Ten Years of Transformative Progress in Alzheimer's Dementia Research: From DIAN Insights to AI-Powered Discovery: Alzheimer's Prevention, Aging, and Artificial Intelligence

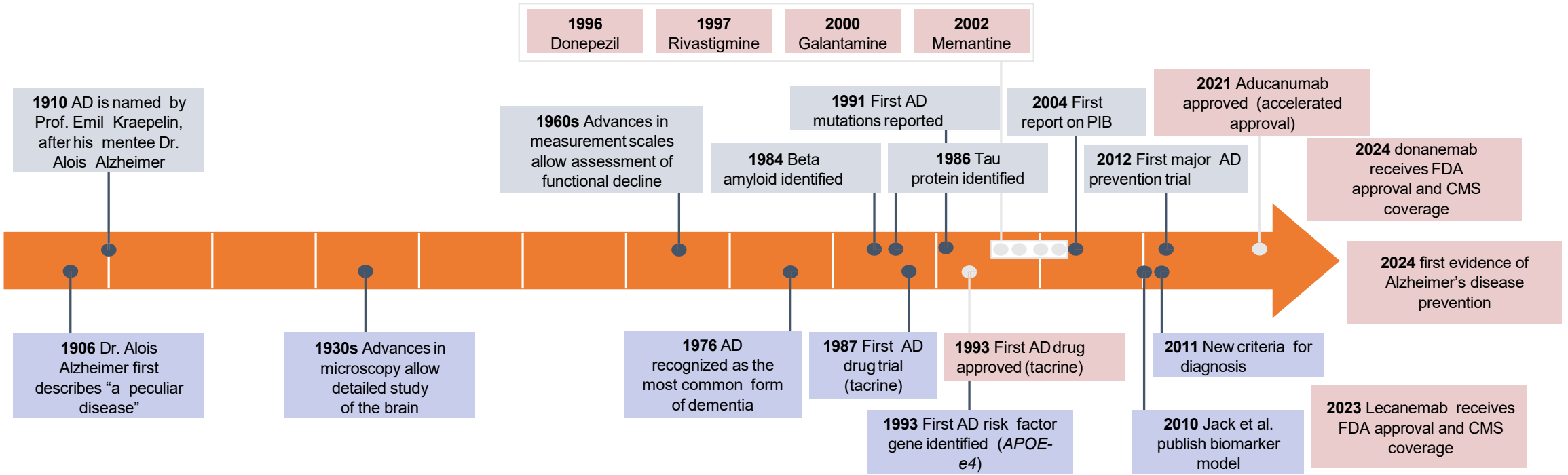
Randall Bateman M.D.
Charles F. and Joanne Knight Distinguished Professor of Neurology
DIAN and DIAN-TU PI and Director
Washington University School of Medicine

Alzheimer's disease – the challenge

- The most common form of dementia
  - Pathology of loss of synapses and neurons, and amyloid and tau aggregation (specific diagnosis) with other associated proteinopathies
  - Progressive memory loss, decreased judgment, communication challenges, personality changes & confusion
  - Worsens over time until death
  - Has common pathophysiology but may have a variety of pathogenic causes
- ***Alzheimer's is age dependent, regardless if due to dominantly inherited mutations, APP duplication, ApoE4 risk factor or other causes. Why is the disease so age dependent?***
- Alzheimer's disease is a unique disease of humans (unlike cancer, stroke, atherosclerosis, etc.). Why?

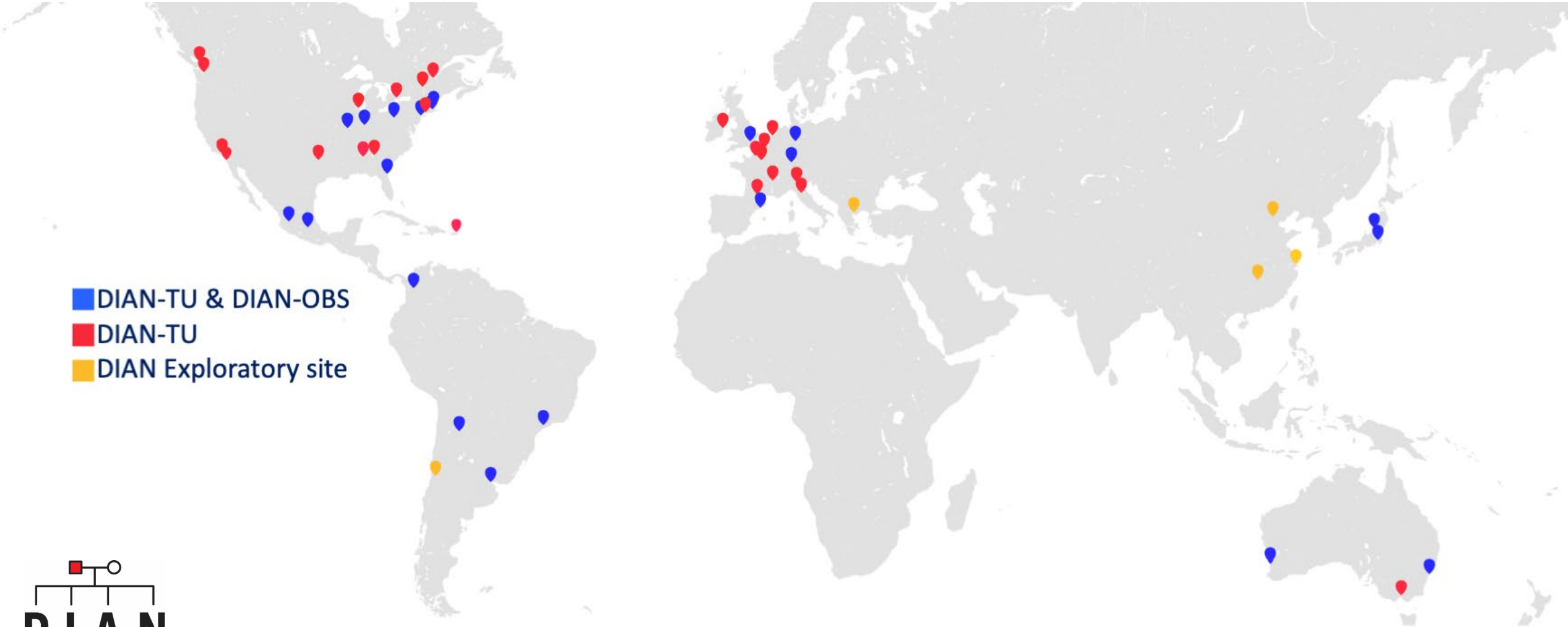
Aging Clue

100+ years of Alzheimer's disease (AD)

