2023, in press

Agreement between visual image interpretation and quantitative analysis of [18F]flutemetamol PET in the Geneva Memory Center cohort





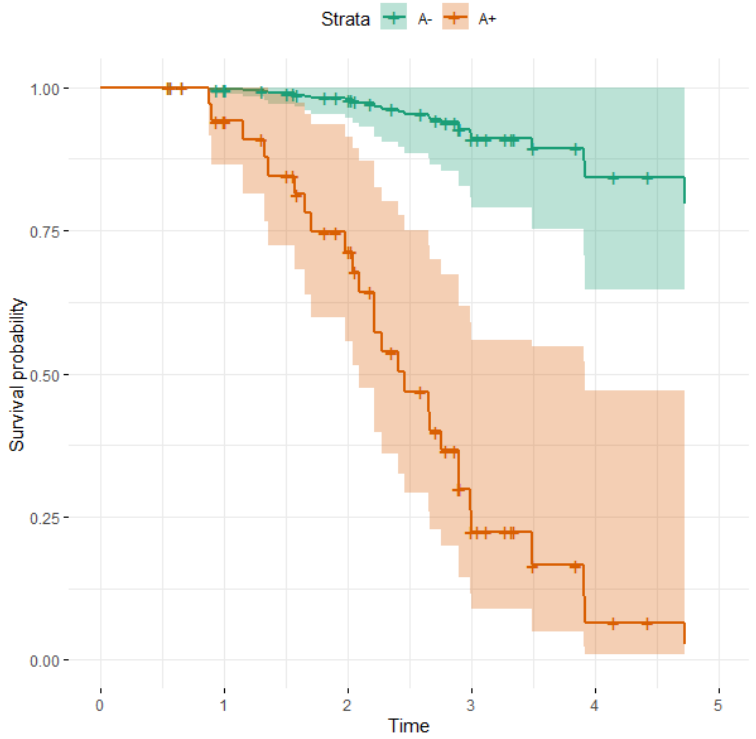
Percentage of agreement = 95.4%
Cohen's kappa = 0.91 ($p < 0.01$)
Number of discordant cases = 3

Threshold reference: https://doi.org/10.1016/j.jalz.2016.08.005

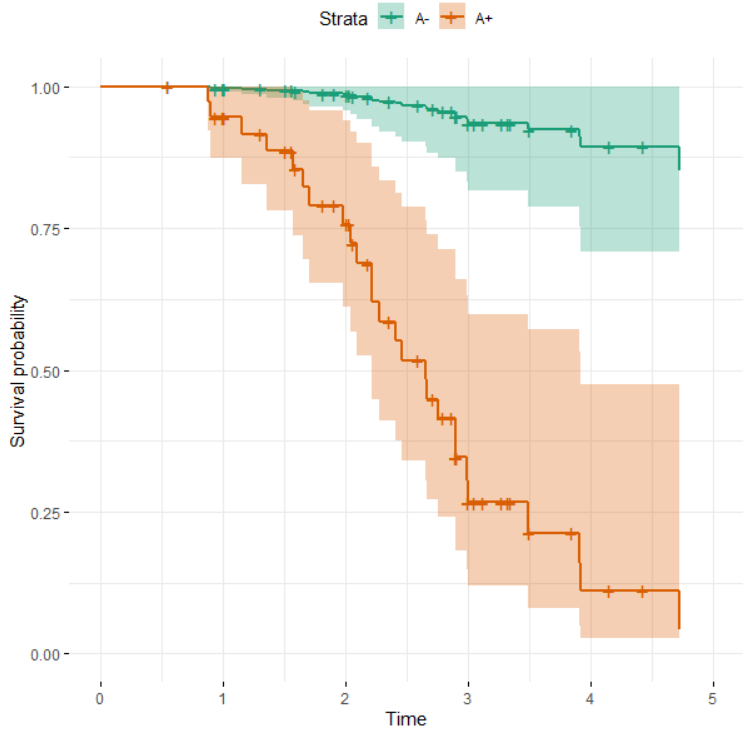
Visual image interpretation and quantitative analysis of [18F]flutemetamol PET to predict cognitive progression in MCI patients at the Geneva Memory Center

Model : **Amyloid** status (PET) cov. Age, sex and education

A – visual



A – centiloid (cut point 19)



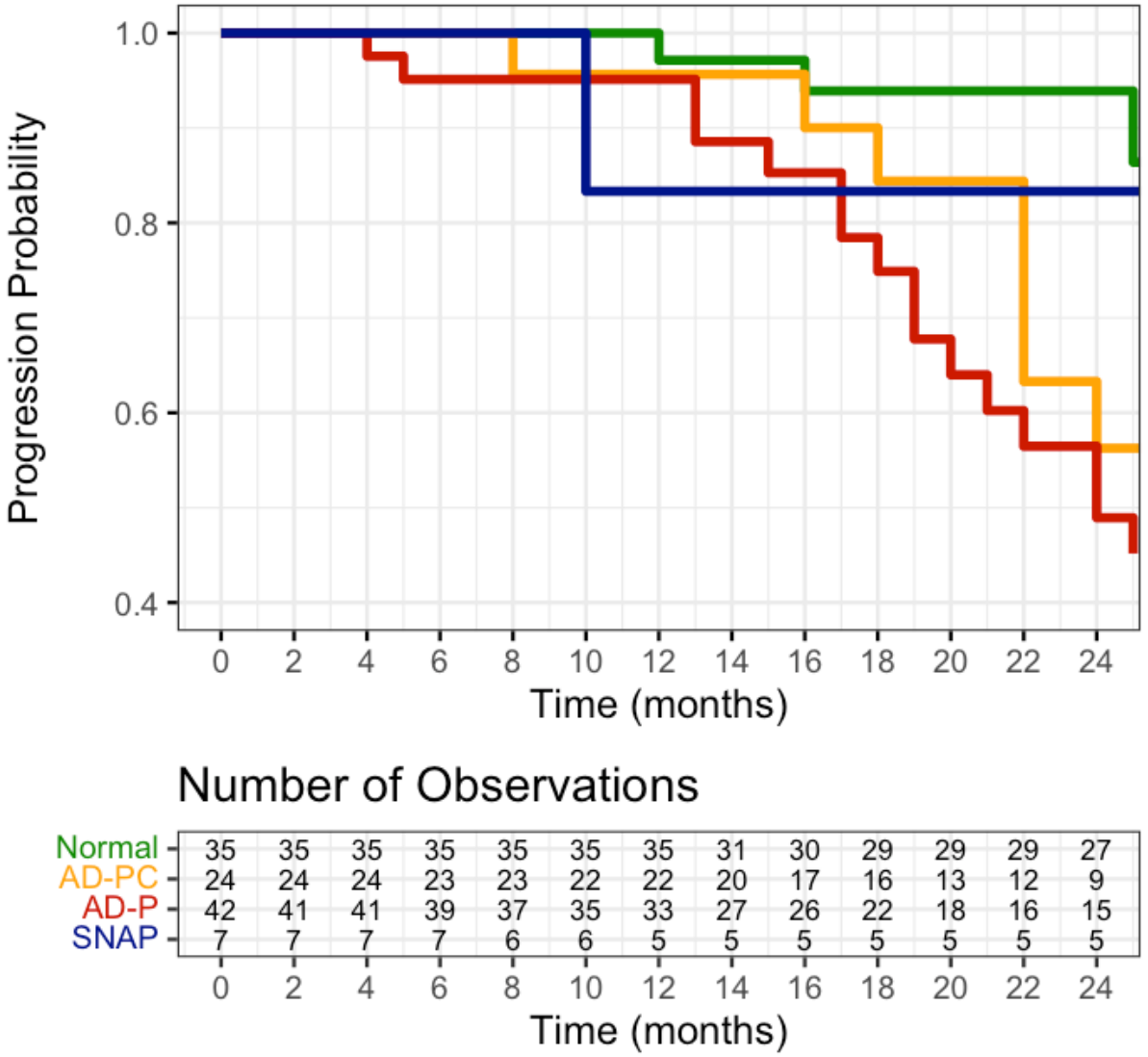
Peretti et al., submitted

A multisite analysis of the concordance between visual interpretation and quantitative analysis of [18F]flutemetamol PET

Table 3 a Summary of discordant and concordant scans when examining visual vs SUVr (Pons, optimized cut-off). b Summary of discordant scans when examining visual vs SUVr (Pons, 0.62 cut-off)

Study	Total cases	Total concordant V+Q+	Total concordant V-Q-	Total discordant	% Disc	Total borderline/Q+	Total borderline/Q-	Agreement
a								
GE	172	71	100	1	1%	-	-	99.4%
KAROLINSKA	207	94	97	0	0%	7	9	100%
MCK	928	634	242	52	6%	-	-	94.4%
ALFA+	361	24	311	24	7%	1	1	93.3%
BIOFINDER	401	117	270	14	3%	-	-	96.5%
AIBL	276	96	160	13	5%	2	5	95.2%
Total	2345	1036	1180	104	4% (mean)	10	15	94.4% (mean)

MCI A+T+ rapidly progress to dementia
A-T+ is a lower risk group



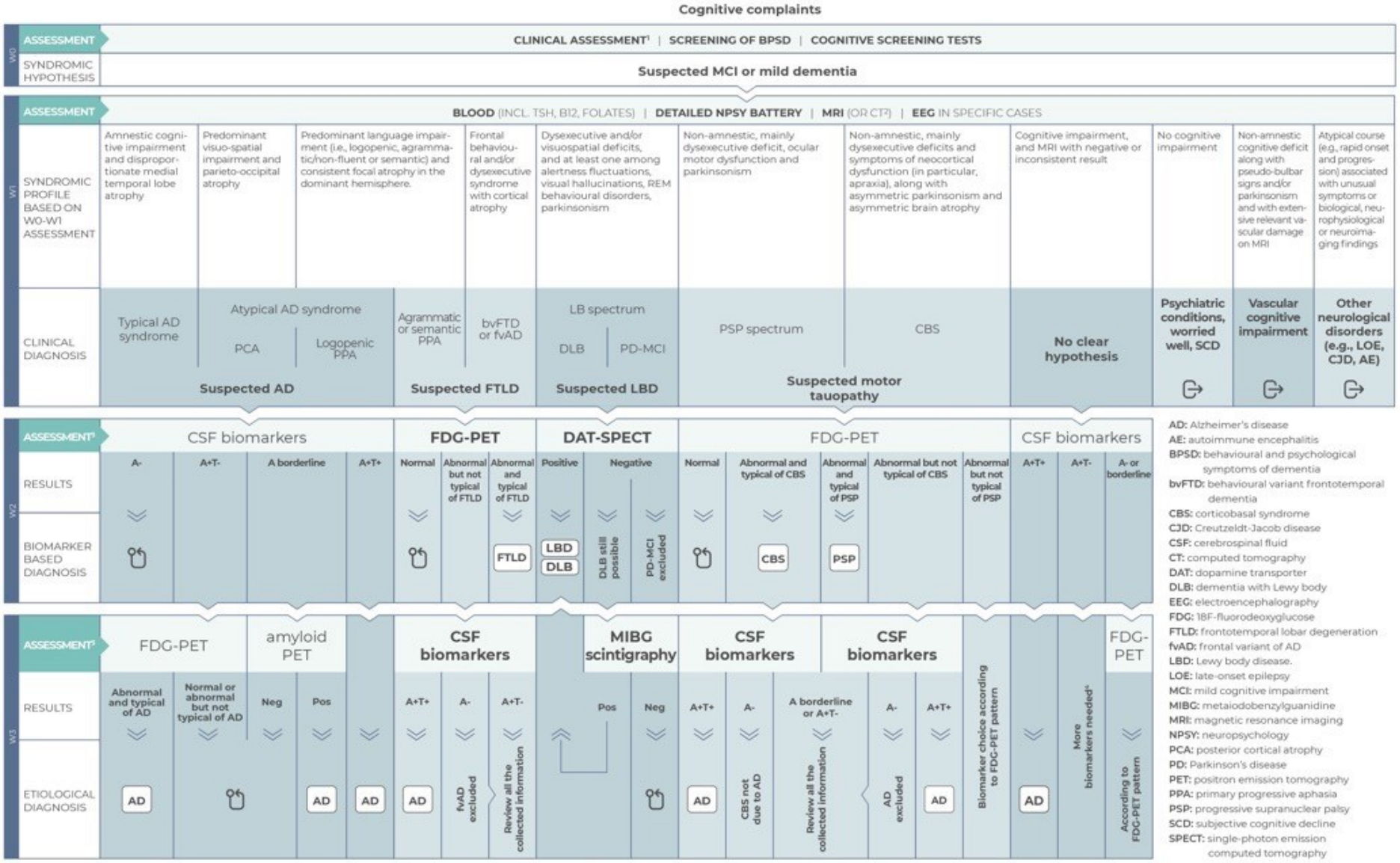
Peretti et al., 2023 in press

The biomarker-based diagnosis of cognitive complaints in the memory clinic

An inter-societal European Delphi workflow

The biomarker-based diagnosis of cognitive complaints in memory clinics

An inter-societal European Delphi workflow

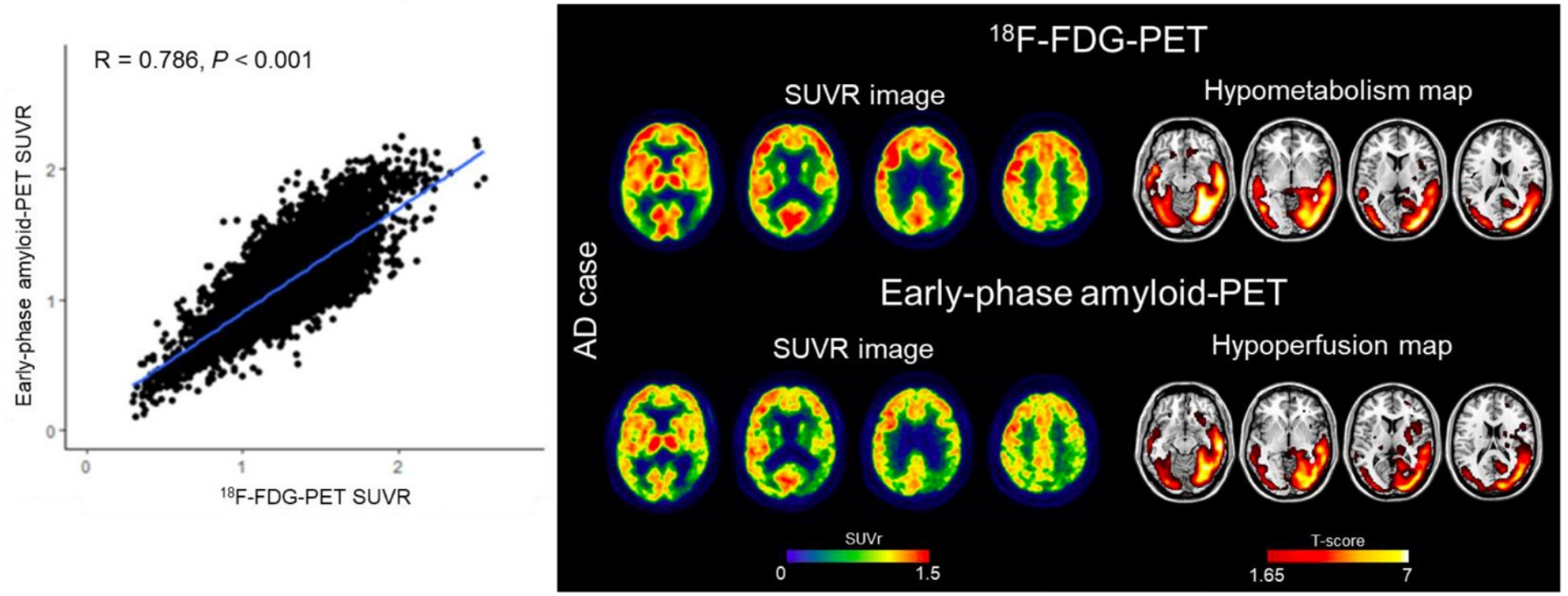


AD: Alzheimer's disease
AE: autoimmune encephalitis
BPSD: behavioural and psychological symptoms of dementia
bvFTD: behavioural variant frontotemporal dementia
CBS: corticobasal syndrome
CJD: Creutzeldt-Jacob disease
CSF: cerebrospinal fluid
CT: computed tomography
DAT: dopamine transporter
DLB: dementia with Lewy body
EEG: electroencephalography
FDG: 18F-fluorodeoxyglucose
FTLD: frontotemporal lobar degeneration
fvAD: frontal variant of AD
LBD: Lewy body disease.
LOE: late-onset epilepsy
MCI: mild cognitive impairment
MIBG: metaiodobenzylguanidine
MRI: magnetic resonance imaging
NPSY: neuropsychology
PCA: posterior cortical atrophy
PD: Parkinson's disease
PET: positron emission tomography
PPA: primary progressive aphasia
PSP: progressive supranuclear palsy
SCD: subjective cognitive decline
SPECT: single-photon emission computed tomography

