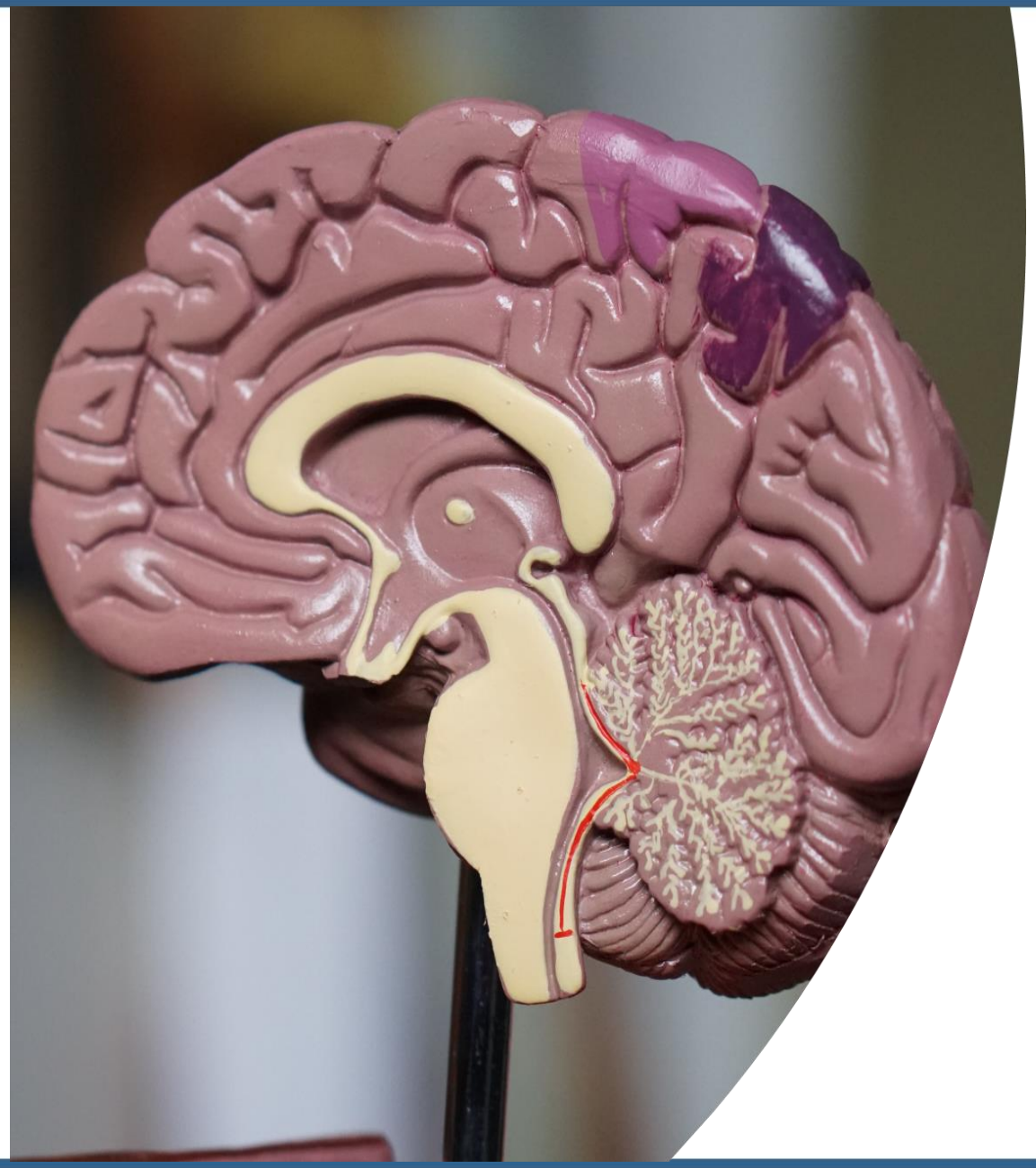


ACT-AD
Accelerate Cures/Treatments for ALL DEMENTIAS

Welcome to the 13th Annual FDA/ACT-AD Allies Meeting!

The program will begin momentarily.