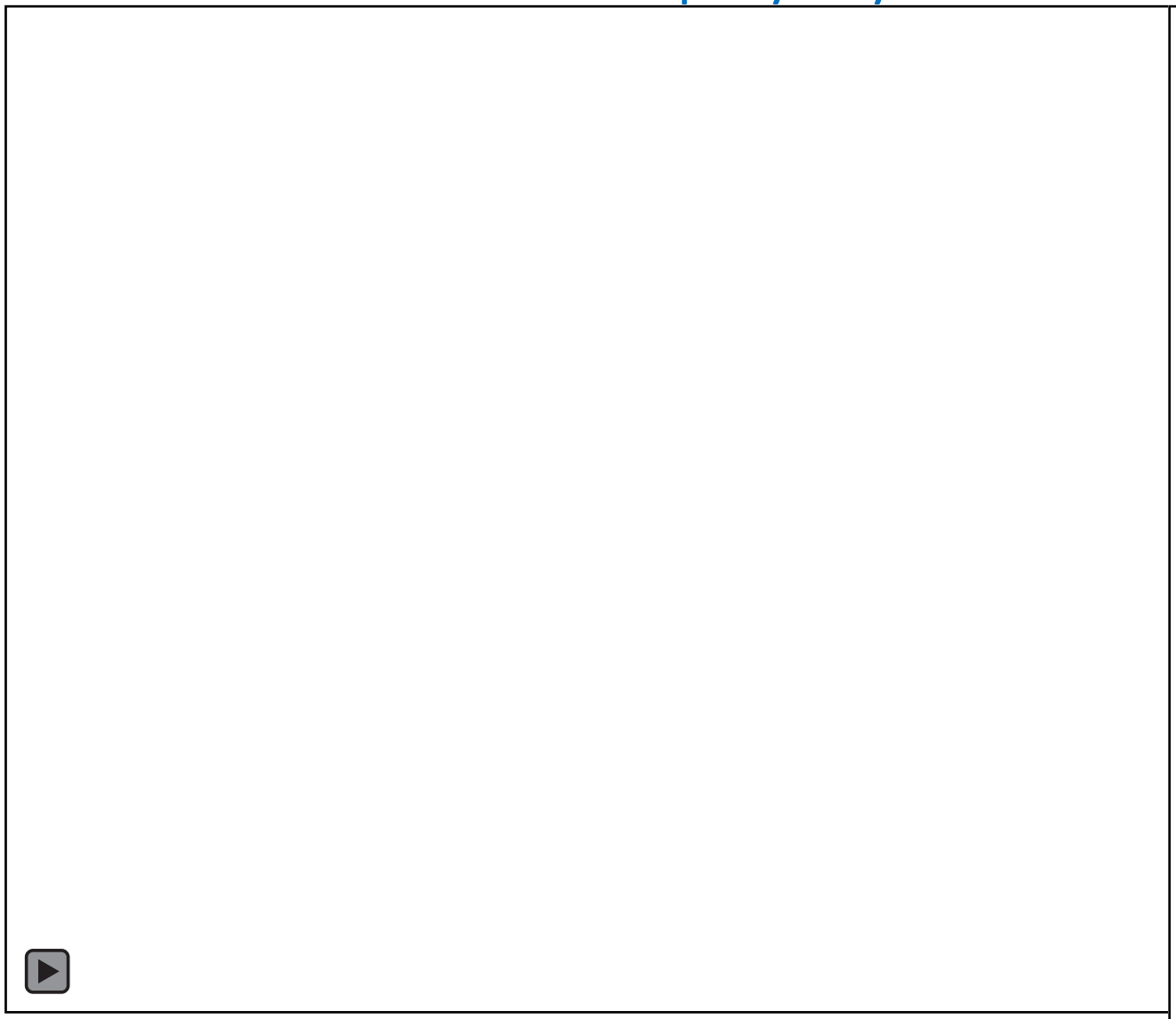


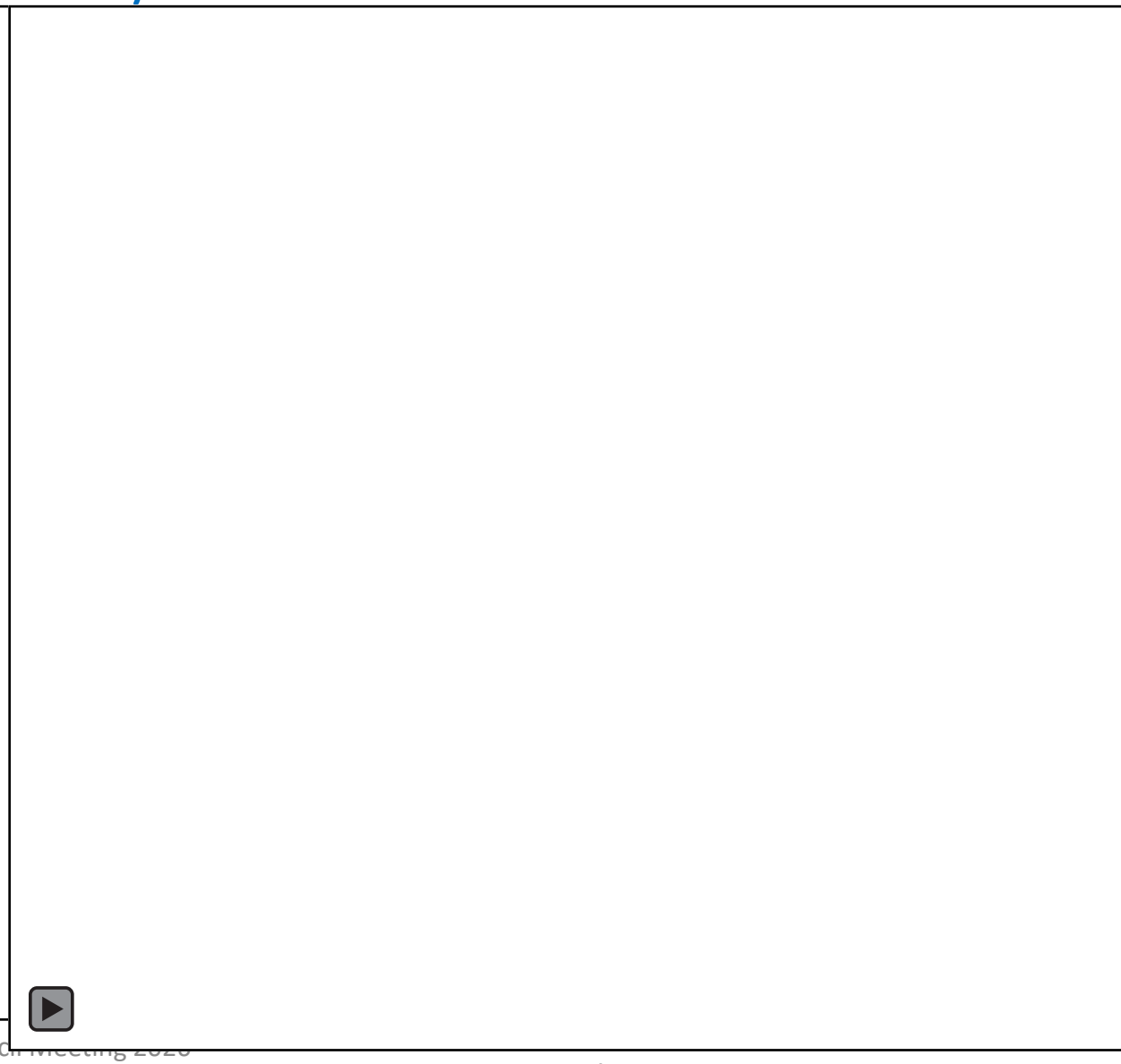
Modified - Courtesy of Ali Atri

The Dominantly Inherited Alzheimer Network Observational (DIAN-Obs) and Trials Unit (DIAN-TU) study sites



DIAN amyloid deposition, hypometabolism, and cortical atrophy by estimated years to onset