Maximising information from amyloid PET in the clinic

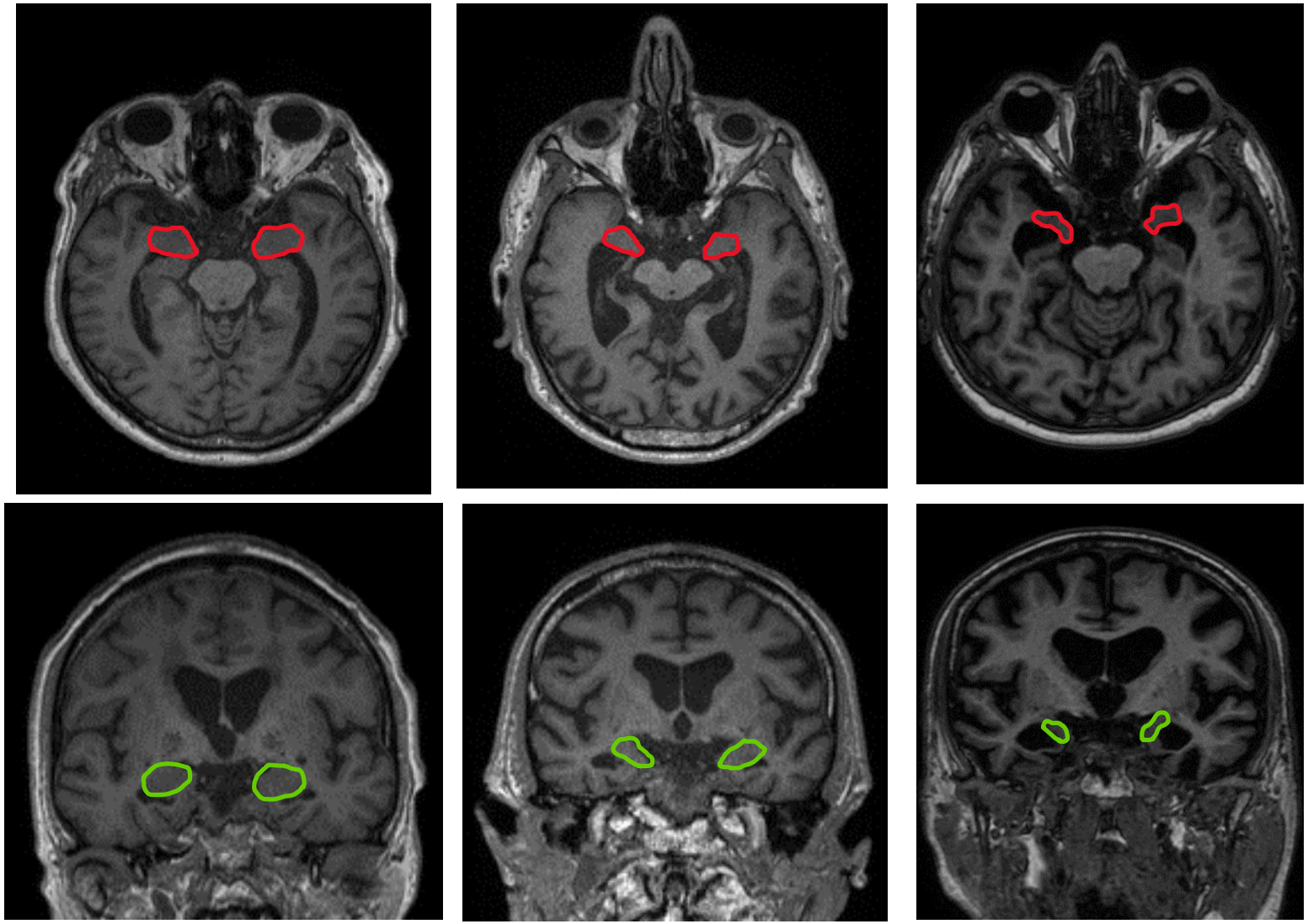
Early scans to assess cortical perfusion

AT GROUP LEVEL AND SINGLE-SUBJECT LEVEL



Boccalini et al., J Nucl Med 2022

Patients with Alzheimer phenotype and severe amygdalar atrophy (LATE - limbic predominant age-associated TDP-43 encephalopathy)



Normal
MTA+/Amygdala–

Mild atrophy
MTA+/Amygdala ±

Severe atrophy
MTA+/Amygdala+

Pizzini et al., in preparation

Dementia with Lewy bodies patients and amyloid comorbidity have poorer outcomes

TABLE 1. Demographics of DLB patients by AD CSF profile at baseline

Variable	AD CSF Profile: Pathological (n = 32)	AD CSF Profile: Normal (n = 68)	*P* Value
Age at baseline	74.22 ± 7.95	71.93 ± 7.79	0.176
Sex (%)			
Male	16 (26.2)	45 (73.8)	0.122
Female	16 (41.0)	23 (59.0)	
Years of education[a]	8.88 ± 3.34	10.63 ± 4.16	0.043
Disease duration[b]	2.79 ± 1.94	3.01 ± 2.58	0.678
MMSE	21.09	22.68	0.200
Median (range)	(5–30)	(6–30)	

Numbers represent mean and SD, if not otherwise stated.
Missing data: [a]education 9 patients; [b]duration 1 patient.

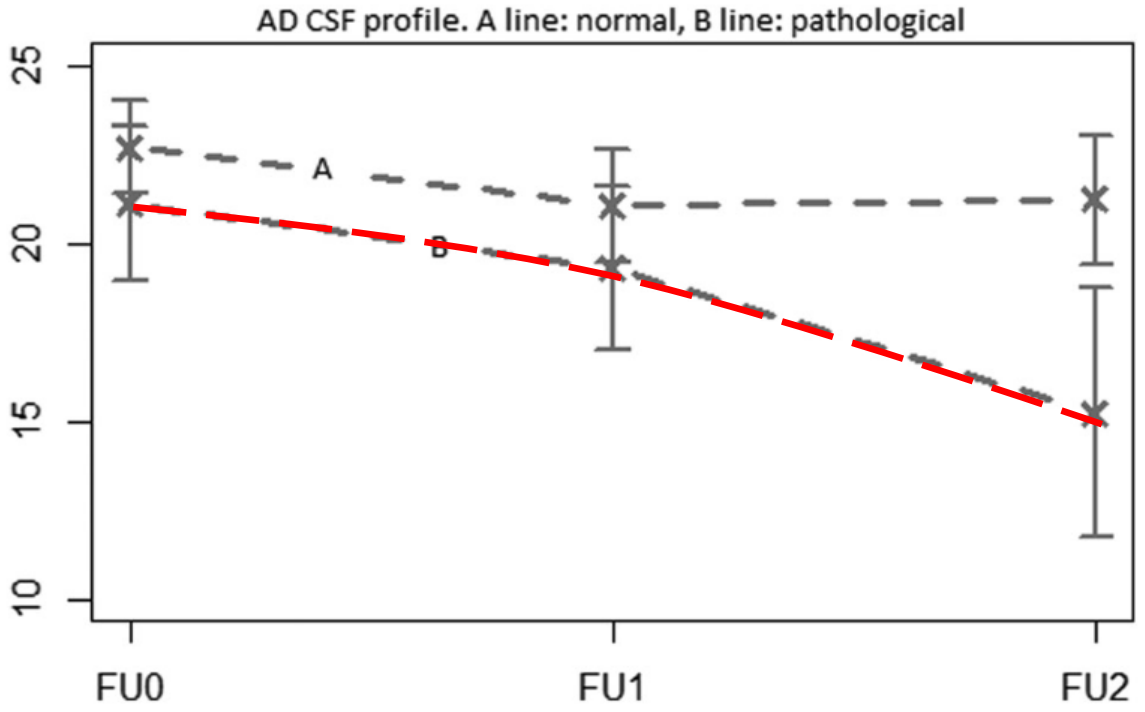


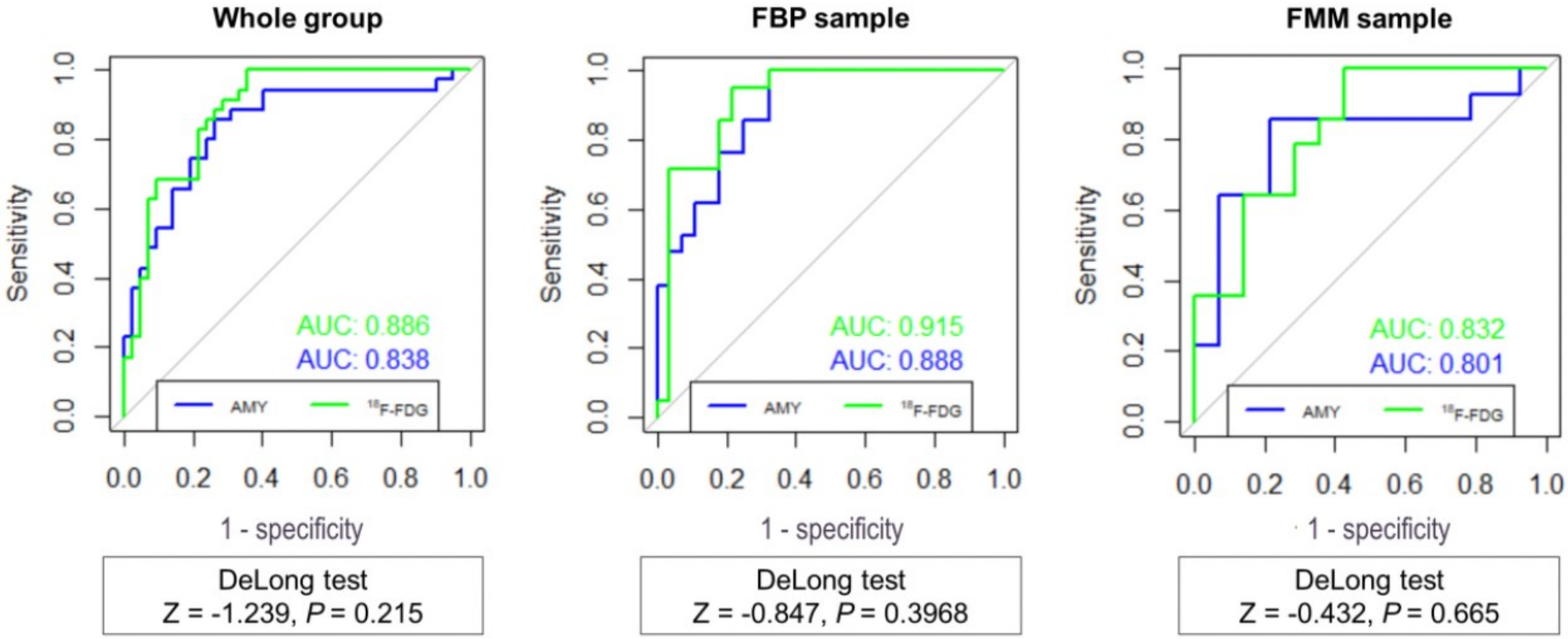
FIG. 1. Change in MMSE from baseline (FU0) to one (FU1) and two (FU2) years follow-up in those with (n = 32, Line B) and without (n = 68, Line A) a CSF AD profile. The difference was statistically significant (LME, $P = 0.04$).

α-syn marker lacking

Abdelnour et al., Mov Disord 2016

Maximising information from amyloid PET in the clinic

Early amy *vs*. FDG PET to discriminate AD from healthy controls



Boccalini et al., J Nucl Med 2022

Amyloid PET in clinical trials

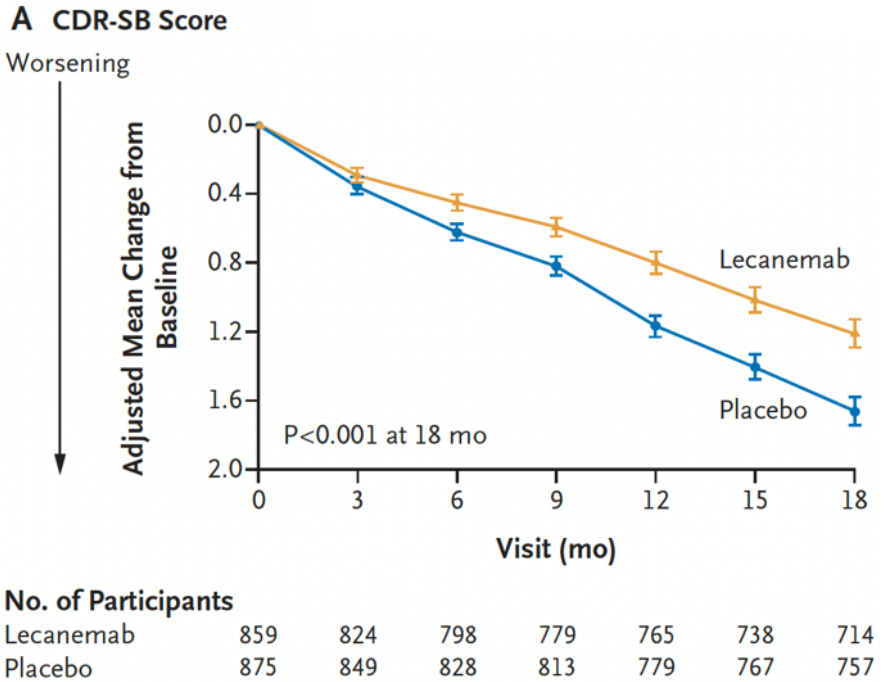
The CLARITY trial with lecanemab

Primary outcome

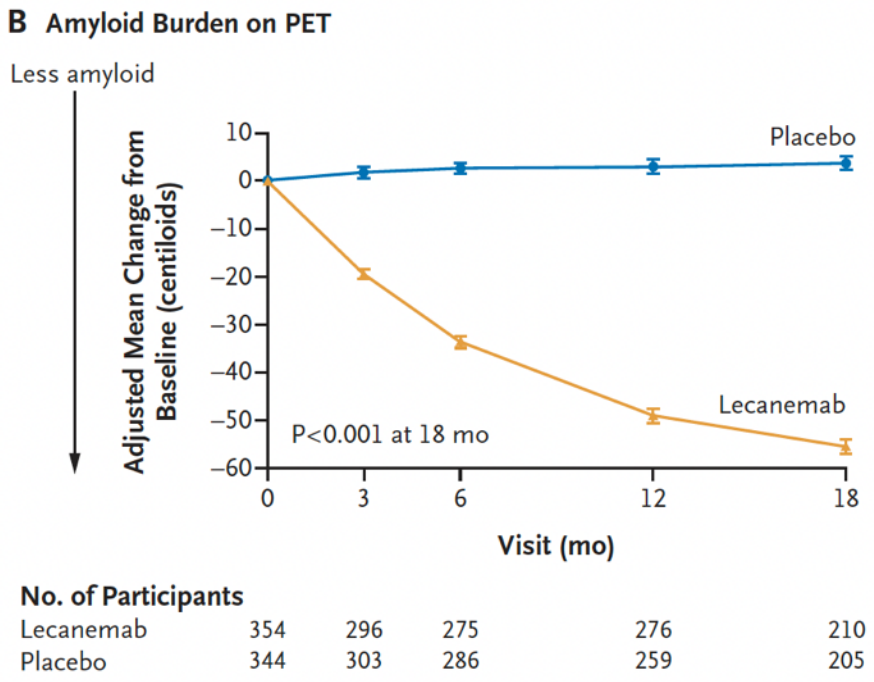
Slower progression on CDR-SOB of 0.45 points at 18 months (27%)

Secondary outcome

Reduction of amyloid PET tracer uptake of 59 centiloids at 18 months



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757



No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

Van Dyck et al. NEJM 2022 DOI: 10.1056/NEJMoa2212948

Why the differential response in clinical trials?