<u>In preparation for the meeting, please:</u>

1. Turn your camera ON
2. MUTE your microphone
3. Rename yourself using the following format: *[First Name] [Last Name] – [Org. Name]*

ACT-AD
Accelerate Cures/Treatments for ALL DEMENTIAS

13th Annual FDA/ACT-AD Allies Meeting:
Common Threads: Learning from the Related Dementias

Agenda

Welcome and Introductions	10:30 AM – 10:40 AM (ET)
The Quest to Develop Biomarkers for Vascular Cognitive Impairment *Steven Greenberg, M.D., Ph.D., Harvard Medical School/Massachusetts General Hospital*	10:40 AM – 11:00 AM (ET)
Discussion	11:00 AM – 11:15 AM (ET)
Federal Investment in Alzheimer's Disease and Related Dementia Clinical Research *Suzana Petanceska, Ph.D., and Laurie Ryan, Ph.D., National Institute on Aging*	11:15 AM – 11:55 PM (ET)
Discussion	11:55 PM – 12:15 PM (ET)
Lunch Break	12:15 PM – 12:30 PM (ET)
An Exploration into the Dementia Therapeutic Pipeline *Jeffrey Cummings, M.D., Sc.D., University of Nevada, Las Vegas*	12:30 PM – 12:50 PM (ET)
Discussion	12:50 PM – 1:05 PM (ET)
Research into Molecular Underpinning of Dementia *David Bennett, M.D., Rush Alzheimer's Disease Center*	1:05 PM – 1:35 PM (ET)
Discussion	1:35 PM – 1:50 PM (ET)
Dementia Clinical Development Questions and Challenges: Industry Perspective *Samantha Budd Haeberlein, Ph.D., Biogen, Sanjay Dube, M.D., Avanir, and Eva Kohegyi, M.D., M.S., Otsuka*	1:50 PM – 2:25 PM (ET)
Closing Remarks	2:25 PM – 2:30 PM (ET)

Housekeeping Rules

At the start of the meeting:

- Turn your camera ON.
- MUTE your microphone
- Rename yourself with the following format: *[First Name] [Last Name] – [Org. Name]*
  - To rename yourself in Zoon: Click on the “Participants” button (at the bottom of the screen) to open up the Participants Panel.
  - Hover over your name and click on the blue “More” button. Select “Rename.”
  - Enter your name in the format mentioned above. Click the blue “OK” button.

Housekeeping Rules

During Presentations

- Keep your microphone MUTED.
- Submit questions through the Chat feature.
  - To submit a question through the Chat feature: Click the “Chat” button (at the bottom of the screen). The Chat function will pop up.
  - Ensure you are sharing your question with “Everyone” and type your question in the text field.
  - Submit your question by hitting “Enter.”

Housekeeping Rules

During Discussion

- Have your camera ON.
- Your submitted questions will be fielded by the moderators.
- After questions are read, you may UNMUTE your microphone to respond.
- The meeting is a roundtable format, so engagement is encouraged!

Discussion

- Your questions submitted through the Chat feature will be fielded by a moderator.
- After a question is read, you may unmute to respond. Please state your name and affiliation when asking or answering question.
- The meeting is a roundtable format, so engagement is encouraged!

Housekeeping Rules

Technical Issues

- Please reach out to Sarah DiGiovine via email (sdigiovine@agingresearch.org) or the Zoom Chat feature.

Off the Record

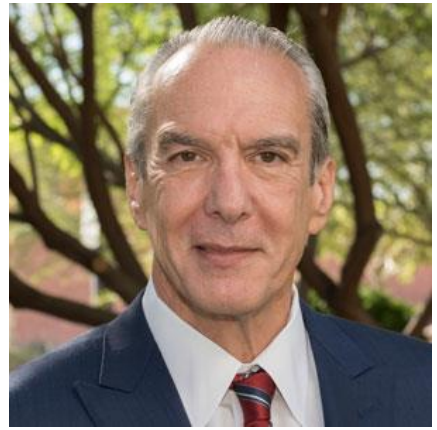
- The meeting is off-the-record event. Please do not quote speakers or participants on social media (Twitter, LinkedIn, Facebook, etc.)