Bateman et. al NEJM 2012

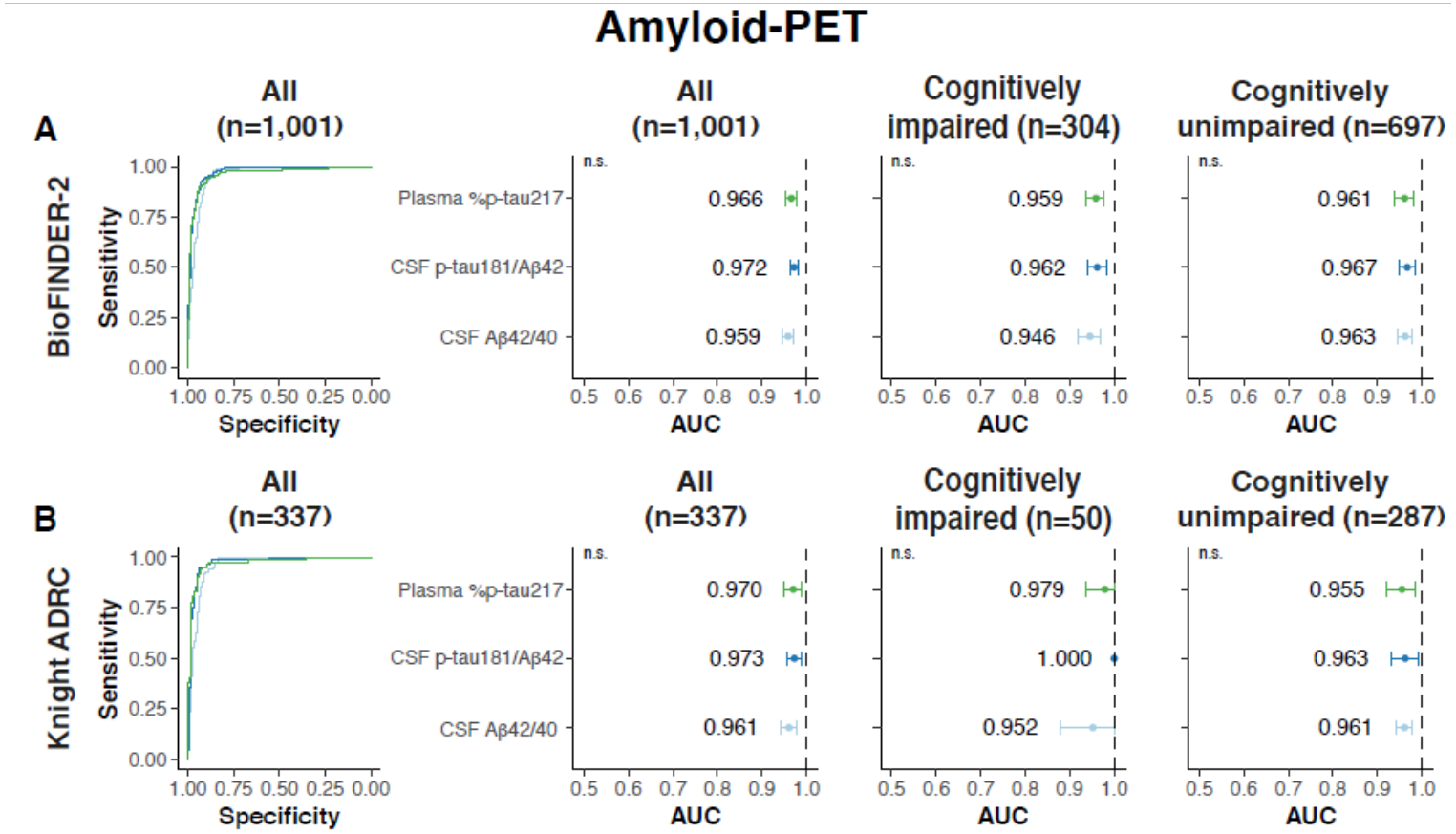
Benzinger et. al 2015 PNAS

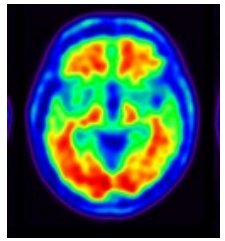
Plasma %ptau217/tau ratio predicts amyloid positivity as well as FDA approved CSF tests

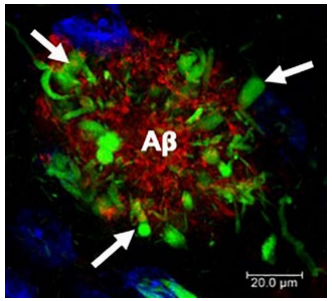
Plasma biomarker of **amyloid plaques**

THE SWEDISH BIOFINDER STUDY

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS







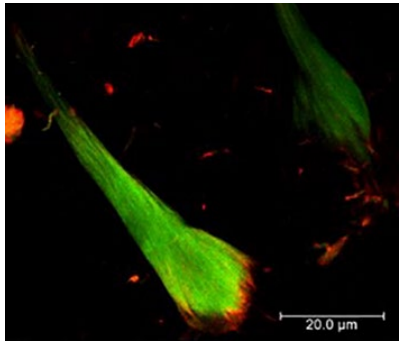
- Plasma ptau217 performs as well as FDA-approved CSF assays for predicting amyloid positivity
- Plasma ptau217 accurately predicts amyloid positivity in <u>cognitively unimpaired individuals</u>

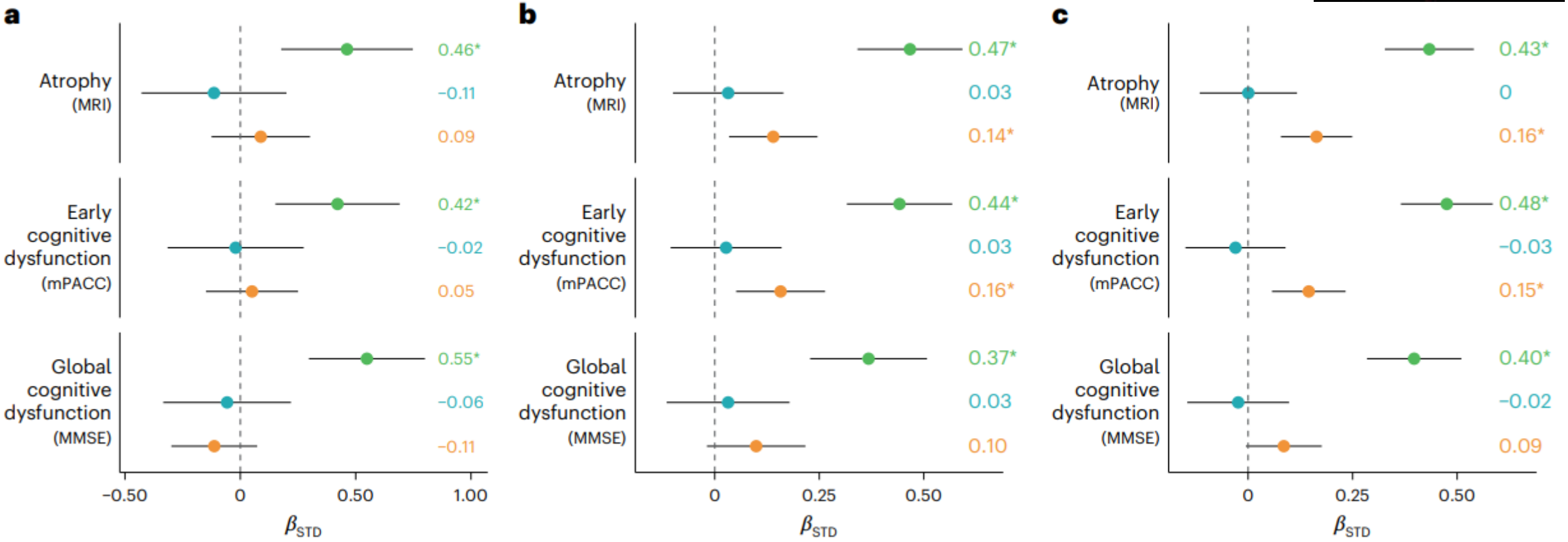
First Highly Specific Blood Test for Alzheimer's tau tangles

nature medicine

Plasma MTBR-tau243 biomarker identifies tau tangle pathology in Alzheimer's disease

Horie K, Salvadó G, ..Hansson O, Bateman RJ.
Nature Medicine 2025





2025

How are scientific advances in understanding, biomarkers, and clinical treatments being applied now and in the future for clinical treatment, and soon, prevention?

Highly accurate AD blood tests are clinically available now

nature medicine

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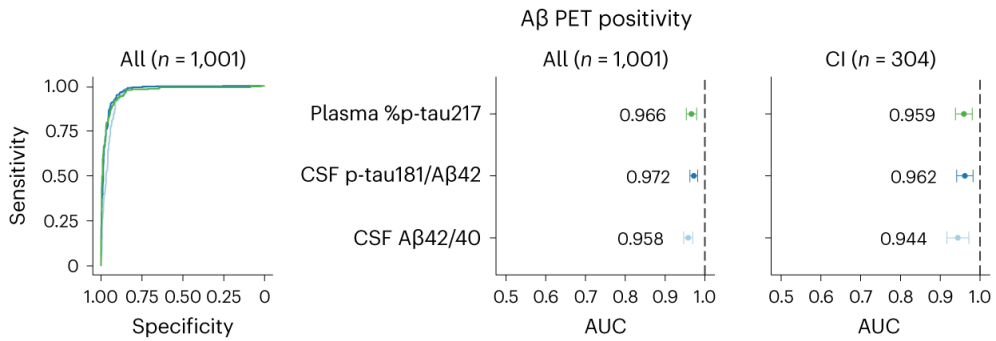
nature › nature medicine › articles › article

Article | Open access | Published: 21 February 2024

Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests

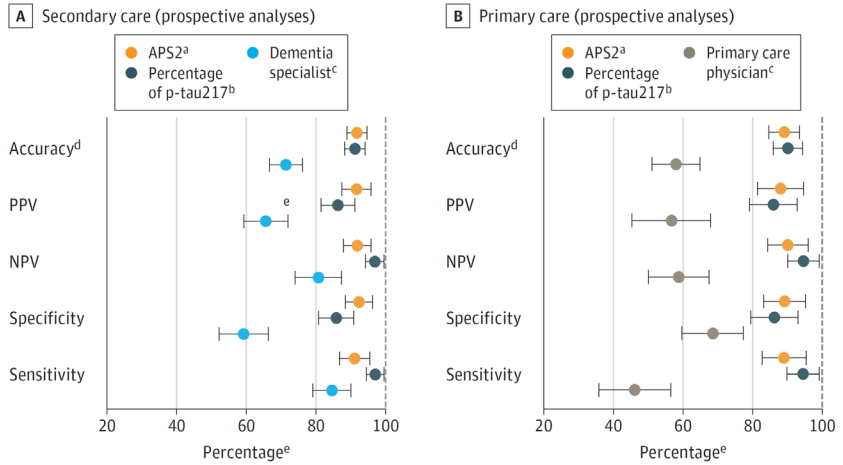
Nicolas R. Barthélemy, Gemma Salvadó, Suzanne E. Schindler, Yingxin He, Shorena Janelidze, Lyduine E. Collij, Benjamin Saef, Rachel L. Henson, Charles D. Chen, Brian A. Gordon, Yan Li, Renaud La Joie, Tammie L. S. Benzinger, John C. Morris, Niklas Mattsson-Carlgren, Sebastian Palmqvist, Rik Ossenkoppele, Gil D. Rabinovici, Erik Stomrud, Randall J. Bateman & Oskar Hansson