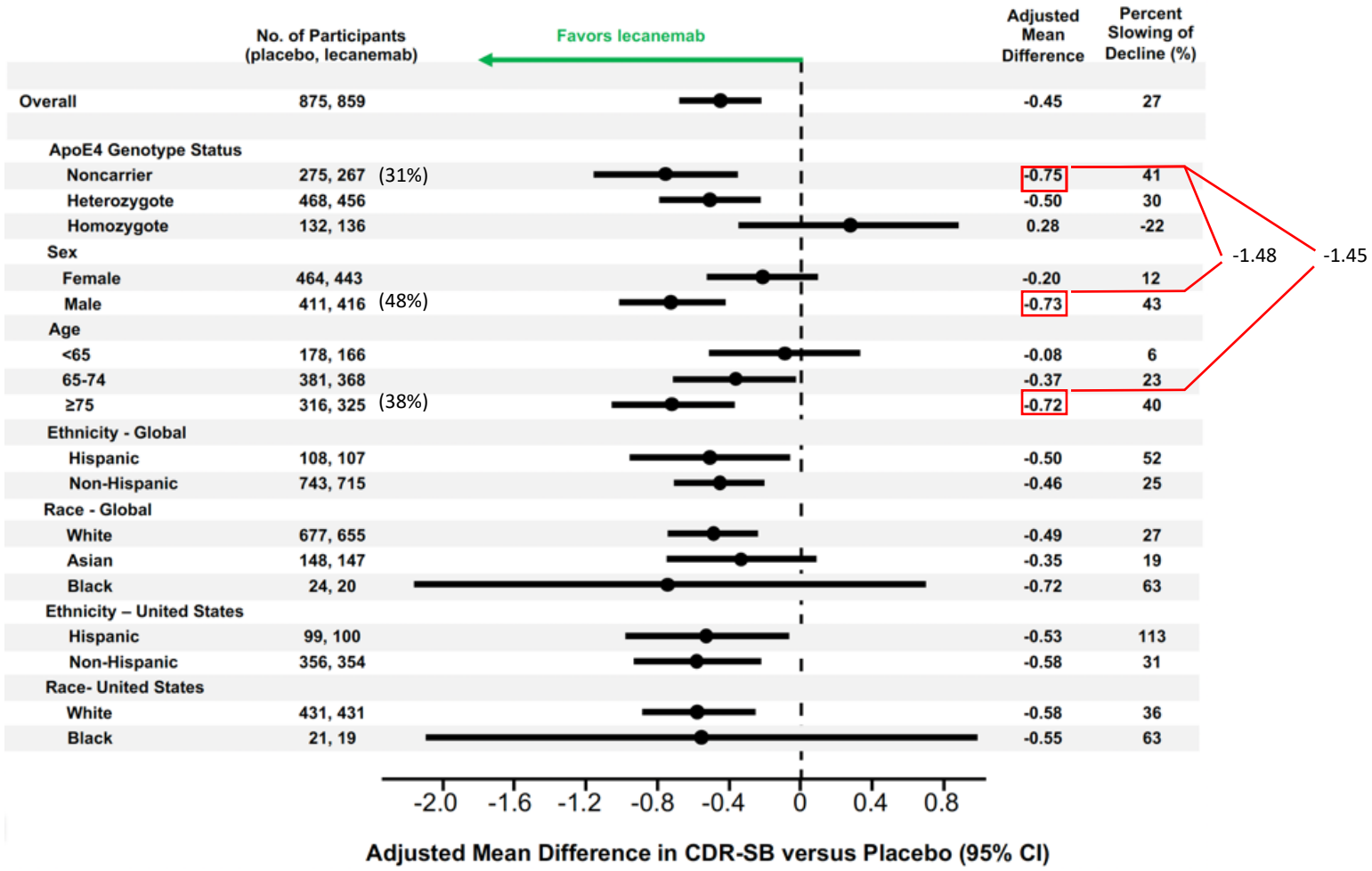
Trial	Antibody	Duration (yrs)	Baseline amyloid (centiloids)	Residual amyloid (centiloids)	CDR-SB (Δ vs placebo)
EMERGE (Ph3)	Aducanumab	1.5	85	25	-22% (-0.39; p=0.012)
CLARITY AD (Ph3)	Lecanemab	1.5	78	23	-27% (-0.45; p=0.00005)
Study 201 (Ph2)	Lecanemab	1.5	75	6	-26% (p=0.125)
TRAILBLAZER-ALZ (Ph2)	Donanemab	1.5	108	23	-23% (-0.36)
Negative					
ENGAGE (Ph3)	Aducanumab	1.5	91	37	2% (+0.03; p=0.833)
GRADUATE I (Ph3)	Gantenerumab	2.25	92	34	-8% (-0.31; p=0.054)
GRADUATE II (Ph3)	Gantenerumab	2.25	98	51	-6% (-0.19; p=0.2998)

-22% to -27% slowed decline at 18 months

Sevigny et al., Nature 2016; Budd Haeberlein et al., J PrevAlzDis 2022; Budd Haeberlein et al., AD/PD 2021; Castrillo-Vigueraet al., CTAD2021; clinicaltrials.gov; Van Dyck et al., NEJM 2022; Swanson et al., Alzheimer's Res Ther. 2021, Biogen news releases July 25, 2018 & Sept 27, 2022 https://investors.biogen.com, Mintunet al., NEJM 2021; Bateman et al., CTAD2022.

Courtesy of Roger NITSCH, Uni Zurich

Complete amyloid removal might explain some unexpected results of sub-group analysis

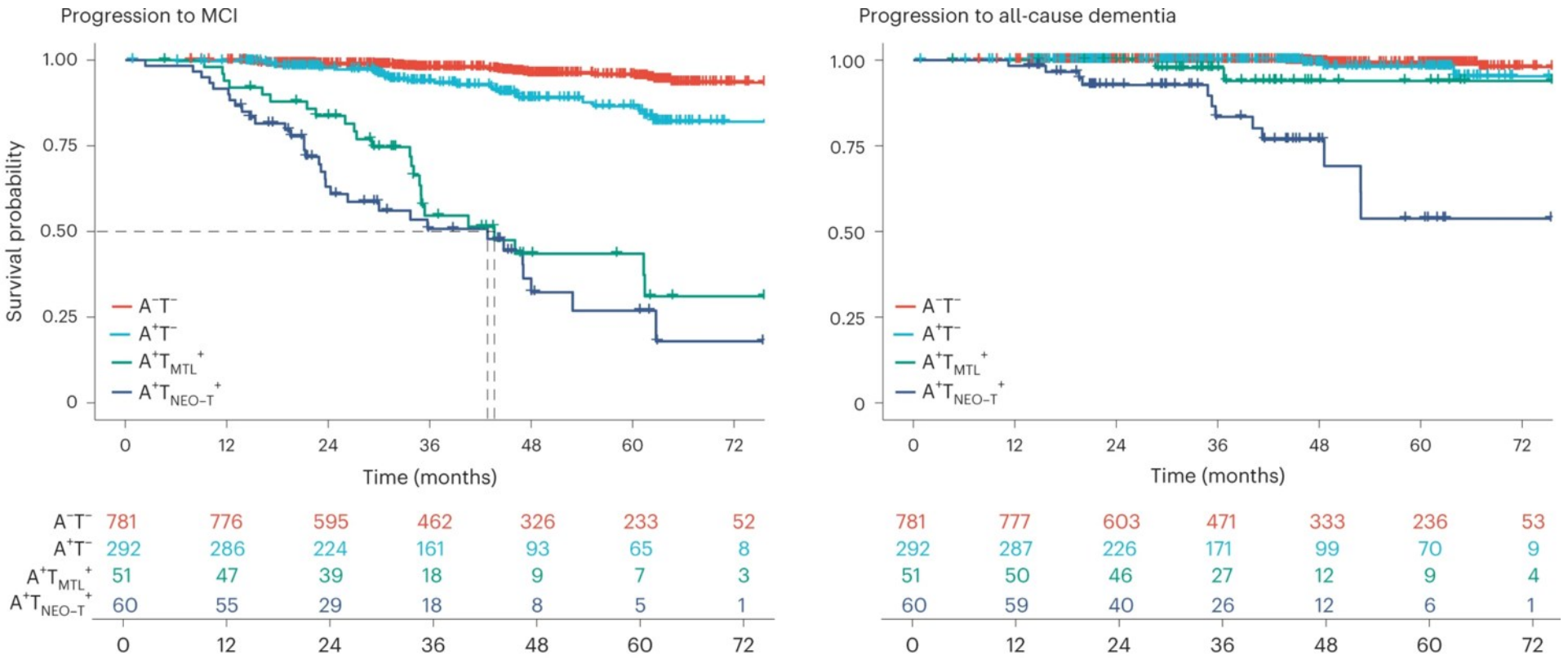


Van Dyck et al. NEJM 2022 DOI: 10.1056/NEJMoa2212948

Amyloid PET in secondary prevention

Cognitively unimpaired Amy+ and Tau+ on PET are at high risk of MCI and dementia

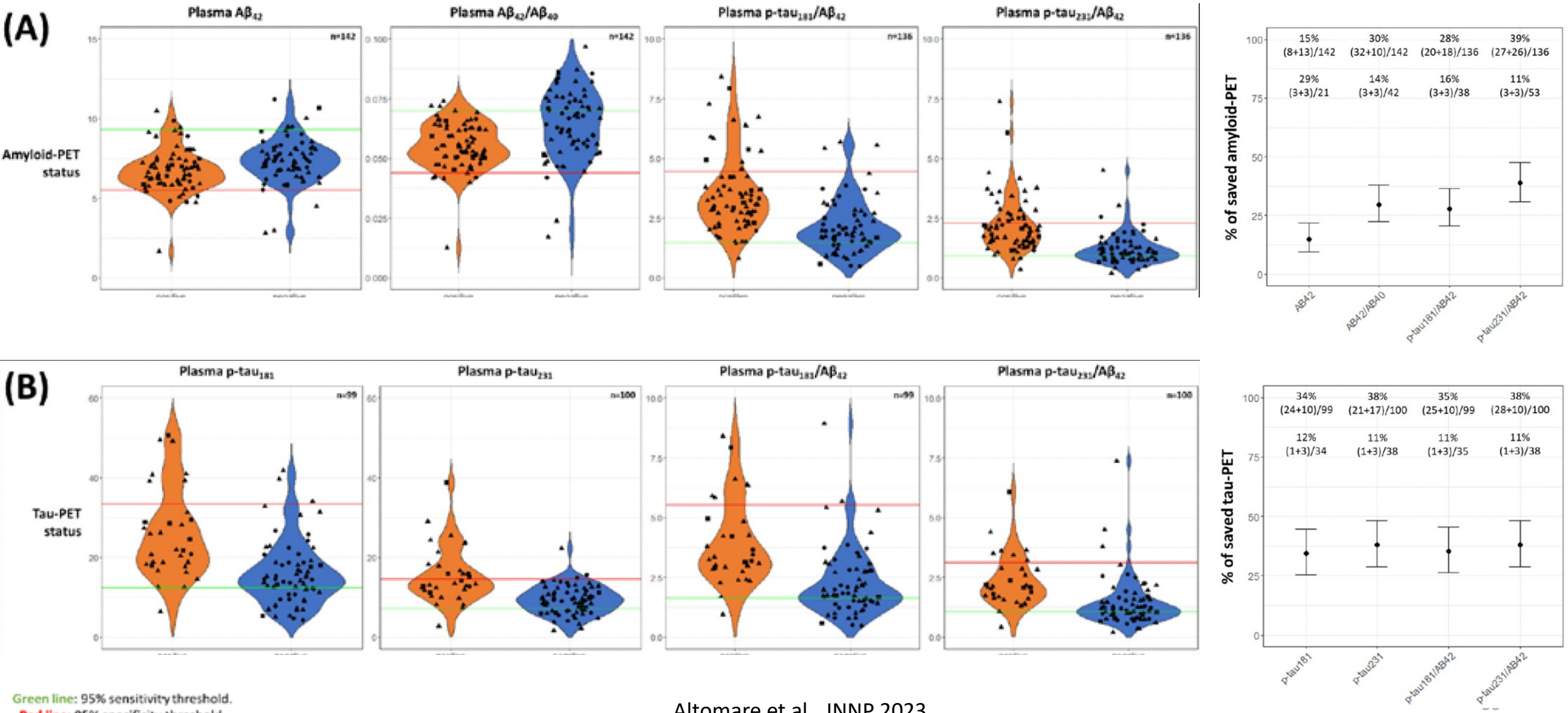
Mayo Clinic Study on Aging



Ossenkoppele et al., Nat Med 2022

Blood biomarkers could save about 40% of amy and tau PET

Geneva Memory Center Cohort



Green line: 95% sensitivity threshold.
Red line: 95% specificity threshold.

Altomare et al., JNNP 2023

Secondary prevention will require new clinical services
Brain Health Services for Dementia

The Lancet Regional Health - Europe
2023;■: 100576

Published Online XXX
https://doi.org/10.1016/j.lanepe.2022.100576

Health Policy

Dementia prevention in memory clinics: recommendations from the European task force for brain health services

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Summary 1 – Amyloid PET in the clinic

- Amyloid PET is a 2nd line mainstay of clinical assessment in memory clinic patients
- Paired with Tau PET it has good predictive value on cognitive progression
- Visual and quantitative assessments are in excellent agreement
- Amyloid PET may be a predictor of clinical efficacy of MAB treatment
- The added value of early perfusion scans in the clinic deserves to be more investigated

Summary 2 – Amyloid PET in development and outlook

PET tracers in clinical trials well suited to vaccine approach for early-stage disease

- Diagnosis of preclinical Alzheimer's disease (up to 10 years before)
- Abeta-PET imaging in clinical trials accelerates the path to approval:
  - Improved patient selection focuses trials on patients with target pathology
    - Led to better clinical trials: donanemab trials used PET tracers to improve patient selection
  - Objective measurement of disease pathology improved (clear endpoint)
    - Enabled positive clinical trials: Clarity AD for lecanemab
- Using PET tracers to enhance vaccine development
  - Combining PET and biofluid biomarkers for prognosis of AD (detect AD before symptoms develop)
  - The goal is to enable early vaccination to prevent symptoms/clinical decline
- Outlook on other PET tracers for Tau, a-syn, TDP-43, etc.
  - Developing tracers to detect co-pathologies

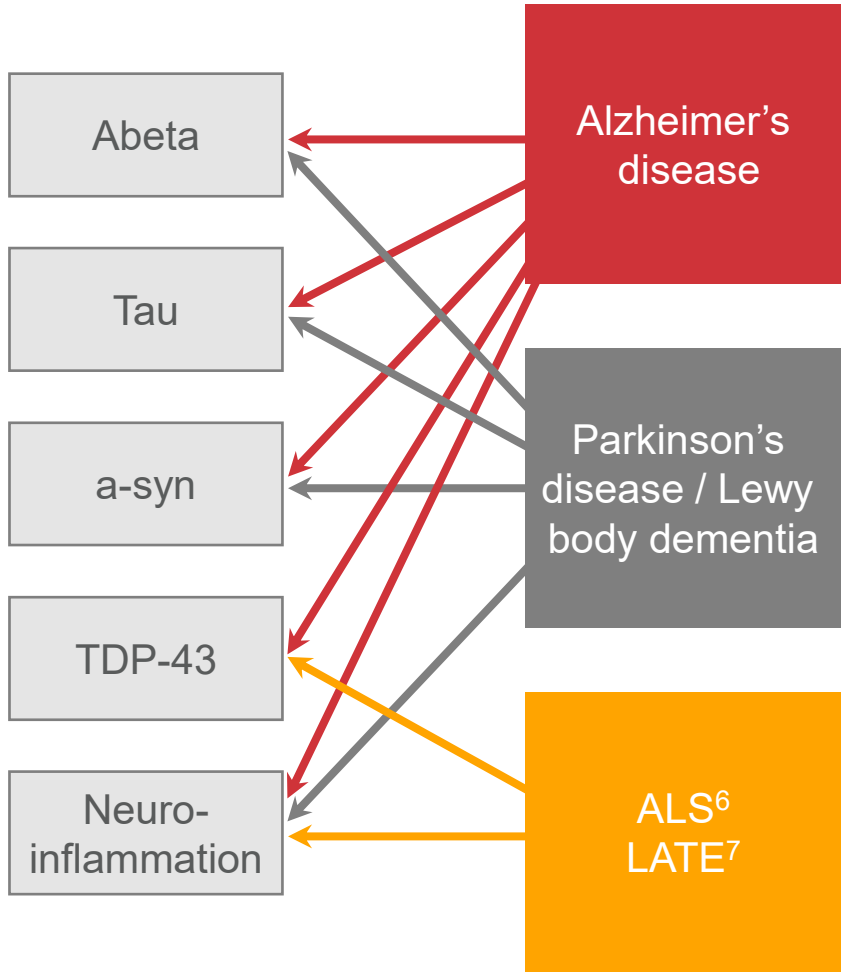
The need for Precision Medicine and neuroimaging to diagnose and treat earlier

Marie Kosco-Vilbois, PhD, Chief Scientific Officer

AC Immune

Brain PET[1] imaging is key for precision medicine in NDDs[2]

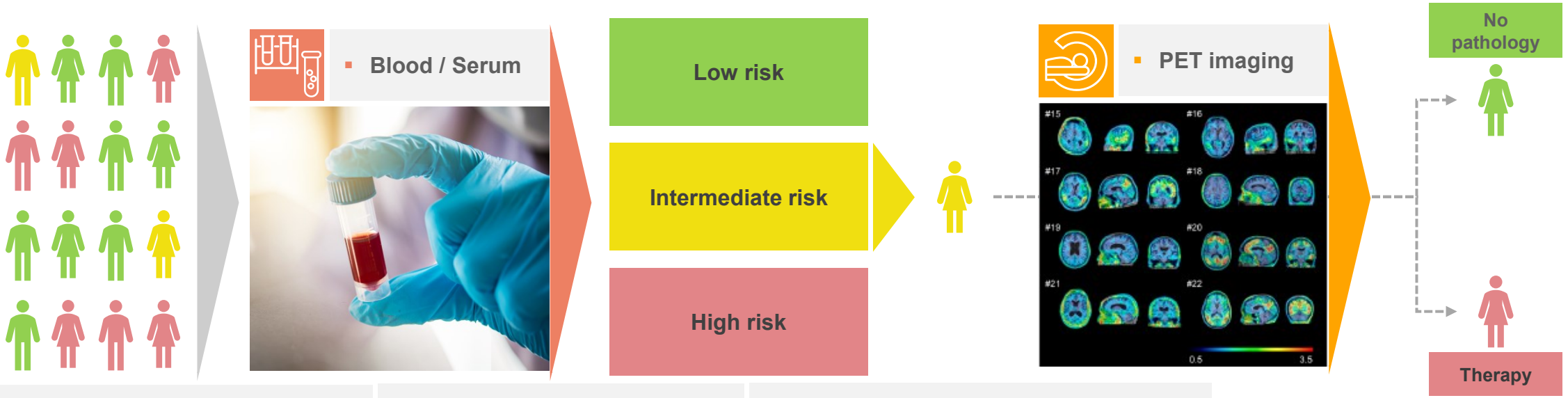
1. Genetic testing is not a solution, in most cases NDDs are sporadic, and mixed pathologies complicate therapeutic outcomes
2. PET tracers monitor temporal *and* spatial progression of pathologies
3. PET tracers allow informed stratification of patient populations
4. Abeta-PET already validated as a surrogate biomarker, enabling biomarker-based trial designs in AD[3]
5. PET-tracers for targets such as a-syn[4] and TDP-43[5] are still needed