JAMA | Original Investigation

Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care

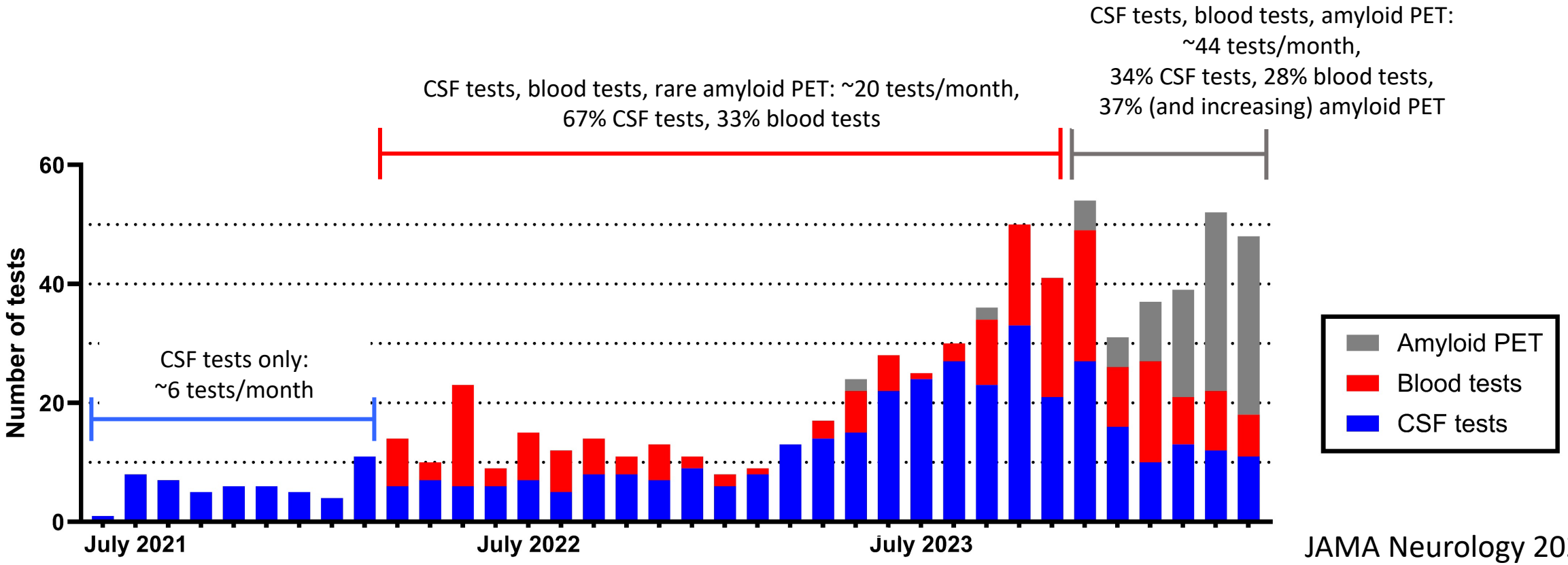
Sebastian Palmqvist, MD, PhD; Pontus Tideman, MSc; Niklas Mattsson-Carlgren, MD, PhD; Suzanne E. Schindler, MD, PhD; Ruben Smith, MD, PhD; Rik Ossenkoppele, PhD; Susanna Calling, MD, PhD; Tim West, PhD; Mark Monane, MD, MBA; Philip B. Verghese, PhD; Joel B. Braunstein, MD, MBA; Kaj Blennow, MD, PhD; Shorena Janelidze, PhD; Erik Stomrud, MD, PhD; Gemma Salvadó, PhD; Oskar Hansson, MD, PhD



	Primary care	Secondary care
Medical history, No./total (%)		
Cardiovascular disease	355/511 (69.5)	337/692 (48.7)
Hyperlipidemia	269/512 (52.5)	230/692 (33.2)
Chronic kidney disease	134/511 (26.2)	117/691 (16.9)
Diabetes	113/512 (22.1)	103/691 (14.9)

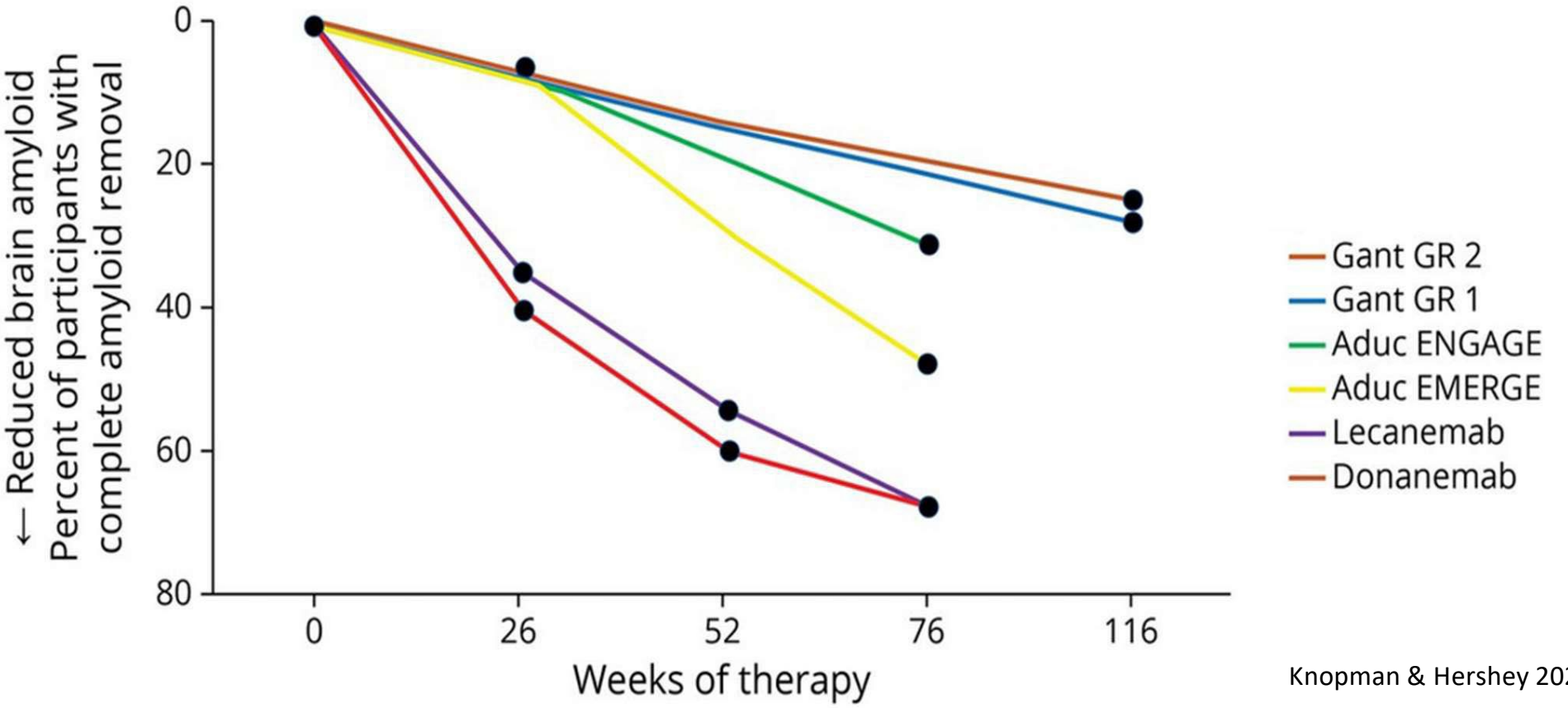
Clinical biomarker testing at Washington University

- Biomarker testing has increased ~7-fold over the past 3 years
- AD blood tests have been used in clinical diagnosis and decision making for >2 years
- The modality used for biomarker testing is greatly affected by practical considerations such as reimbursement



JAMA Neurology 2025

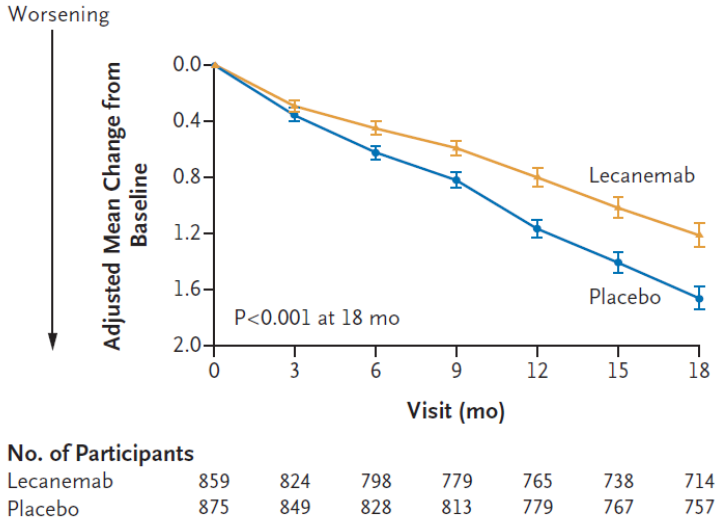
Drugs which completely remove detectable amyloid plaques (by PET scan) have consistently shown less cognitive and clinical decline in mild early Alzheimer's disease

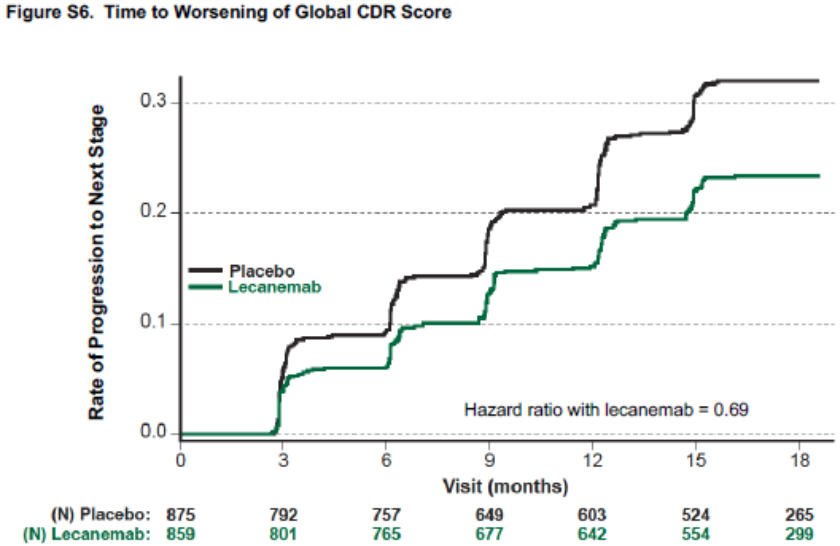


Knopman & Hershey 2023

Advent of disease-modifying treatments for AD

- Lecanemab was the first fully FDA-approved disease modifying treatment for early symptomatic AD
- The CLARITY AD trial demonstrated that lecanemab slowed clinical progression by 27% on the primary endpoint, the Clinical Dementia Rating® Sum of Boxes (CDR®-SB), which measures both cognitive and functional features typically affected by AD





Van Dyck *et al. NEJM* 2023

KNIGHT FAMILY DIAN TU Dominantly Inherited Alzheimer Network Trials Unit

Translation from Alzheimer's disease treatment to prevention trials

DIAN-TU Secondary Prevention

DIAN-TU AD Prevention Trial Platform

KNIGHT FAMILY DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

Secondary Prevention

Solanezumab (Lilly)
Gantenerumab (Roche)
NIA U01 AG042791
NIA R01 AG046179
Alz. Assoc.
GHR Foundation
Anonymous Org
~200 participants

Roche
Gantenerumab
OLE
Alz. Assoc.
GHR Found.
~73 pts

Eisai
Amyloid Removal Trial with Lecanemab

Alzheimer's Association
GHR Foundation
~50 participants

Janssen
NexGen
Atabecestat
Stopped July 2018
NIA R56/R01 AG053267

Eisai
Cognitive Run-in
E2814 + Lecanemab
2 yr Bio Endpoint
4 yr Cog Endpoint

Tau NexGen 5th Drug Arm

Tau NexGen 6th Drug Arm

Biomarker Interims

Population
EYO -10 to +10

197 participants
NIA R01 AG053267
Alzheimer's Association
GHR Foundation

100 participants
Anonymous Organization

100 participants
NIA R01 AG068319
Alzheimer's Association
GHR Foundation

Primary Prevention

Population
EYO -25 to -11

Lilly
Cognitive Run-in
Remternetug

240 participants

NIA U01 AG059798
Alzheimer's Association
GHR Foundation
Private Donors

Asymptomatic participants at baseline treated with gantenerumab the longest had delayed symptom onset and probability of progression free compared to controls

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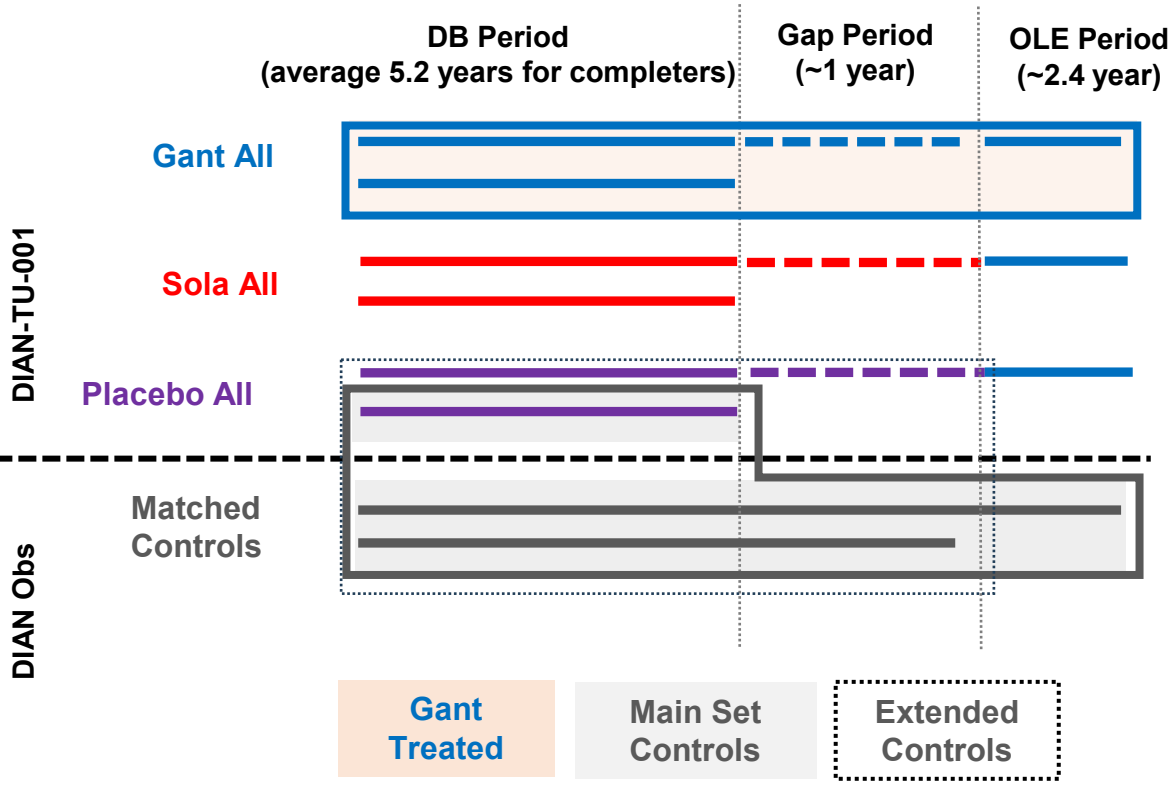
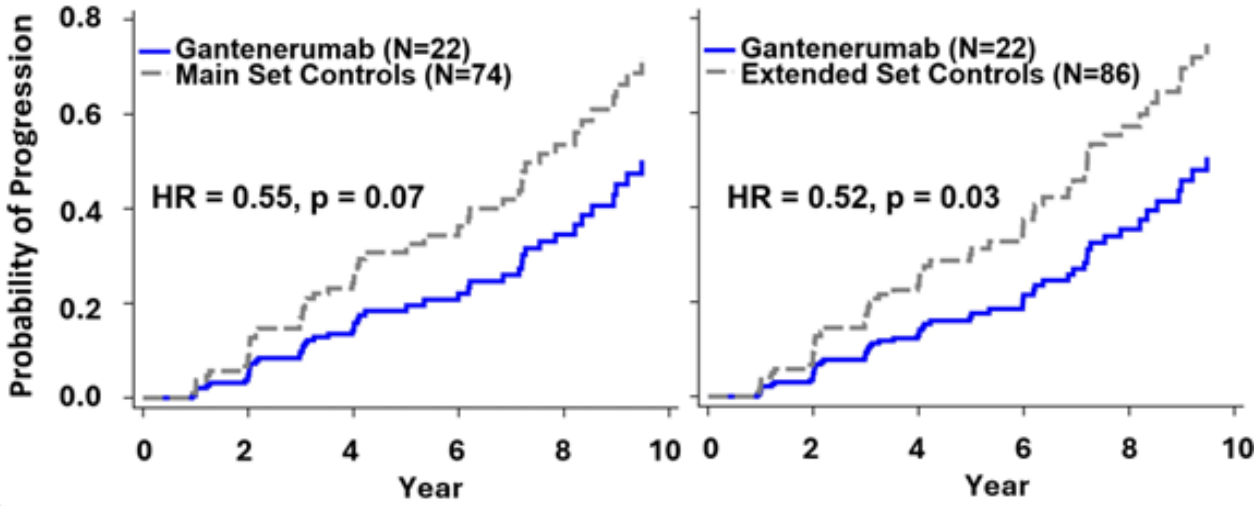
Dominantly Inherited Alzheimer Network Trials Unit
DIAN-TU-001 •GANT OLE