(1) Positron emission tomography; (2) Neurodegenerative diseases; (3) Alzheimer's disease; (4) Alpha-synuclein; (5) TAR DNA-binding protein 43; (6) Amyotrophic lateral sclerosis; (7) Limbic-predominant age-related TDP-43 encephalopathy

Precision medicine for early, accurate diagnosis to accelerate development

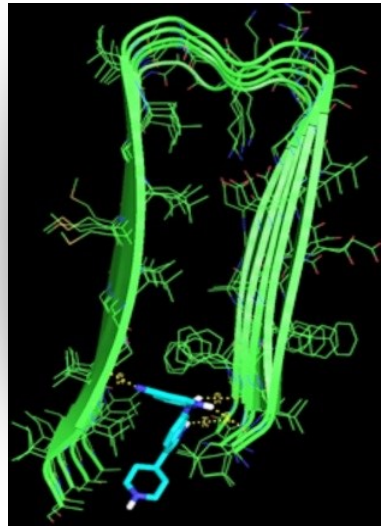
Complementary diagnostic modalities for rational clinical trial designs

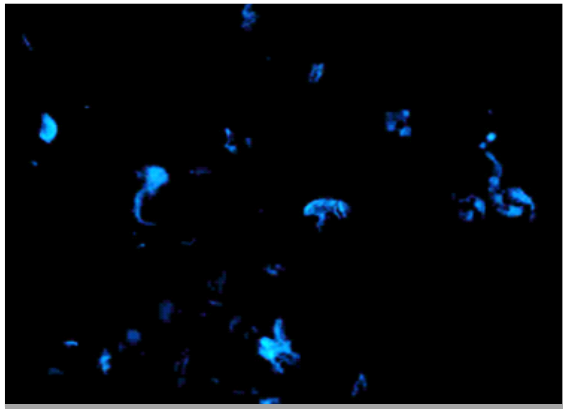


- Successfully preventing neurodegenerative diseases requires precision medicine
- Combining and optimizing the diagnostic workflow will enable prevention in at-risk subjects

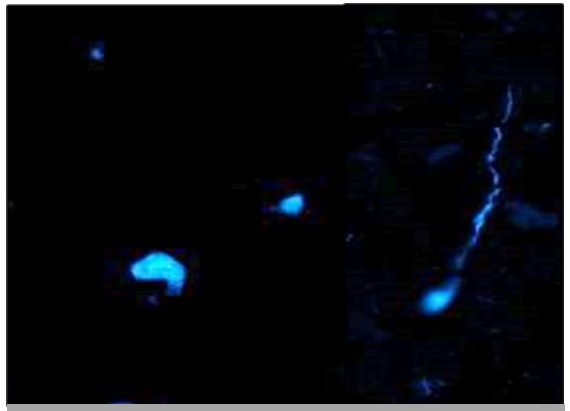
Precision medicine approach enabled by the Morphomer® platform

Developing a suite of PET[1] tracers against emerging targets in NDD[2]

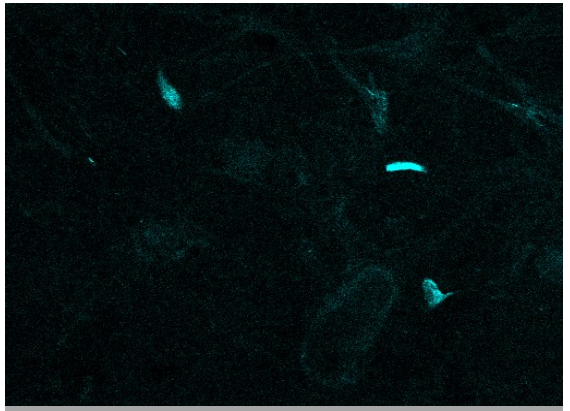




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43[5] inclusions

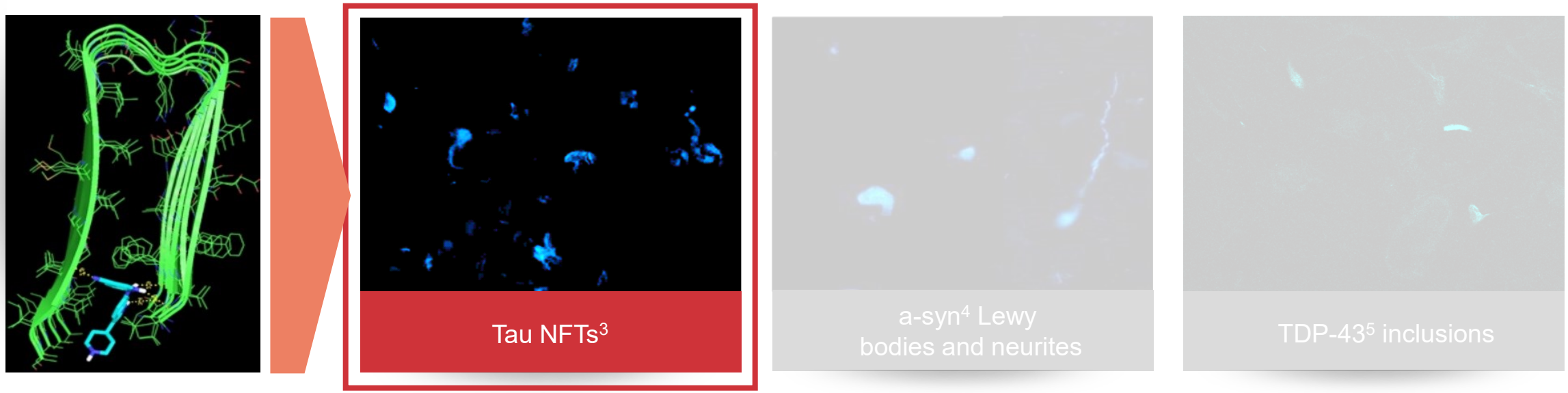
Leverage our Morphomer® small molecule platform:

- Non-peptidic, small molecules with CNS-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, a-syn[3], TDP-43[4])
- Pharmacokinetics suitable for brain PET imaging

(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Alpha synuclein; (4) TAR DNA binding protein-43

Precision medicine approach enabled by the Morphomer® platform

Developing a suite of PET[1] tracers: PI-2620 for Tau



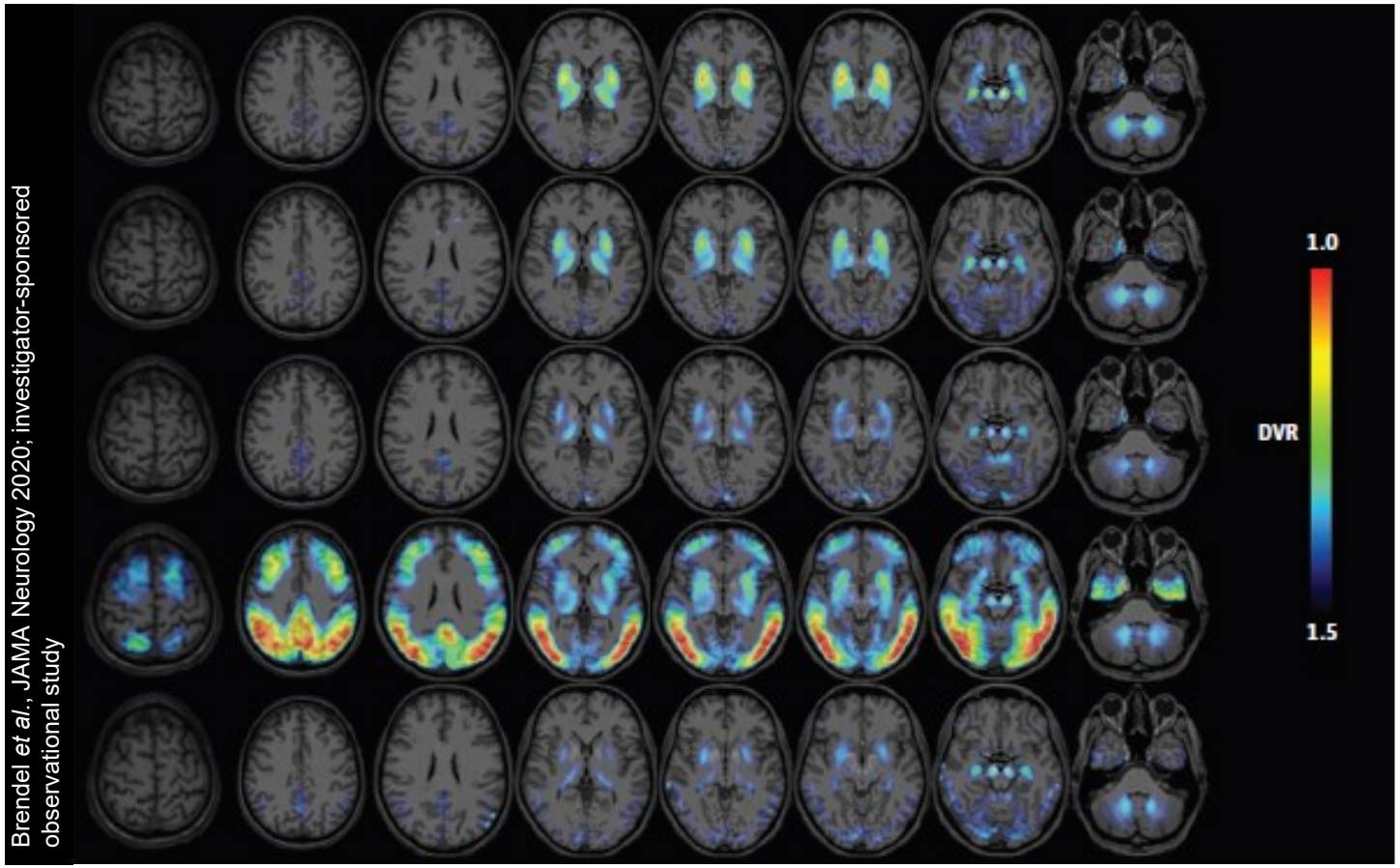
Leverage the Morphomer® small molecule platform:

- Non-peptidic, small molecules with CNS-drug properties for brain penetration
- Conformation-specificity (pathologic protein species)
- Selectivity against co-pathologies (Abeta, Tau, a-syn[2], TDP-43[3])
- Pharmacokinetics suitable for brain PET imaging

(1) Positron emission tomography; (2) Alpha synuclein; (3) TAR DNA binding protein-43

Tau-PET[1] imaging: Phase 3 study in AD[2] and Phase 1 in PSP[3]

PI-2620 – Potential for best-in-class PET tracer for 3R/4R and 4R tauopathies



Brendel *et al.*, JAMA Neurology 2020; investigator-sponsored observational study

Scans from participants by DVR[6]

- PSP-RS[4]
- PSP-non-RS[5]
- α-synucleinopathies
- AD (3R/4R)
- Healthy control

Disease specific

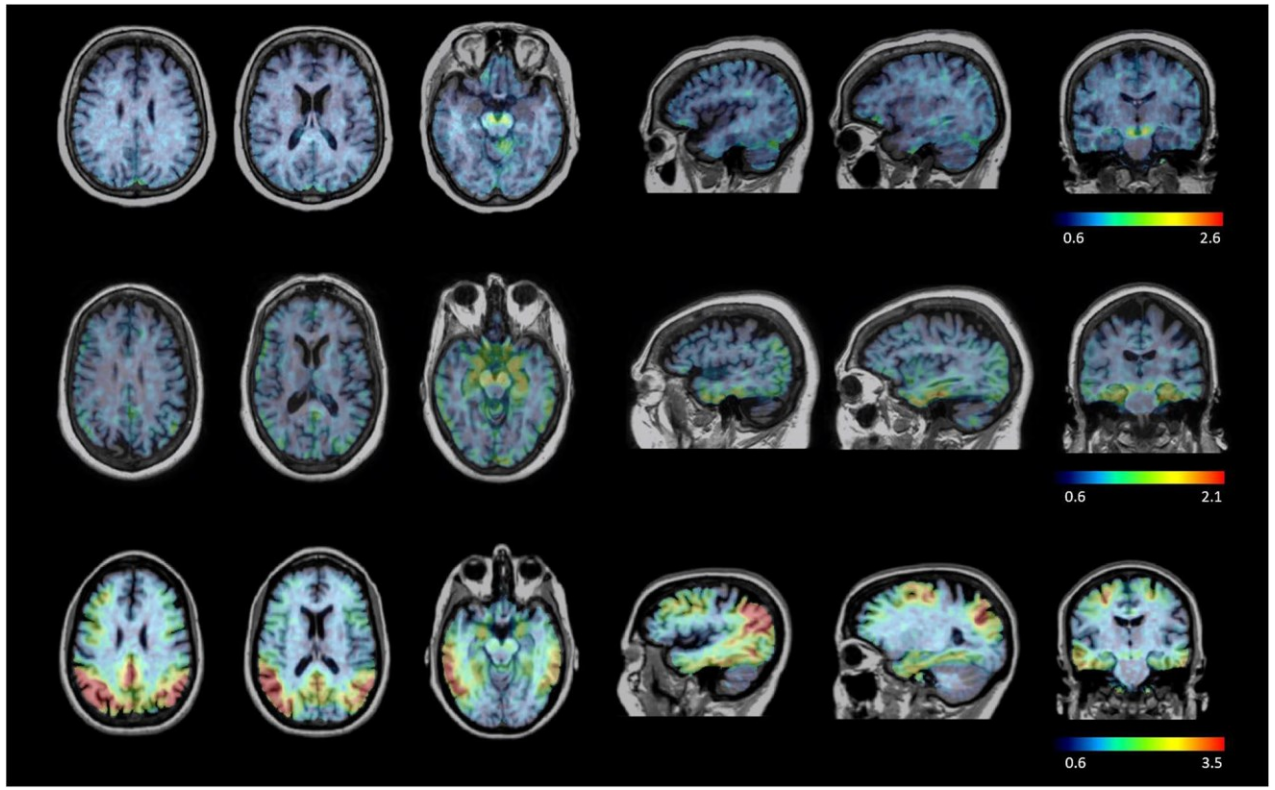
Tau selective

- PI-2620 is a Tau selective and disease specific PET tracer for AD and non-AD tauopathies; interventional trials against Tau in PSP will strongly benefit using this biomarker
- These results are in contrast to plasma pTau which does not change in tauopathies or dementias other than AD

(1) Positron emission tomography; (2) Alzheimer's disease; (3) Progressive supranuclear palsy; (4) PSP Richardson syndrome; (5) PSP non-Richardson syndrome; (6) Distribution volume ratio

Tau-PET[1] imaging: in MCI[2] and mild AD[3] dementia

PI-2620 visualizes Tau deposition in early AD subjects (a MissionAD Tau sub-study)



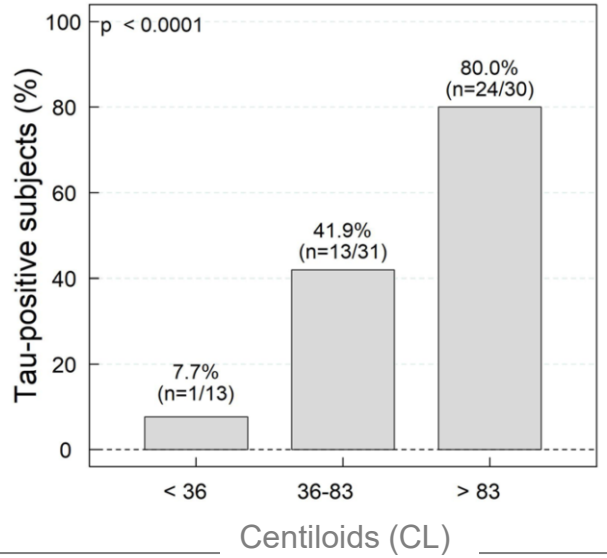
Tau-negative

Tau-positive:

a. mesial temporal cortex uptake

b. extensive neocortical uptake

% Tau-positive subjects by amyloid-beta load



36-83 CL: considered positive for amyloid pathology
>83 CL: considered high amyloid-load

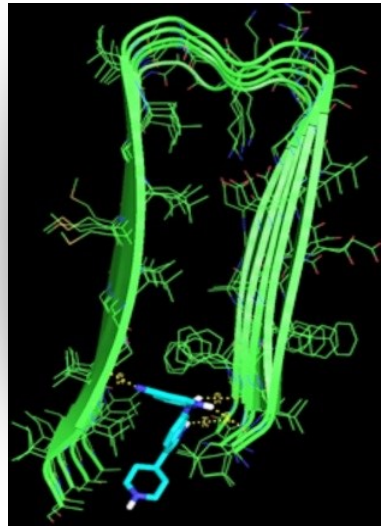
Bullich *et al.*, Alzheimer's Research & Therapy 2022

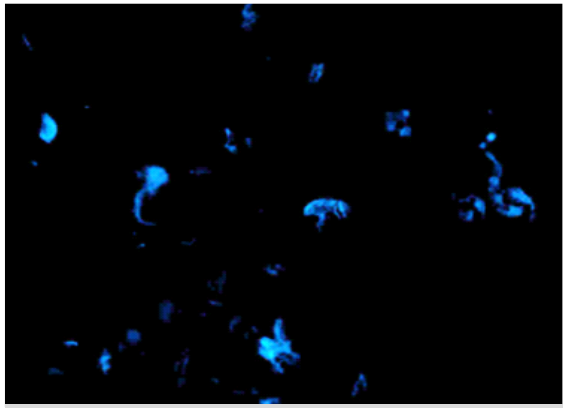
- Signal retention for Tau observed in early patient population (>36 CL) with longitudinal follow up revealing a statistically significant increase in Tau deposition over 1 year
- Quantifiable Tau load and its corresponding increase supports the utility of PI-2620 to assess Tau deposits in early AD population

(1) Positron emission tomography; (2) Mild cognitive impairment; (3) Alzheimer's disease

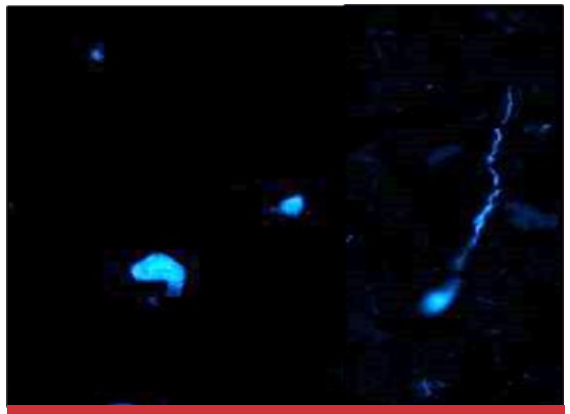
Precision medicine approach enabled by the Morphomer® platform

Developing a suite of PET[1] tracers: ACI-12589 for a-syn[2]

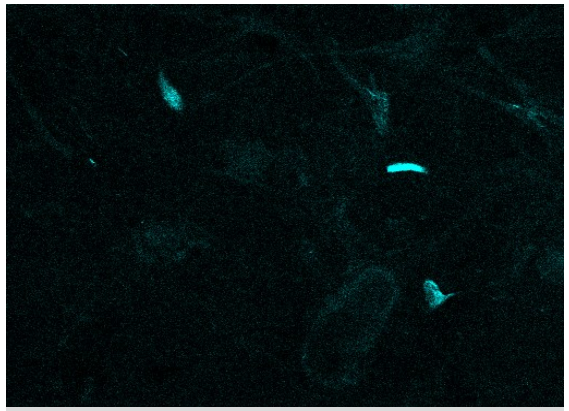




Tau NFTs[3]



a-syn Lewy bodies and neurites



TDP-43[5] inclusions

Leverage the Morphomer® small molecule platform:

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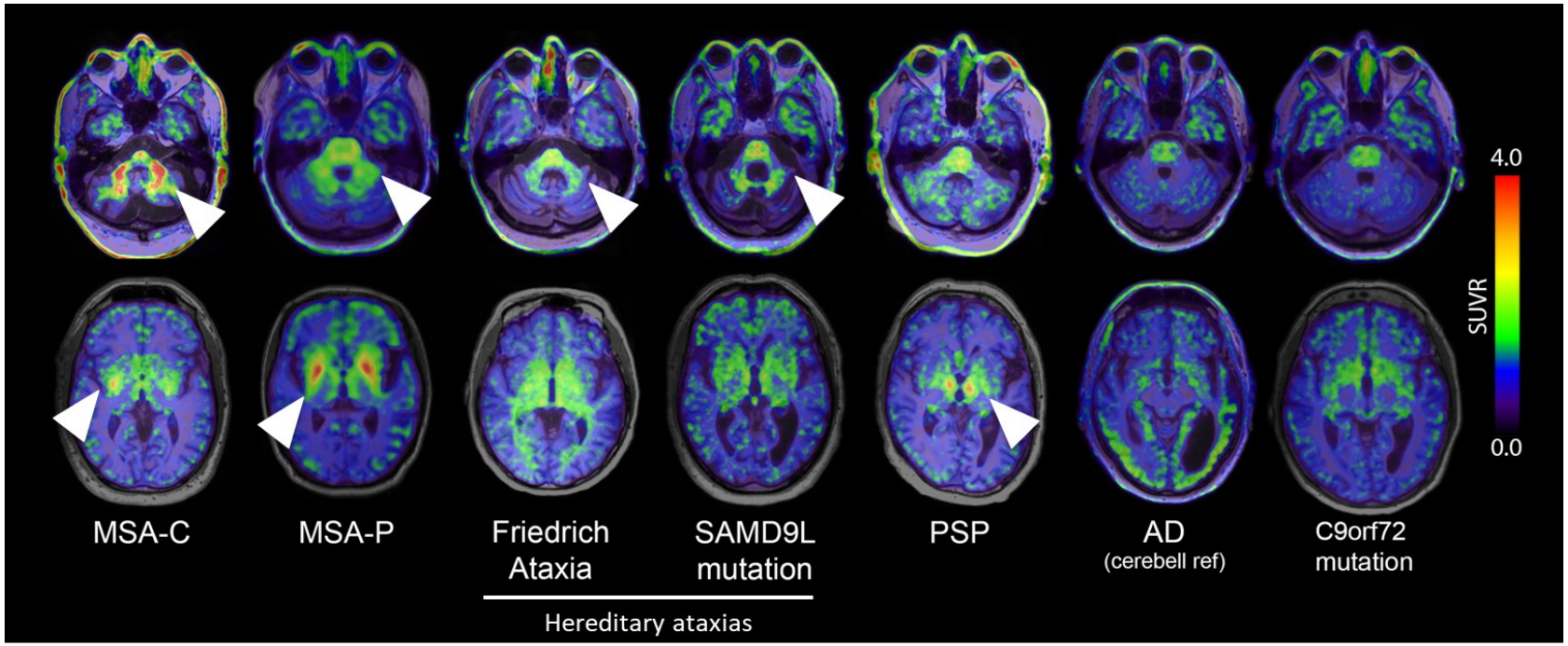
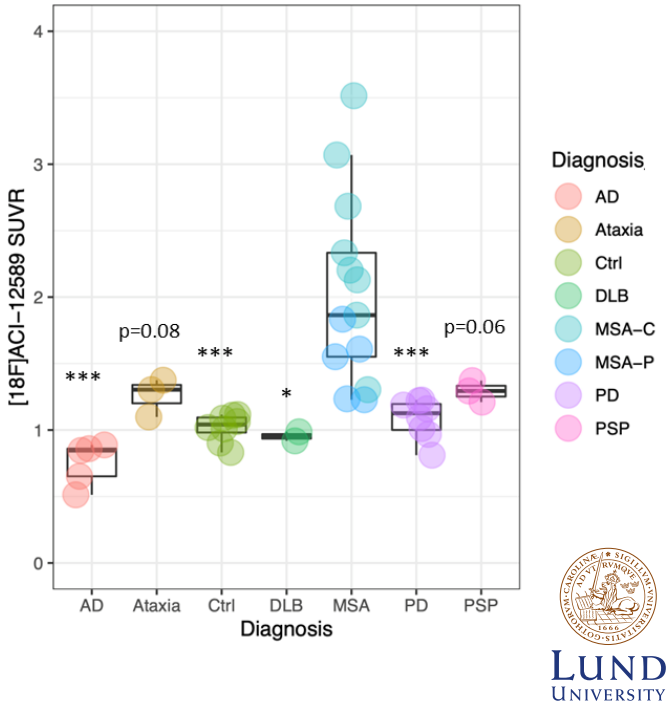
- Pharmacokinetics suitable for brain PET imaging

(1) Positron emission tomography; (2) Alpha synuclein; (3) TAR DNA binding protein-43

a-syn-PET[1] imaging: [18F]ACI-12589 differentiates MSA[2] from other NDD[3]

Occipital cortex as reference region





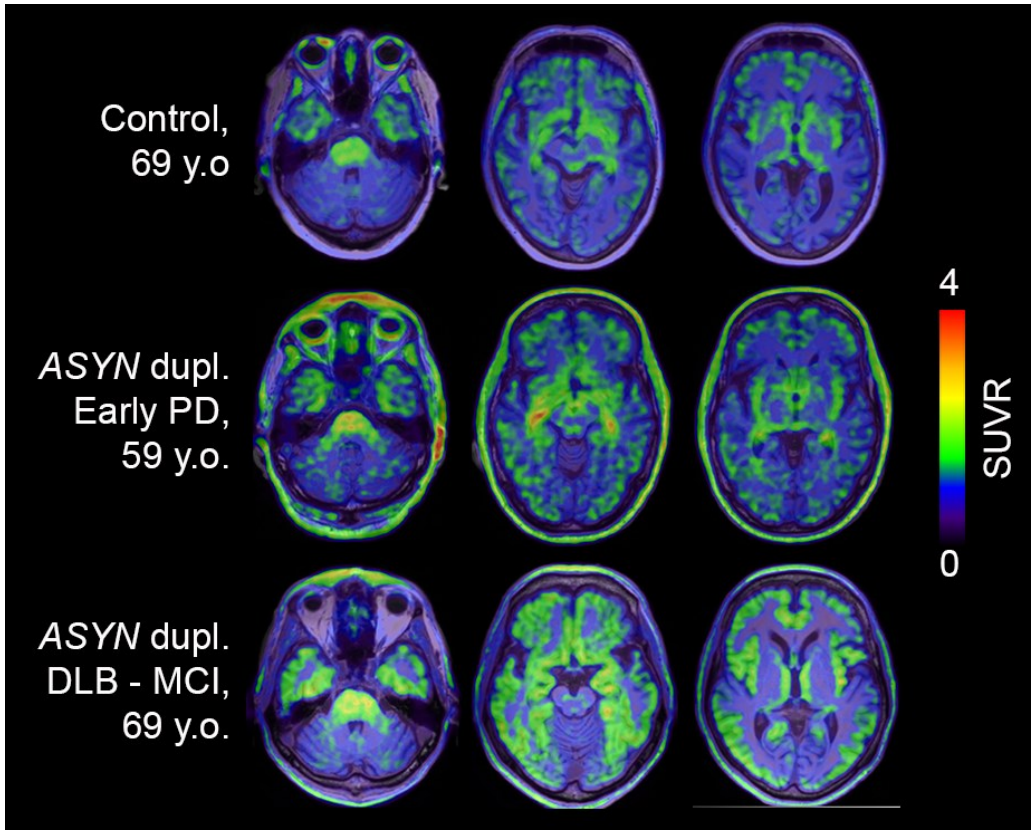
Ref.: Capotosti et al., APDP 2023

- [18F]-ACI-12589 retention in cerebellar peduncles clearly differentiates MSA cases from other NDD
- The lack of labelling in the C9orf72 case, a TDP-43-mediated neurodegeneration, serves to support selectivity for pathological a-syn

(1) Positron emission tomography; (2) Multiple System Atrophy; (3) Neurodegenerative disease

a-syn-PET[1] imaging: [18F]ACI-12589 uptake in genetic PD[2] cases

Differentiation from control subject using cerebellar grey as reference region



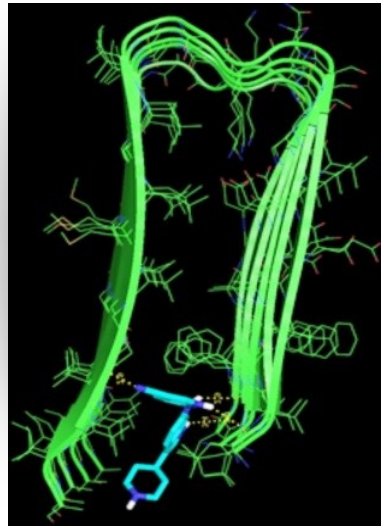
- Signal retention is observed in disease-relevant brain regions in genetic PD cases (SNCA duplication carriers)
- The retention is higher in the more advanced symptomatic case
- Signal distribution pattern is compatible with specificity of the signal for pathological a-syn

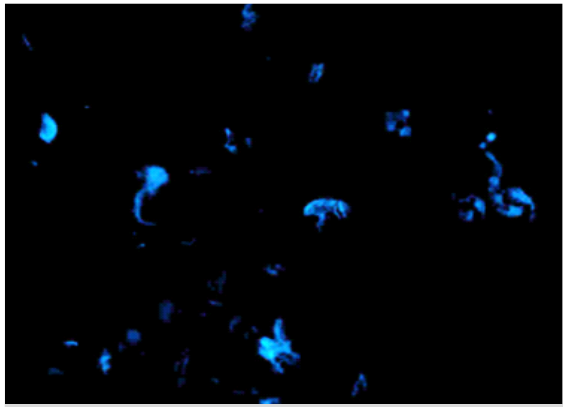
(1) Positron emission tomography; (2) Parkinson's disease

Ref.: Smith et al., AAIC 2022

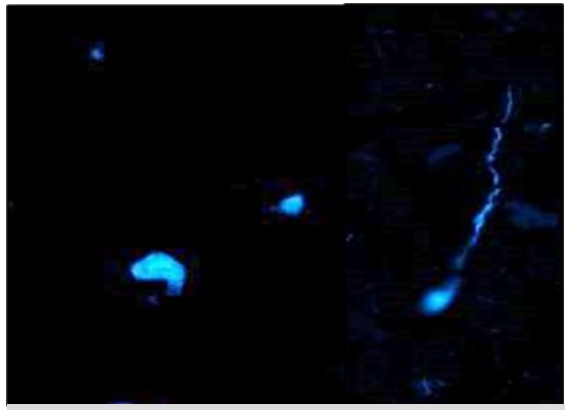
Precision medicine approach enabled by the Morphomer® platform

Developing a suite of PET[1] tracers: ACI-19278 for TDP-43[2]

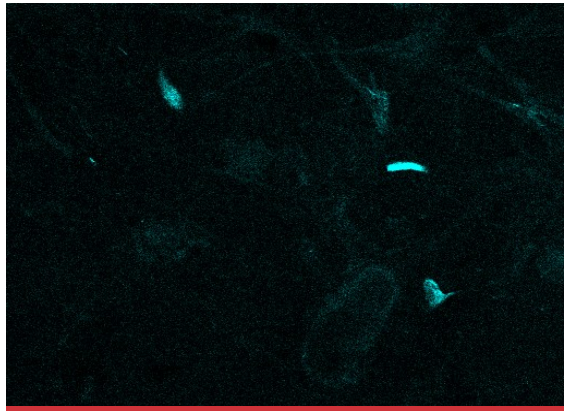




Tau NFTs[3]



a-syn[4] Lewy bodies and neurites



TDP-43 inclusions

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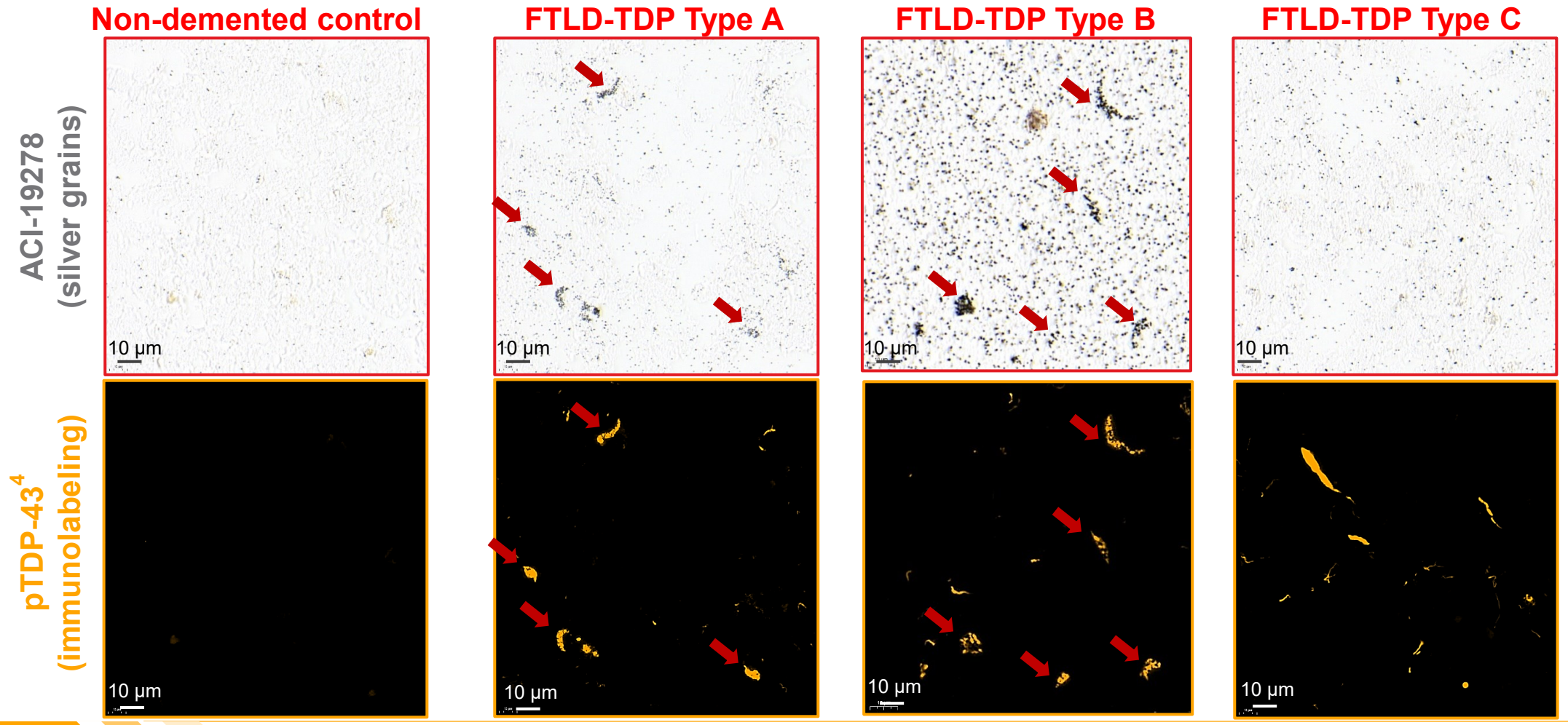
- Pharmacokinetics suitable for brain PET imaging