Longest Gant Treated



50% reduction in the risk of CDR-SB progression in Longest Gant Treated group



Output based on Cox proportional hazard model

- CDR SB: time to recurrent progression
- Event % is the event rate per person year.
- A hazard ratio (HR) of 0.50 would represent a 50% reduction in the risk of progression in the treatment group compared to the control group.

The DIAN-TU trial of gantenerumab provides the first proof of principle that removing amyloid plaques may prevent the onset of Alzheimer's disease dementia.

Safety and efficacy of long-term gantenerumab treatment in dominantly inherited Alzheimer's disease: an open-label extension of the phase 2/3 multicentre, randomised, double-blind, placebo-controlled platform DIAN-TU trial

Bateman et al., The Lancet Neurology, Volume 24, Issue 4, 316 - 330

Model of cognitive decline and treatment effects to delay onset of symptoms from Alzheimer's disease by 5 to 15 years

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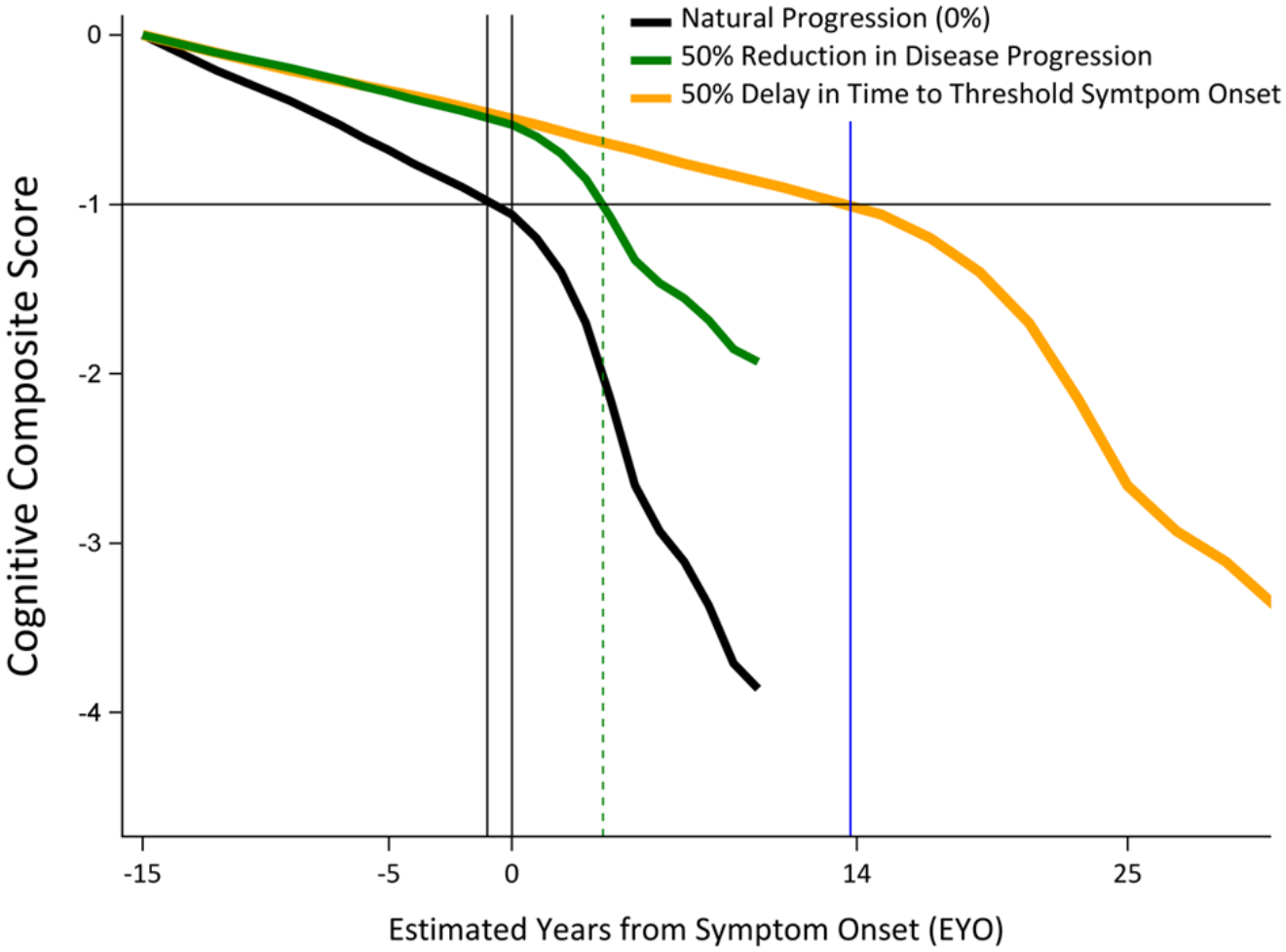
Trials Unit
DIAN-TU-001 • GANT OLE



Delay in cognitive decline (Symptomatic Onset) in years from Natural Progression		
% Change in Decline	**Proportional Reduction**	**Delay in Time**
50%	**5 years**	**15 years**

DIAN-TU-003: Amyloid Removal Trial (ART)

KNIGHT FAMILY DIAN TU Dominantly Inherited Alzheimer Network Trials Unit
DIAN-TU-003 • ART

Former gantenerumab OLE participants treated with lecanemab open-label for 5 years, to assess long-term efficacy (up to 15 years) and safety of removing amyloid plaques.

In DIAD mutation carriers, ART will determine:

1. Clinical effects of anti-amyloid antibodies on delaying dementia onset and risk of progression in treated compared to non-treated participants
2. Long-term effects of anti-amyloid antibodies on the rate and full removal of amyloid plaques
3. Effects of long-term amyloid plaque removal on

    a) longitudinal measures of established and novel fluid biomarkers of amyloid removal and disease progression

    b) amyloid-related imaging abnormalities (ARIA)

Coming Next: the Amyloid Removal Trial (ART)

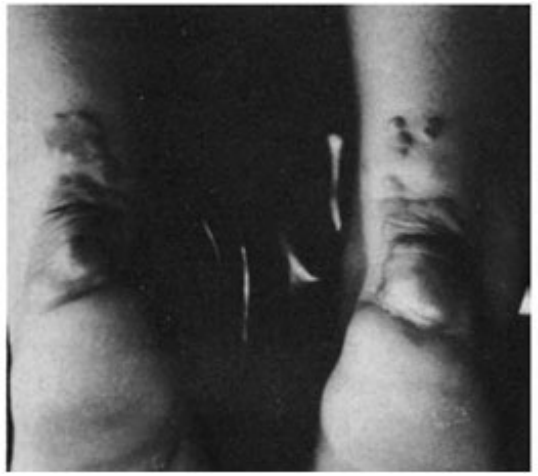
KNIGHT FAMILY DIAN TU
Dominantly Inherited Alzheimer Network Trials Unit
DIAN-TU-003 • ART

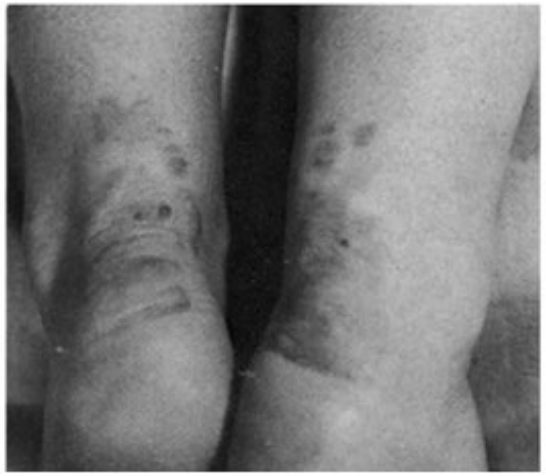
DIAN-TU ART Trial launched in June 2024

- First participant is co-enrolled in the DIAN-TU ART trial and the DIAN Observational study
  - Participant has received therapeutic dosing.

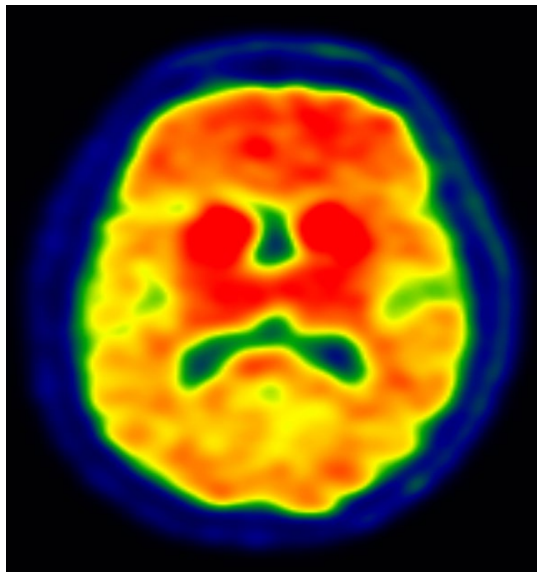
- DIAN-TU ART trial fully enrolled in Q2 2025
  - Participants will be treated for five years
  - Final results will provide up to 15 years of treated participants with annual evaluations of progress

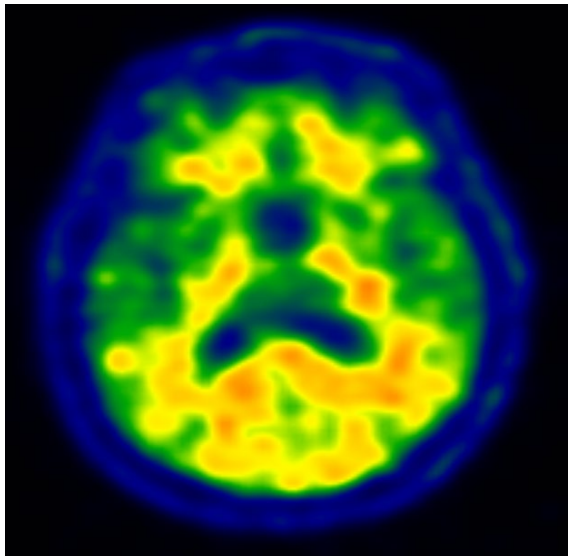
Historical Precedent: Treatment of inherited high cholesterol with statin to decrease pathology before organ failure





Young familial hyper-cholesterolemia patient with cholesterol deposits resolved after treatment with a statin





Young dominantly inherited Alzheimer's participant, still asymptomatic, CDR 0 treated with gantenerumab to remove amyloid plaques

Pre-treatment

Post-treatment

How will we solve aging causes of Alzheimer's?

- Join forces across labs and fields – bring together fundamental biology of aging research with Alzheimer's disease research
- Develop systems capable of handling immense biological complexity (i.e. aging)
  - Omics
  - Machine Learning
  - Deep Learning – neural nets AI
- Accelerating the rate of biomedical discoveries that lead to human health improvement
  - Create scalable scientific partners through generative AI (e.g. LLMs, knowledge structures, and agentic AI)

Consortium for Biomedical Research and Artificial Intelligence in Neurodegeneration (C-brAIn)

www.c-brain.org

A Pioneering Initiative in AI-Driven Discovery

Randall J. Bateman, MD

What Health Problem Are We Trying To Solve?

Developing an AI Scientific Assistant for Biomedical Research

To ***multiply*** the effectiveness of biomedical research efforts, addressing the challenge of making impactful health advances quickly enough for current patients' benefit.

Initial focus on Alzheimer's disease and neurodegeneration as the Proof of Concept:

Affects **tens of millions globally, urgent need for new strategies**

(1) Expertise in Alzheimer's disease and neurodegeneration

(2) Cross-field support with multiple stakeholders in academia, industry, and government

(3) Large research community

(4) Neuroscientists inherently trained in thinking, reasoning, and intelligence

Core Objectives:

Accelerate & improve **accuracy and future success of hypothesis generation** (e.g., asking the right questions, the killer experiment, elegant design, insight)

Transform experimental design with doubling or tripling success rates of durable findings that lead to impactful human health discoveries

Revolutionize data interpretation (doing analyses not possible with traditional human/computer approaches)

Enable cross-disciplinary collaboration that wouldn't otherwise be possible.

Harnessing Artificial Intelligence to Transform Alzheimer's Disease Research, Nature Medicine 2025

How Is It Done Today? What Are The Limitations Of Present Approaches?

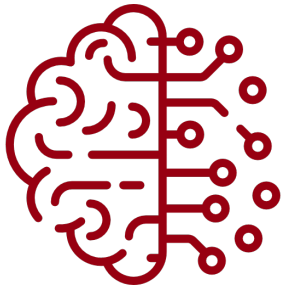
Current limitations:

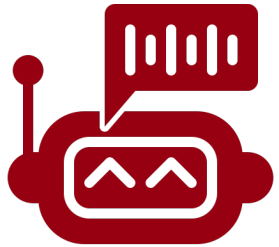
- Several decades required to train new expert scientists
- Too few ground-breaking scientists available for demand/need
- Siloed knowledge limits capacity as information grow at exponential pace
- Researchers limited to increasingly narrow knowledge domains
- Manual literature review and data analysis become less useful
- Breakthroughs and discoveries bottlenecked by available expertise

Data challenges:

- Overwhelming volume of new research, data, and interactions
- Difficulty integrating cross-disciplinary findings
- Inefficient or incorrect utilization of existing knowledge

How will we build and train the AI Biomedical Research Scientist Assistant?





Bring together leaders in academic AI, AI tech industry, biomedical researchers and Pharma in a public-private Consortium

World leading Neurodegenerative and Aging researchers with deep expertise and vast biomedical datasets will design, train, and use AI systems

Establish and grow the Consortium with stakeholders aligned in accelerating basic biomedical discoveries to improve human health and brain aging

C-brAIn Members and Interested Stakeholders

Academic Biomedical Researchers	
Albert Einstein College of Medicine	Scripps Research Institute
Amsterdam University Medical Center	Stanford
Baylor College of Medicine	UK Dementia Research Institute
Cardiff University	University College London
Columbia University	University of California, Los Angeles
Harvard	University of California, San Diego
Houston Methodist	University of California, San Francisco
Johns Hopkins University	University of Colorado, Denver
Ludwig Maximilian University Munich	University of Edinburgh
Lund University	University of Massachusetts
Massachusetts General Hospital	University of Pennsylvania
Massachusetts Institute of Technology	University of Southern California
Mayo Clinic, Jacksonville	University of Washington
Michigan State University	Vanderbilt University Medical School
Mount Sinai	VIB-KU Leuven
Northwestern	**Washington University***
Salk Institute	Weill Cornell Medicine

Academic AI Researchers
Berkeley (LBNL)
Berlin Institute of Health (BIH)
Emory / Georgia Tech
Harvard
Imperial College London
Mount Sinai
Stanford
University of Southern California
University of Washington
Washington University

Pharma / Biotech
Bristol Myers Squibb*
Eisai Co. Ltd.
Johnson & Johnson*
Sanofi*
Other Pharma Pending

Major and Key Supporters
AD Data Initiative*
Alzforum*
Alzheimer's Association*
Anonymous Foundation*
The Dolby Family*
Gates Ventures*
Robertson Foundation*
Sage Bionetworks*
The 10,000 Brains Project*