(1) Positron emission tomography; (2) TAR DNA binding protein-43; (3) Alpha synuclein

TDP-43[1]-PET[2] imaging: [^{3}H]ACI-19278 target engagement

High resolution autoradiography with FTLD-TDP[3] pathologies



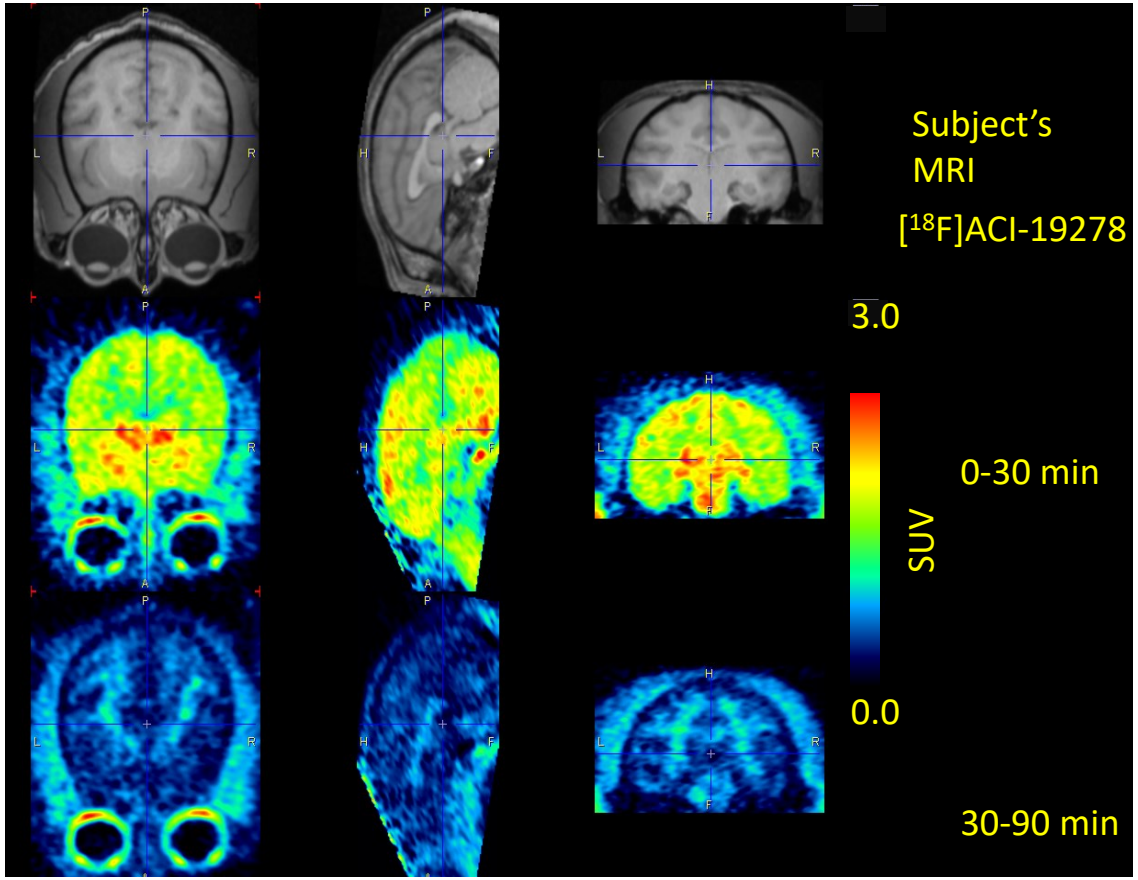
Ref: AC Immune, unpublished data

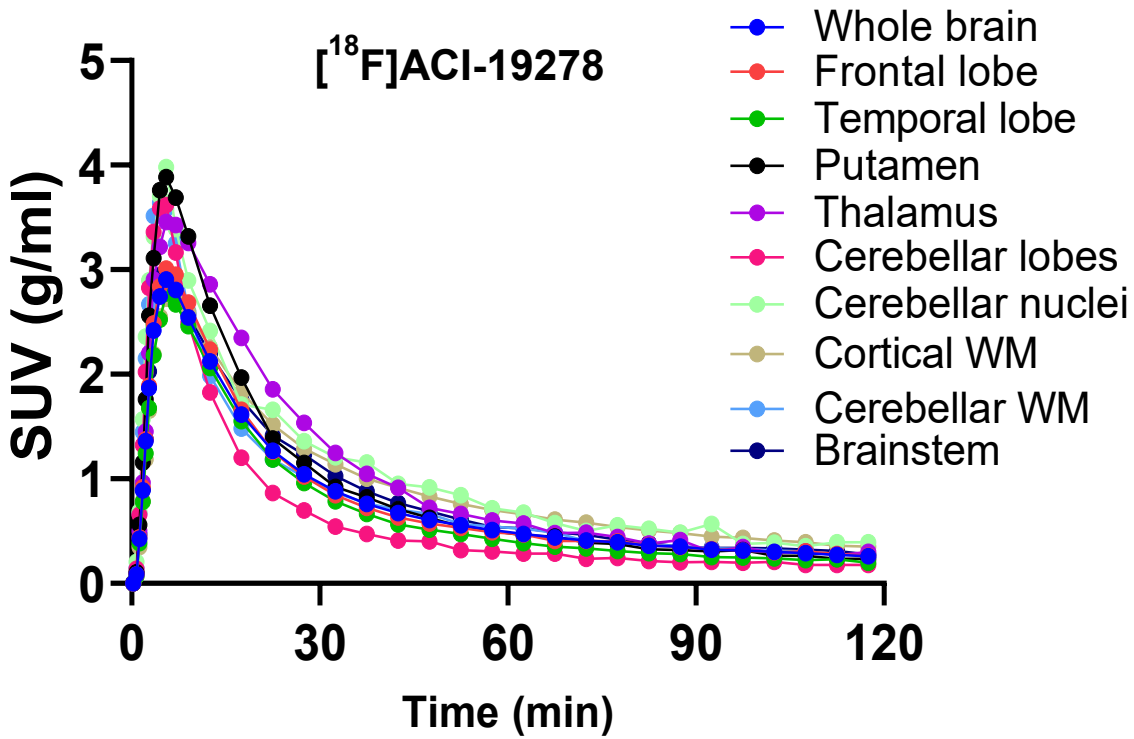
- For the first time, target engagement observed on brain samples with FTLD-TDP type A or B pathology
- Co-localization (arrows) with pTDP-43[4] antibody (yellow) confirms selectivity for the target

(1) TAR DNA binding protein-43; (2) Positron emission tomography; (3) Frontotemporal lobar degeneration with TPD-43 pathology; (4) phosphorylated TAR DNA binding protein-43

TDP-43[1]-PET[2] imaging: [^{18}F]ACI-19278 pharmacokinetic profile (PK)

Brain scans after intravenous administration in non-human primates





Ref: AC Immune, unpublished data

- [^{18}F]ACI-19278 demonstrates a robust and rapid brain uptake post intravenous injection
- Fast washout observed
- All characteristics suitable for advancing into human trials

(1) TAR DNA binding protein-43; (2) Positron emission tomography

AC Immune leadership: first- and best-in-class PET[1] tracers for NDD[2]

Early and accurate identification of primary pathologies and co-pathologies

Tau-PET

Life Molecular Imaging

PI-2620 is a potential best-in-class PET tracer for 3R/4R and 4R tauopathies

In Q1 2023, partner LMI[3] imaged the first patient in ADvance, the pivotal Ph. 3 in AD[4]

a-syn[5]-PET

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

[18F]ACI-12589 is the first tracer detecting pathologic a-synuclein in MSA[6] patients

Newly identified candidates show significantly improved binding properties with potential to detect synucleinopathies including in PD[7]

TDP-43[8]-PET

JPND research

First-in-class candidate available for IND-enabling studies

First-in-Human trial in FTD patients with GRN mutations planned in Q2 2024

(1) Positron emission tomography; (2) Neurodegenerative disease; (3) Life Molecular Imaging; (4) Alzheimer's disease; (5) Alpha-synuclein; (6) Multiple system atrophy; (7) Parkinson's disease; (8) TAR DNA binding protein-43

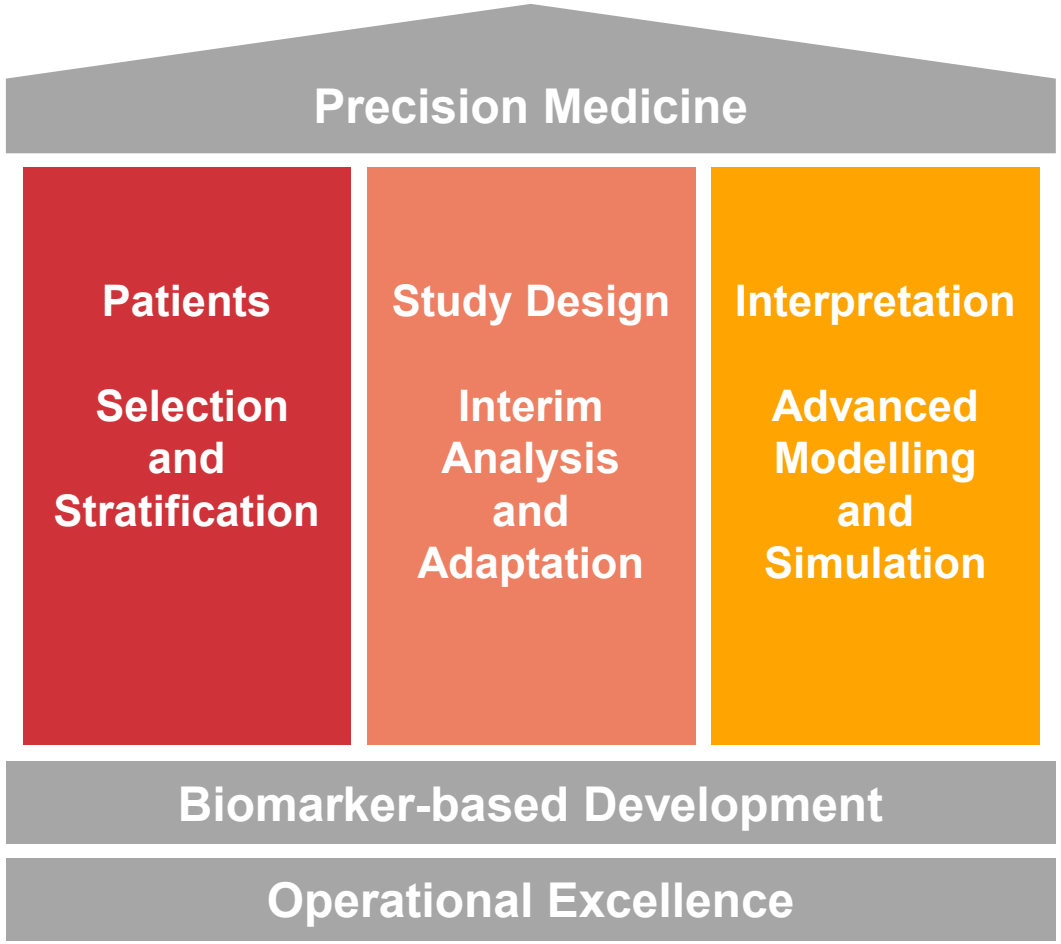
Clinical vaccine programs

Johannes Streffer, MD, Chief Medical Officer

AC Immune

Precision Medicine as the cornerstone of ACIU's Clinical Strategy

Enhance value creation through acceleration and de-risking of our portfolio



Patient selection and stratification

- Patient populations defined using clinical and biomarker measures to detect disease-specific patterns – Pathology and early detection
- Identify the right time to treat in the disease continuum and stratify patients accordingly

Clinical study design to support fast decision making

- Interim analyses for early de-risking by demonstrating specific antibody response and preference for pathologic protein species
- Early demonstration of biomarkers for accelerated approval reduces development time and de-risks investment

Modelling predicted treatment response

- Advanced modelling informs sample size and power calculations
- Simulation of novel treatment effects on natural disease allows meaningful regulatory discussions

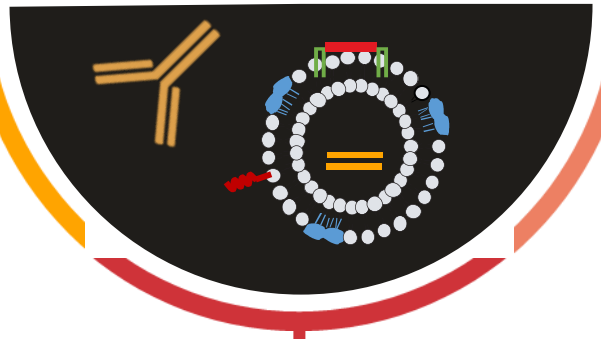
Vaccines as a new class of treatment for neurodegenerative disease

AC Immune vaccines: Potential for profound social and economic impact

Treatment

High efficacy with:

- Multiple epitope targeting
- Long-lasting immune response
- Steady titers
- Favorable safety and tolerability
- Convenient, annual dosing



Prevention

- Vaccination is the best strategy to preserve function and quality of life
- Cost-effective and global application

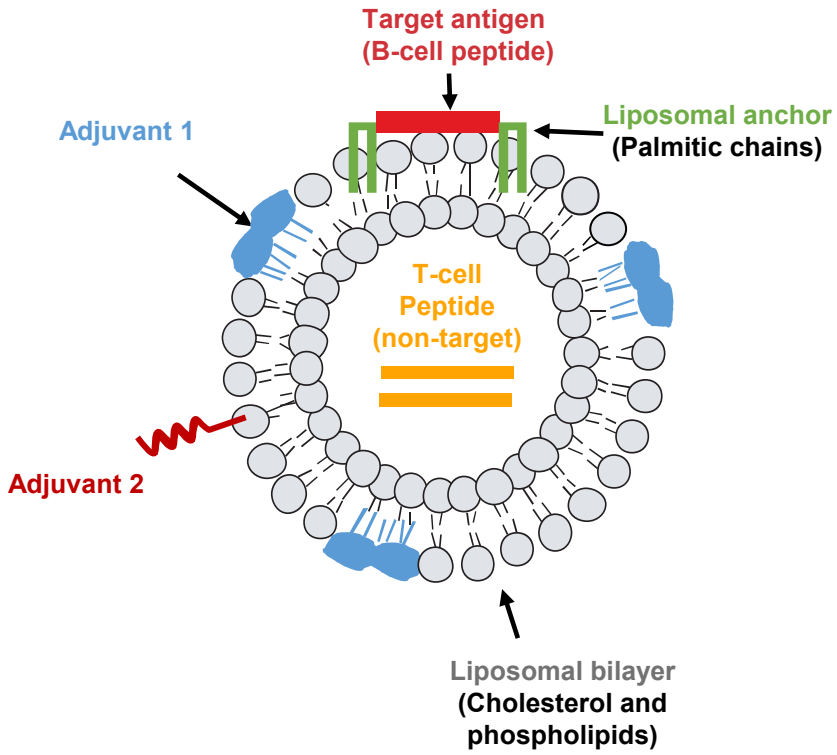
Maintenance

- Use as maintenance therapy after monoclonal anti-Abeta antibodies
- Convenient, annual dosing to maintain low plaque levels

- Goal: Global vaccines for neurodegenerative diseases

Disruptive potential of SupraAntigen®-V

Optimized vaccines delivering superior results in neurodegenerative diseases



Generates target-specific antibody response

Safely engages target-unrelated T-cells to enhance & maintain response

Unprecedented Clinical Performance

Immunogenicity	++++[1]
Target specificity	++++[2]
Conformation specificity	+++
Avidity increase over time	+++
Sustainability of response	+++
Boosting	+++
Class switching IgM to IgG	+++
Evidence of memory B cells	+++

- Robust immunogenicity and strong safety demonstrated in humans
- Evidence for lasting immune response supporting a disease prevention approach

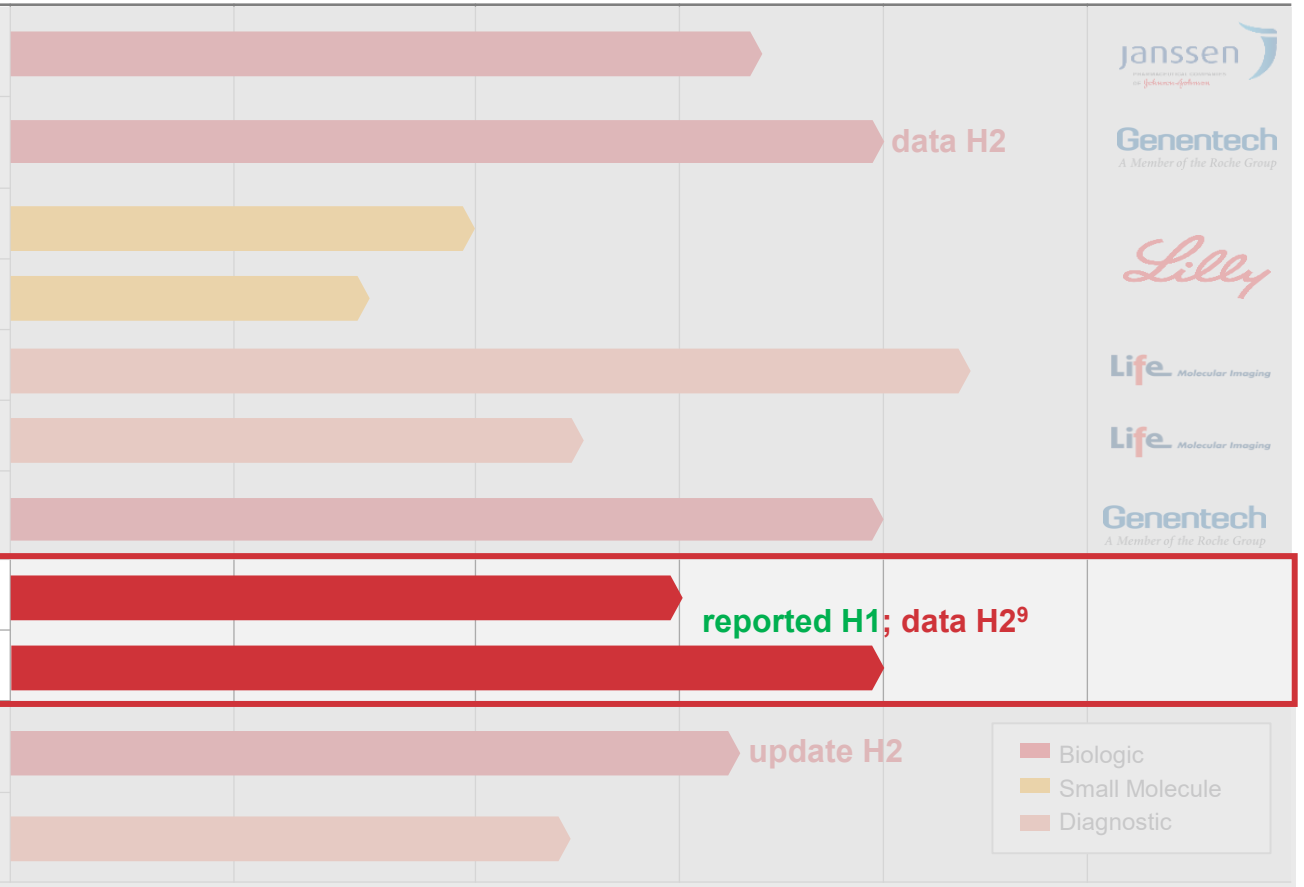
(1) 100% response after 1st injection; (2) Increases over time

ACI-24.060: Vaccine targeting two pathological forms of Abeta

ACI-24.060 targets pyroGlu- and oligomeric Abeta, which are believed to drive AD progression

Clinical Stage Programs

TARGET	PRODUCT CANDIDATE	INDICATION	PARTNER
Tau	ACI-35.030 *(anti-pTau vaccine)*	AD[1] treatment	janssen
	Semorinemab *(anti-Tau antibody)*	AD treatment *(mild-to-moderate)*[2]	Genentech
	Morphomer® Tau aggregation inhibitor	Rare Tauopathies	Lilly
		AD treatment	
	Tau-PET[3] tracer	AD diagnostic	Life Molecular Imaging
		PSP[4] diagnostic	Life Molecular Imaging
Abeta	Crenezumab *(anti-Abeta antibody)*	AD prevention[5]	Genentech
	ACI-24.060 *(anti-Abeta vaccine)*	AD treatment (*Down syndrome*[6])	
		AD treatment	
a-syn[7]	ACI-7104.056 *(anti-a-syn vaccine)*	PD[8], a-synucleinopathies	
	a-syn-PET tracer	a-synucleinopathies (e.g. MSA[10])	



(1) Alzheimer's disease; (2) Open label extension study is ongoing; (3) Positron emission tomography; (4) Progressive supranuclear palsy; (5) Prevention trial API-ADAD in Colombia; (6) Down syndrome-related Alzheimer's disease; (7) alpha-synuclein; (8) Parkinson's disease; (9) Refers to expected readouts from a Phase 1b/2 trial of an optimized formulation of ACI-24 (ACI-26.060) in patients with AD and patients with Down syndrome; (10) Multiple system atrophy

AC Immune

Innovative biomarker-based clinical development

Accelerating, while simultaneously de-risking, our clinical programs: Example

Precision Medicine

- **Defined populations** using clinical and biomarker measures to detect Amyloid pathology and disease severity in **sporadic AD**[1] and **individuals with DS**[2]

Interim Analysis: Decision Points

- Amyloid PET[3] lowering as key marker to benchmark against current monoclonal antibodies (e.g., lecanemab and donanemab)
- Allows for early **interim analysis (IA)** for safety, immunogenicity and pharmacodynamics

Acceleration and De-Risking

- **Fast and informed transition** between cohorts and generation of meaningful readout on Amyloid PET to allow **accelerated initiation of pivotal program**

Primary Prevention: Amyloid PET

- DS is the largest **genetic AD population** with Abeta overproduction
- AβATE[4] will inform use of Amyloid PET as an outcome for primary prevention

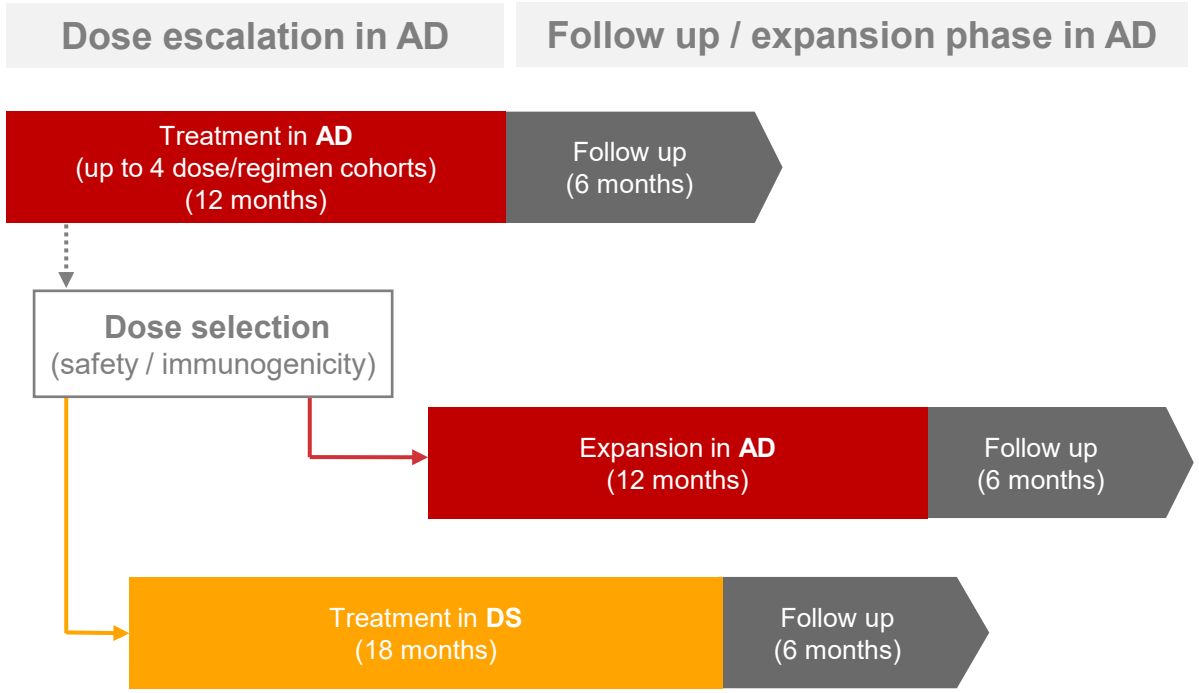
(1) Alzheimer's disease; (2) Down syndrome; (3) Positron Emission Tomography; (4) ABATE is the name for the ongoing ACI-24.060 clinical trial

ABATE: Biomarker-based Phase 1b/2 study in AD[1] and AD in DS[2]

Placebo-controlled Phase 1b/2 Study Overview

Inclusion criteria	Both	Multicenter, adaptive, placebo-controlled, dose-escalation, double-blind, randomized Phase 1b/2 study in people with: ▪ Abeta pathology confirmed by PET[3] scan
	AD	▪ Prodromal AD (CDR[4]-Global Score 0.5; age 50-75 years)
	DS	▪ Non-demented people living with DS (age 35–50 years)
Study design	Both	▪ IA[5] of safety/tolerability and immunogenicity ▪ Biomarker analyses including Abeta PET and others
	AD	▪ Up to 4 different doses and/or dose regimens ▪ Expansion of one cohort to assess effect on Abeta PET
	DS	▪ Initiation using selected dose identified in AD (based on safety/tolerability and immunogenicity)
Outcome measures	Both	▪ Safety/tolerability ▪ Pharmacodynamics: Serum anti-Abeta antibody titers ▪ Exploratory biomarkers and clinical endpoints

Trial Schematic



Interim analyses

- Safety/tolerability
- Immunogenicity – antibody titers
- Biomarkers – Abeta-PET, pharmacodynamics, target engagement

(1) Alzheimer's disease; (2) Down syndrome-related AD; (3) Positron emission tomography; (4) Clinical Dementia Rating; (5) Interim analyses

Biomarker-based design enhances progress, exemplified by Aβ ABATE

Novel opportunity by Amyloid PET[1] as accepted surrogate endpoint for accelerated approval

1

Program de-risking and acceleration[2]

- Early interim data to demonstrate equipotency of ACI-24.060 with respect to Abeta mAb[3]
- Opportunity to initiate pivotal program aiming for accelerated approval

2

Primary prevention in DS[4]

- Individuals with DS are the biggest genetic AD[5] population, with strongly predictable initiation of amyloid pathology in the brain
- Primary prevention can leverage both population and novel endpoints

3

Maintenance therapy by a safe and well tolerated vaccine

- mAbs demonstrate clinical effect, but remain challenging for chronic treatment (e.g., frequent infusions and ADA[6])
- Demonstration of continued amyloid PET lowering to position ACI-24.060 for maintenance

(1) Positron emission tomography; (2) Abate refers to the name of the ACI-24.060 clinical trial; (3) Monoclonal Antibodies; (4) Down syndrome; (5) Alzheimer's disease; (6) Anti-drug antibodies

ACI-35.030: Anti-pTau vaccine being developed for AD[1]

Further clinical development in AD and milestone payment expected in H2

Clinical Stage Programs

TARGET	PRODUCT CANDIDATE	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	PARTNER
Tau	**ACI-35.030** *(anti-pTau vaccine)*	AD[1] treatment						Janssen
	Semorinemab *(anti-Tau antibody)*	AD treatment *(mild-to-moderate)*[2]					data H2	Genentech
	Morphomer® Tau aggregation inhibitor	Rare Tauopathies						Lilly
		AD treatment						
	Tau-PET[3] tracer	AD diagnostic						Life Molecular Imaging
		PSP[4] diagnostic						Life Molecular Imaging
Abeta	**Crenezumab** *(anti-Abeta antibody)*	AD prevention[5]						Genentech
	ACI-24.060 *(anti-Abeta vaccine)*	AD treatment (*Down syndrome*[6])					reported H1; data H2[9]	
		AD treatment						
a-syn[7]	**ACI-7104.056** *(anti-a-syn vaccine)*	PD[8], a-synucleinopathies				update H2		
	a-syn-PET tracer	a-synucleinopathies (e.g. MSA[10])						

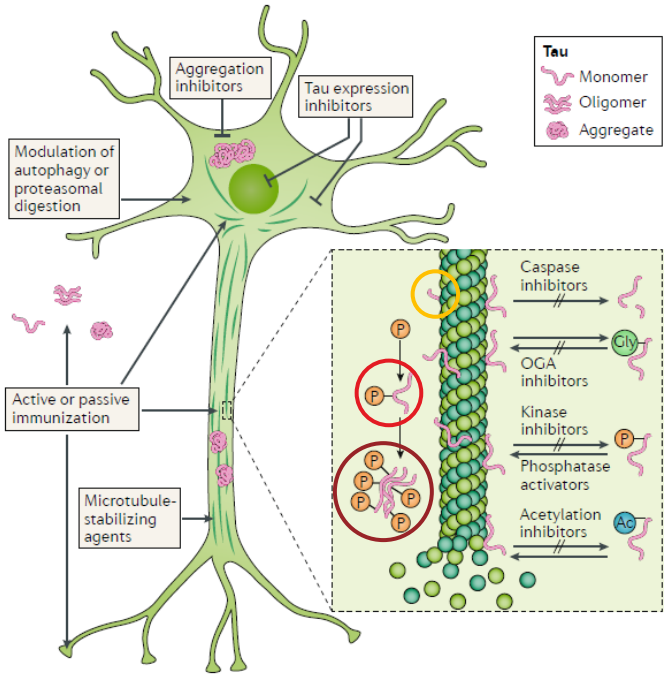
Biologic
Small Molecule
Diagnostic

(1) Alzheimer's disease; (2) Open label extension study is ongoing; (3) Positron emission tomography; (4) Progressive supranuclear palsy; (5) Prevention trial API-ADAD in Colombia; (6) Down syndrome-related Alzheimer's disease; (7) alpha-synuclein; (8) Parkinson's disease; (9) Refers to expected readouts from a Phase 1b/2 trial of an optimized formulation of ACI-24 (ACI-26.060) in patients with AD and patients with Down syndrome; (10) Multiple system atrophy

Active immunization for early intervention in Alzheimer's Disease

Preventing Tau spreading and disease progression

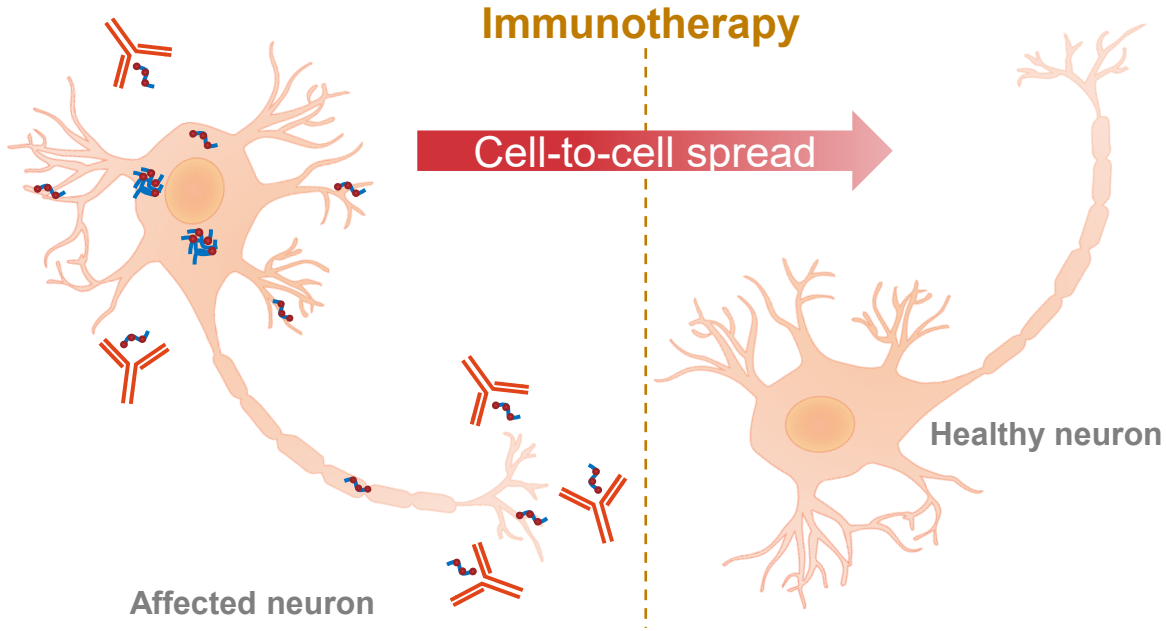
Hyperphosphorylated Tau aggregates in Alzheimer's disease



Congdon et al., Nature Reviews Neurology, 2018

Study measures antibodies against:

- Non-phosphorylated Tau protein
- Phosphorylated Tau protein
- Enriched Paired Helical Filaments (ePHF)



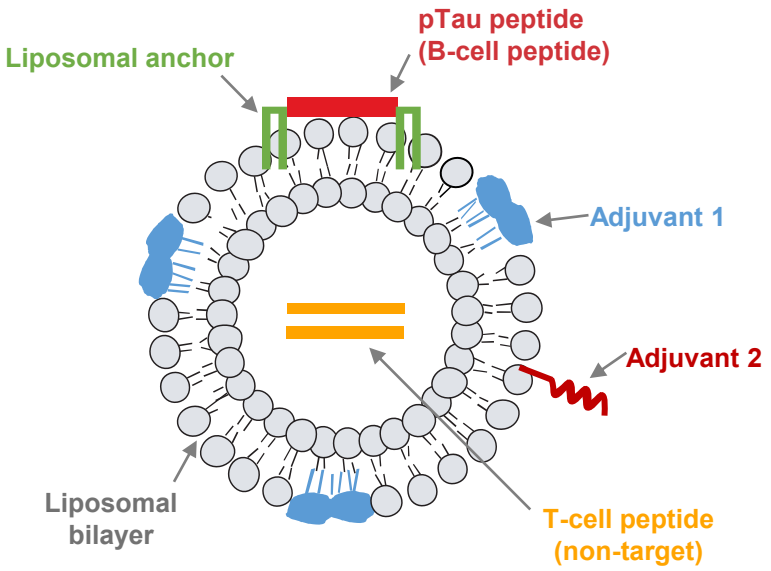
- Targeting Tau is well validated by neuro-pathology and pre-clinical results
- Antibodies are suggested to selectively bind, trap and remove pathological Tau species to prevent cell-to-cell spread