***Major Contributing Members**

To visit C-BRAIN website (c-brain.org):

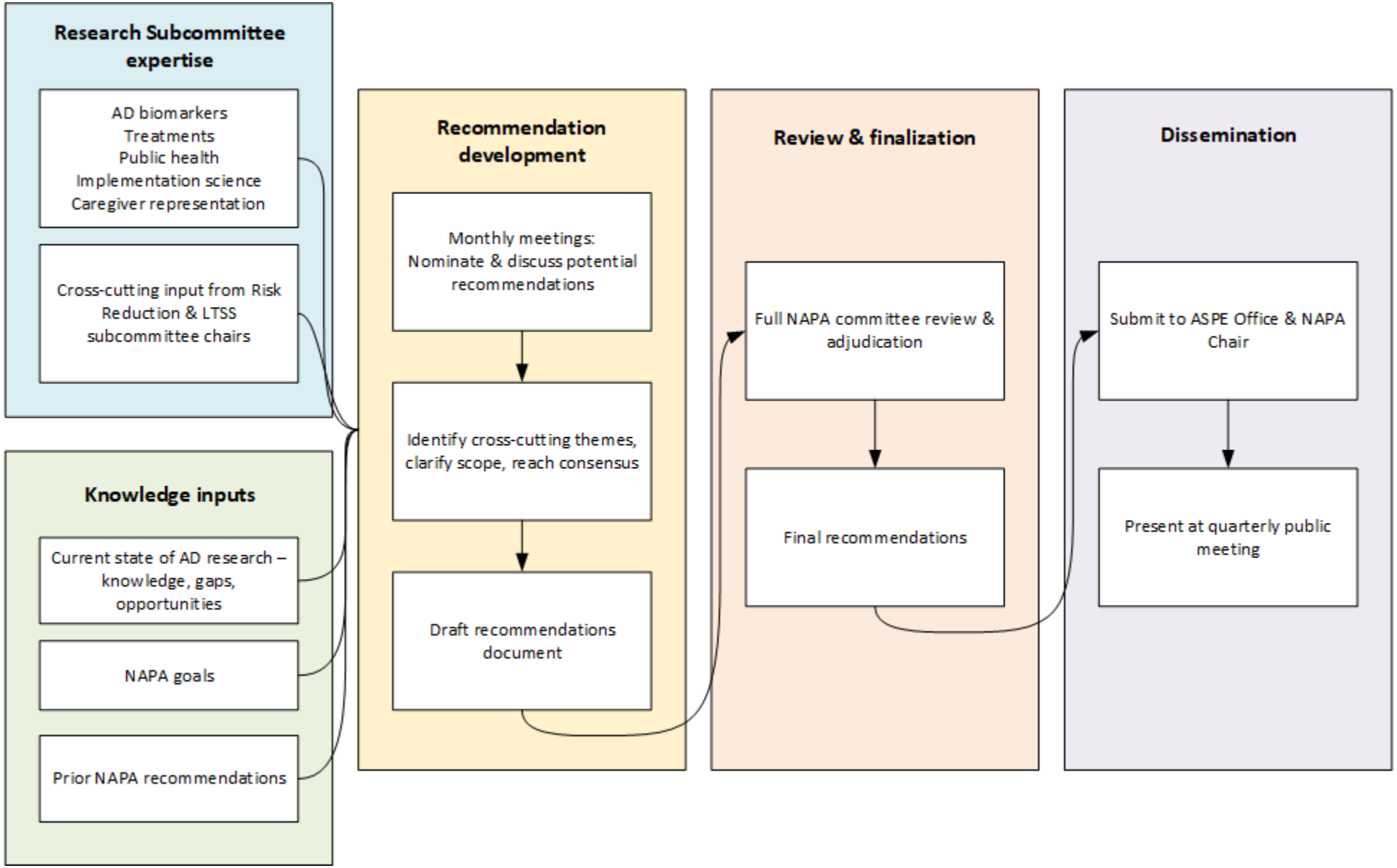
To register for updates or collaborations, enter contact info at:

tiny.cc/BRAINC

or

https://washu.qualtrics.com/jfe/form/SV_efBkXKL3KwRloPA

How do research results turn into actionable NAPA recommendations?



NAPA impact

- Recommendations toward NAPA goal of treating and preventing Alzheimer's disease have contributed to increased federal funding for ADRD research
- Multiple breakthroughs in recent years:
  - First disease-modifying treatments for AD
  - Diagnostic tests, including blood tests, being used in the clinic to diagnose patients with 90-95% accuracy
  - Multiple prevention trials launched, with emerging evidence that AD might be prevented years before symptom onset

ACKNOWLEDGMENTS

The research participants

Collaborators: Biofinder: Oskar Hansson, Gemma Salvaldo, Shorena Janelidze
ADRC: John Morris, **Suzanne Schindler**, Chengjie Xiong, Tammie Benzinger, Anne Fagan, Brian Gordon, **David Holtzman**
SILQ Center: Nupur Ghoshal, Donald Elbert, Paul Kotzbauer, Tim Miller, Ross Paterson, Bruce Patterson

Prior Members of the Bateman Lab: *Alaina Baker-Nigh, Anna Bareiss, Abby Brand, Melissa Budelier, Karen Browning, Derica Cartwright, Jingdao Chen, Rose Connors, Paul Dalba, Justyna Dobrowolska, Tamara Donahue, Brian Finn, Audrey Gabelle, Tinishia Greene, Melinda Hamilton, Terry Hicks, Yafei Huang, Kim Ingersoll, Tom Kastan, Farhan Khatchi, Haiyan Liu, Brendan Lucey, Paul Moiseyev, Sergio Molina, Kelly Moor, Kwasi Mawuenyega, Ling Munsell, Caroline Ogunware, Katrina Paumier, Rachel Potter, Yuriy Pyatkivsky, Randy Qian, Kara Ramsey, Kaleigh Roberts, Anna Santacruz, Theresa Schneider, Shirley Shih, Melissa Sullivan, Mengxuan Tang, Kalyan Tripathy, Kate Walter, Michelle Wegscheid, Alex Wen, Norelle Wildburger, Kristin Wildsmith, Wanwan Xu, Lily Zhang*

Current Members of the Bateman Lab:
Brendan Androff
Nicolas Barthelemy, PhD, Asst Professor
James Bollinger, PhD
Gina Collins
John Coulton, PhD, Instructor
Chloe He, PhD
Kanta Horie, PhD, Visiting Assoc Professor
Rama Krishna Koppisetti
Yan Li, PhD, Assoc Professor
Melody Li, MS
Samir Lopez Chahin
Justin Melendez, PhD
Soumya Mukherjee, PhD, Asst Professor
Sarah Naylor, PhD, Asst Professor
Nicholas Oatts
Vitaliy Ovod, MS
Manohar Pradhan
Kaleigh Roberts MD PhD
Chihiro Sato, PhD, Asst Professor
Deanna Simon
Brunda Tumala, PhD

Clinical Coordinators
Melanie Burton
Rickey George
McCrae Johnson
Olivia Kersting
Lisa Soke
Britt Wagner
Georgia Stobbs-Cucchi

The DIAN (NIH U19AG032438)

Performance Sites

Argentina

Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Buenos Aires & Salta, *Ricardo Allegri*

Australia

Edith Cowan Univ, Perth, *Ralph Martins*

Neuroscience Research Australia, Sydney, *Emma Devenney*

Colombia

Grupo Neurociencias de Antioquia, Medellin, *David Aguillón*

Germany

German Center for Neurodegenerative Diseases (DZNE), München, *Johannes Levin*

University of Tübingen, *Mathias Jucker*

Japan

Niigata University, *Kensaku Kasuga*

University of Tokyo, *Yoshiki Niimi*

Mexico

Instituto Nacional de Neurologia y Neurocirugla, Mexico City, *Ana Luisa Sosa Ortiz*

South Korea

Asan Medical Center, *Jae-Hong Lee*

United Kingdom

Univ College London, *Nick Fox*

United States

Butler Hospital/Brown University, *Edward Huey*

Indiana University, *Martin Farlow*

Mayo Clinic, Jacksonville, *Gregory Day*

Mass General Hospital/Brigham & Women's Hospital, *Jasmeer Chhatwal*

University of Pittsburgh, *Sarah Berman*

University of Washington, *Suman Jayadev*

Washington University, *Randall J. Bateman*

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*Financial support has also been provided by anonymous sources.

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U01 AG042791, R01 AG046179, R01/R56 AG053267, R01 AG068319, R13 AG055232, U01 AG059798

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