- ACI-35.030 induces antibodies targeting the toxic forms of Tau (pTau and ePHF) to prevent spreading of the pathology from cell-to-cell

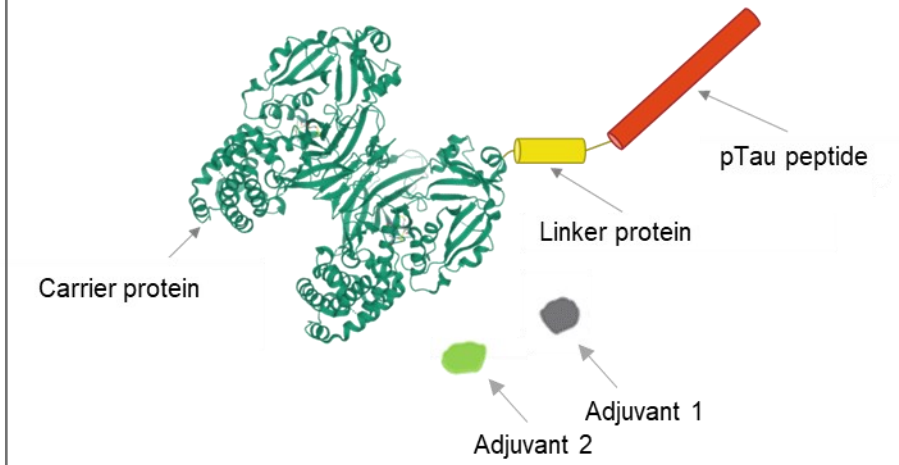
Next generation anti-phospho Tau (pTau) vaccines

Liposomal ACI-35.030 and conjugate JACI-35.054 vaccines

ACI-35.030: SupraAntigen® liposomal platform



JACI-35.054: Carrier protein-Tau peptide

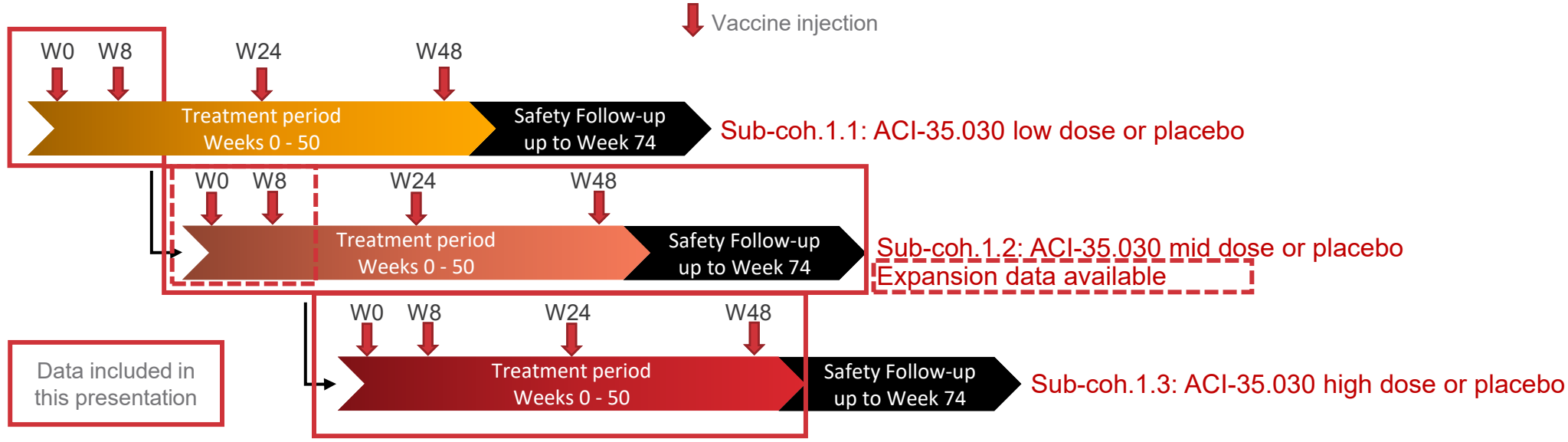


Anti-phospho-Tau vaccine

- The same pTau peptide used in two vaccine formulations

Phase 1b/2a study ACI-35-1802

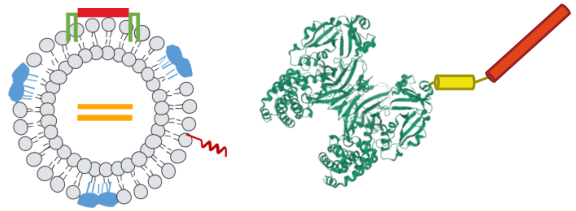
Study design for Cohort 1 (ACI-35.030 or placebo)



- Design features
  - Mild AD or MCI due to AD (NIA-AA criteria)
  - Sequential dose cohorts with escalating doses
  - 8 AD subjects per study sub-cohort (active/placebo ratio: 3:1)
  - Sub-cohort 1.2 expanded (active/placebo ratio: 3:1), data available up to week 10
- Primary Objectives
  - Safety and tolerability
  - Immunogenicity
- Study status
  - Study sub-cohorts 1.1 to 1.3 are fully recruited
  - Sub-cohort 1.2 expansion fully recruited

(1) ClinicalTrials.gov Identifier: NCT04445831

Good safety and tolerability[1]

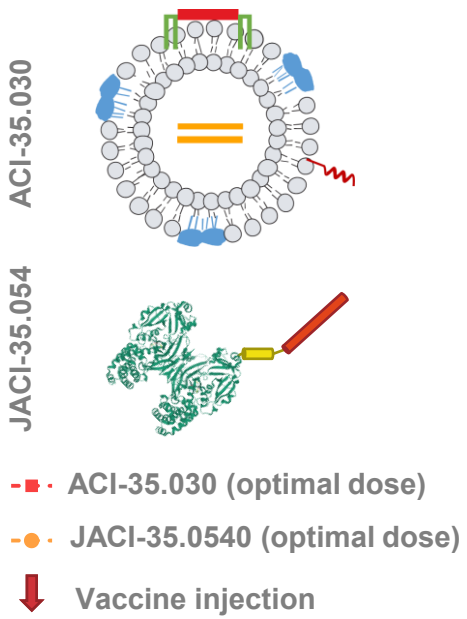


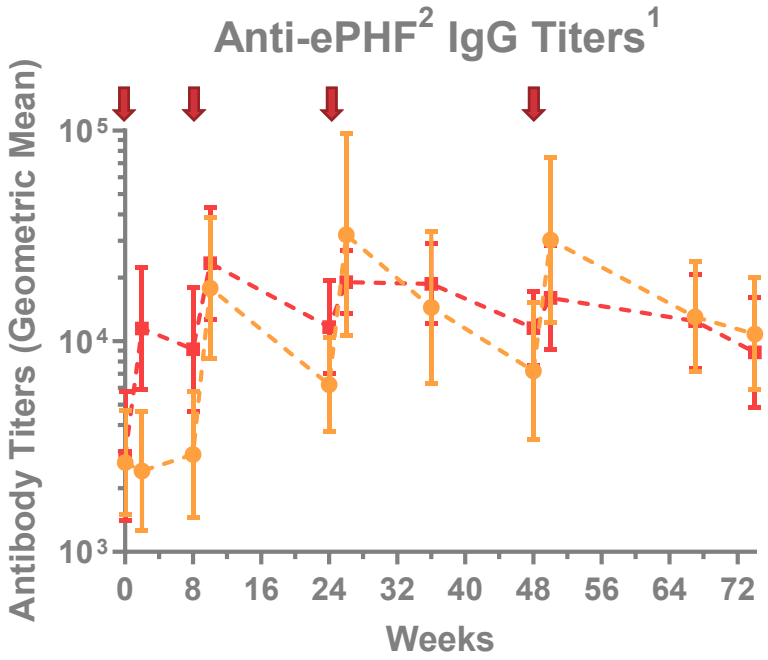
- Both ACI-35.030 and JACI-35.054 were safe and well tolerated with no study vaccine-related safety concerns observed to date
- No withdrawals due to adverse events or adverse events of severe intensity
- No CNS inflammation or other significant changes reported on MRI
- Two SAEs considered unlikely related to the study vaccine reported in the study to date in the first 2 sub-cohorts
  - episode of acute diverticulitis
  - sick sinus syndrome (requiring pacemaker)
- Two safety unrelated study withdrawals in sub-cohort 1.1
  - resulting study data from cohort 1.1 can only be shown until week 10 (2 weeks after 2nd vaccination) to keep study blind

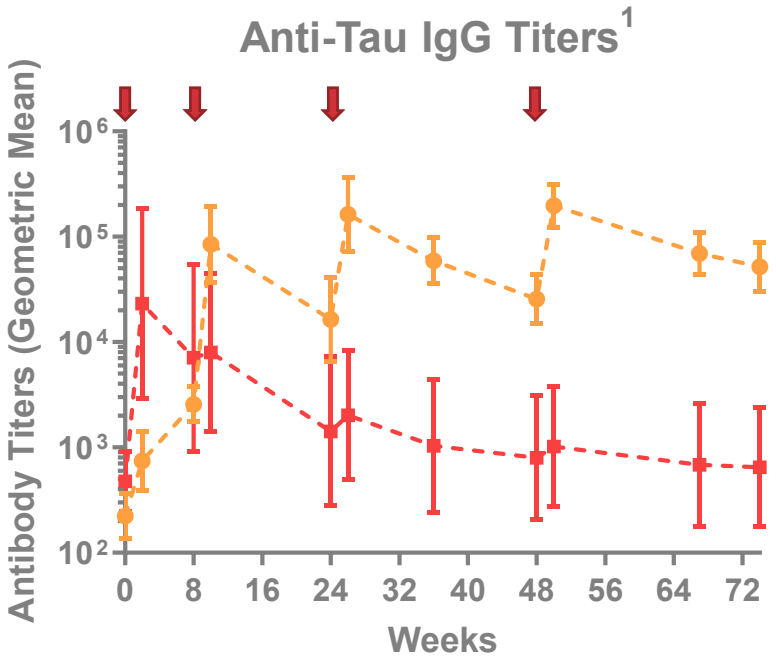
(1) Data cut-off at end of September 2022

ACI-35.030 selected for further development by partner Janssen

Follows data showing ACI-35.030's superior specificity for pathological Tau vs. JACI-35.054







1 JACI-35.054 is a protein conjugate vaccine utilizing the same pTau[3] epitope as ACI-35.030

2 ACI-35.050 and JACI-35.054 were evaluated in parallel in the Phase 1b/2a trial in AD[4] patients

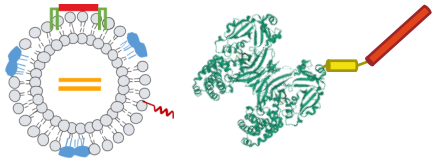
3 ACI-35.030 induced Ab[5] responses in 100% of patients after 1st injection compared to 50% with JACI-35.054

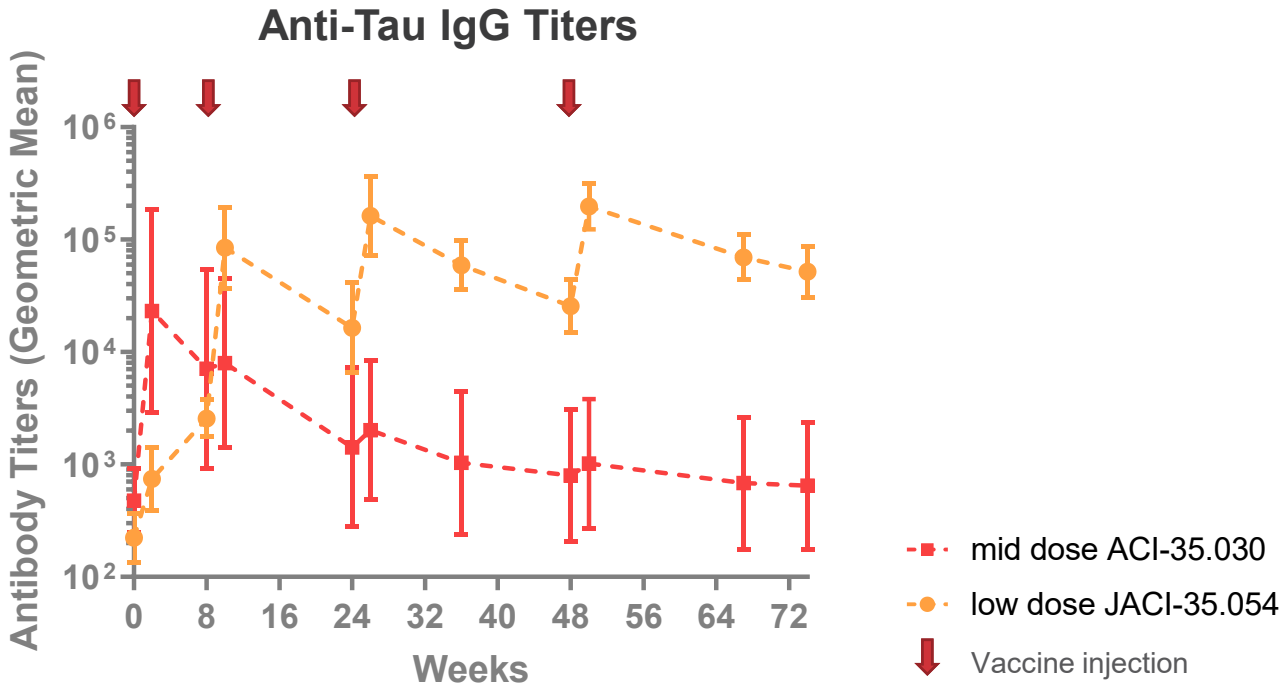
4 ACI-35.030-induced anti-ePHF Abs: longer apparent half-lives, less variability, lower peak-to-trough ratios

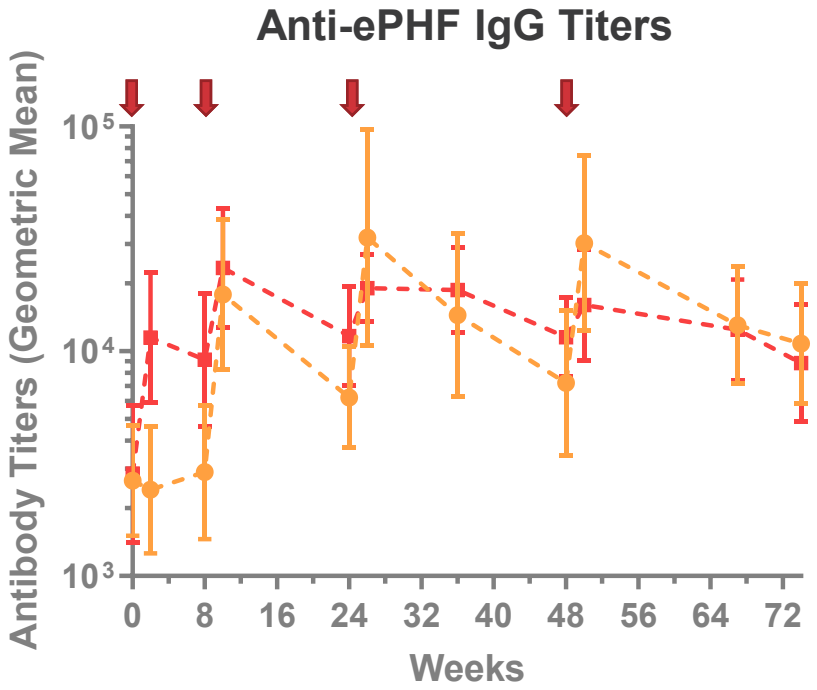
(1) ACI-35.030 original sub-cohort 1.2 data; (2) Enriched paired helical filaments; (3) phosphorylated Tau; (4) Alzheimer's disease; (5) Antibody

Desired antibody response: ACI-35.030[1] compared to JACI-35.054

Superior specificity for pathological Tau







1 ACI-35.030 antibody response preferentially targets pathological Tau species over normal Tau

2 ACI-35.030 antibody response in 100% of patients after 1st injection compared to 50% with JACI-35.054

3 ACI-35.030 induced anti-ePHF antibodies - longer apparent half-lives, less variability, lower peak-to-trough ratios

4 ACI-35.030 shows excellent overall performance in elderly patients with outstanding safety and tolerability

(1) ACI-35.030 original sub-cohort 1.2 data

AC Immune Clinical Development Strategy

Biomarker-based development will de-risk and accelerate the pipeline

Precision Medicine

- Precise definition of patient populations using biomarkers and clinical parameters
- Leading with best- and first-in-class targeted imaging agents (e.g., Tau, a-syn[3], TDP-43[4])

Deliver Vaccine Pipeline

- Advance ACI-35.030 into late stage clinical development
- Accelerate development of ACI-24.060 by including DS[1] as biggest genetic AD[2] population
- Progress ACI-7104 anti-asyn Vaccine into phase 1b/2 VACSYN study

Evaluate new business opportunities

- Maintenance: vaccines to reduce disease progression post acute therapy
- Prevention: vaccines as early first interventions in biomarker-positive, preclinical individuals

Drive Translational Medicine

- Foster translational medicine approach for early signal detection
- Stronger understanding of treatment response
- Creating future perspective by inclusion of new technologies

(1) Down syndrome; (2) Alzheimer's disease; (3) Alpha-synuclein; (4) TAR DNA-binding protein 43; (5) amyloid beta; (6) Positron emission tomography

Q&A and closing remarks