Meeting Presenters

Steven Greenberg, M.D., Ph.D.,
Harvard Medical School and Massachusetts General Hospital

Suzana Petanceska, Ph.D.
National Institute on Aging

Laurie Ryan, Ph.D.
National Institute on Aging



Jeffrey Cummings, M.D., Sc.D.
UNLV School of Allied Health Sciences

David Bennett, M.D.
Rush Alzheimer's Disease Center

Samantha Budd Haeberlein, Ph.D.
Biogen

Sanjay Dubé, M.D.
Avanir

Eva Kohegyi, M.D., MS
Otsuka

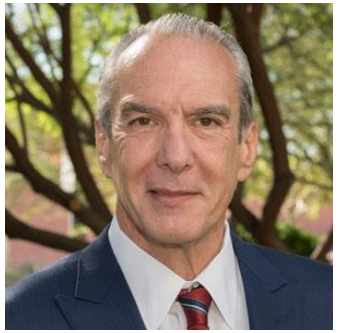
ACT-AD Science Advisory Board

ACT-AD
Accelerate Cures/Treatments for ALL DEMENTIAS

Paul Aisen, M.D.
USC Alzheimer's Therapeutic Research Institute

Phyllis E. Greenberger, MSW
HealthyWomen

Janice Hitchcock, Ph.D.
Acumen



Jeffrey Cummings, M.D., Sc.D.
UNLV School of Allied Health Sciences

Russell Katz, M.D.
(Retired) Food and Drug Administration

George Perry, Ph.D.
University of Texas, San Antonio

Creighton (Tony) Phelps, Ph.D.
(Retired) National Institute on Aging

Reisa A. Sperling, MD, MMSc
Brigham and Women's Hospital

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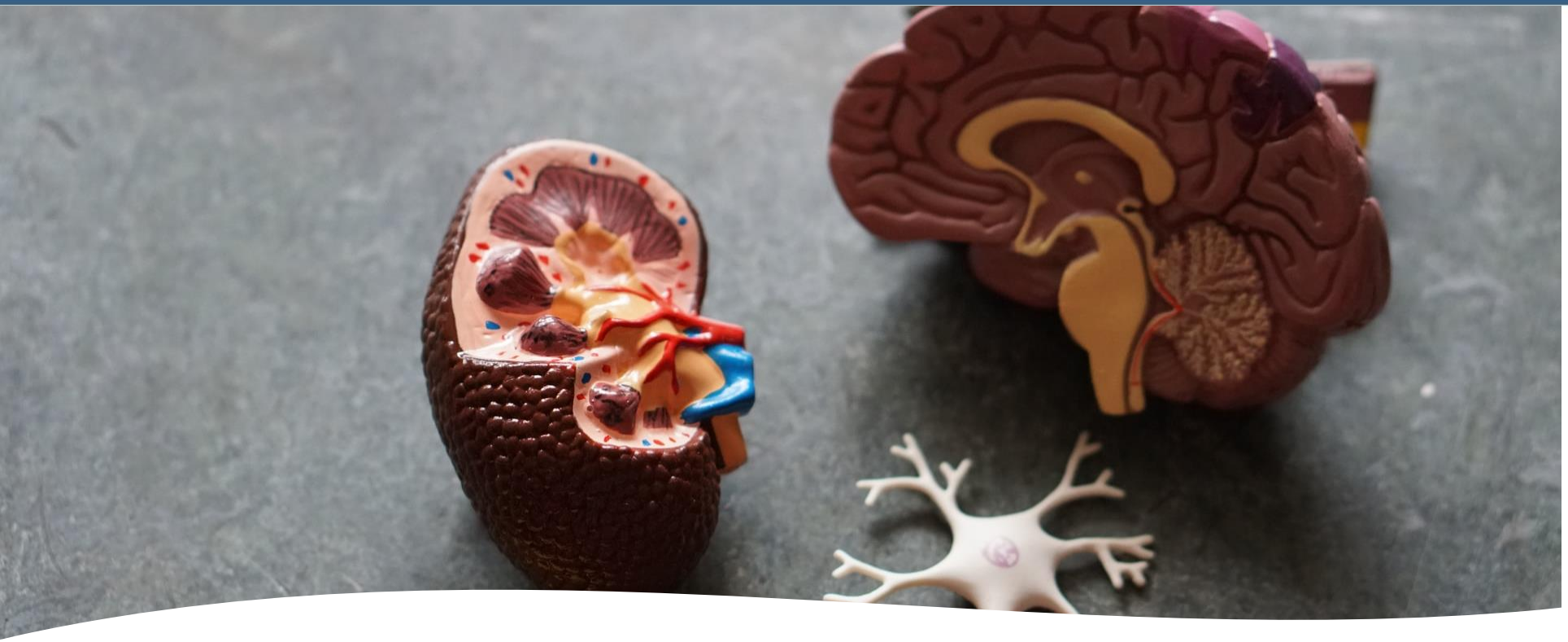


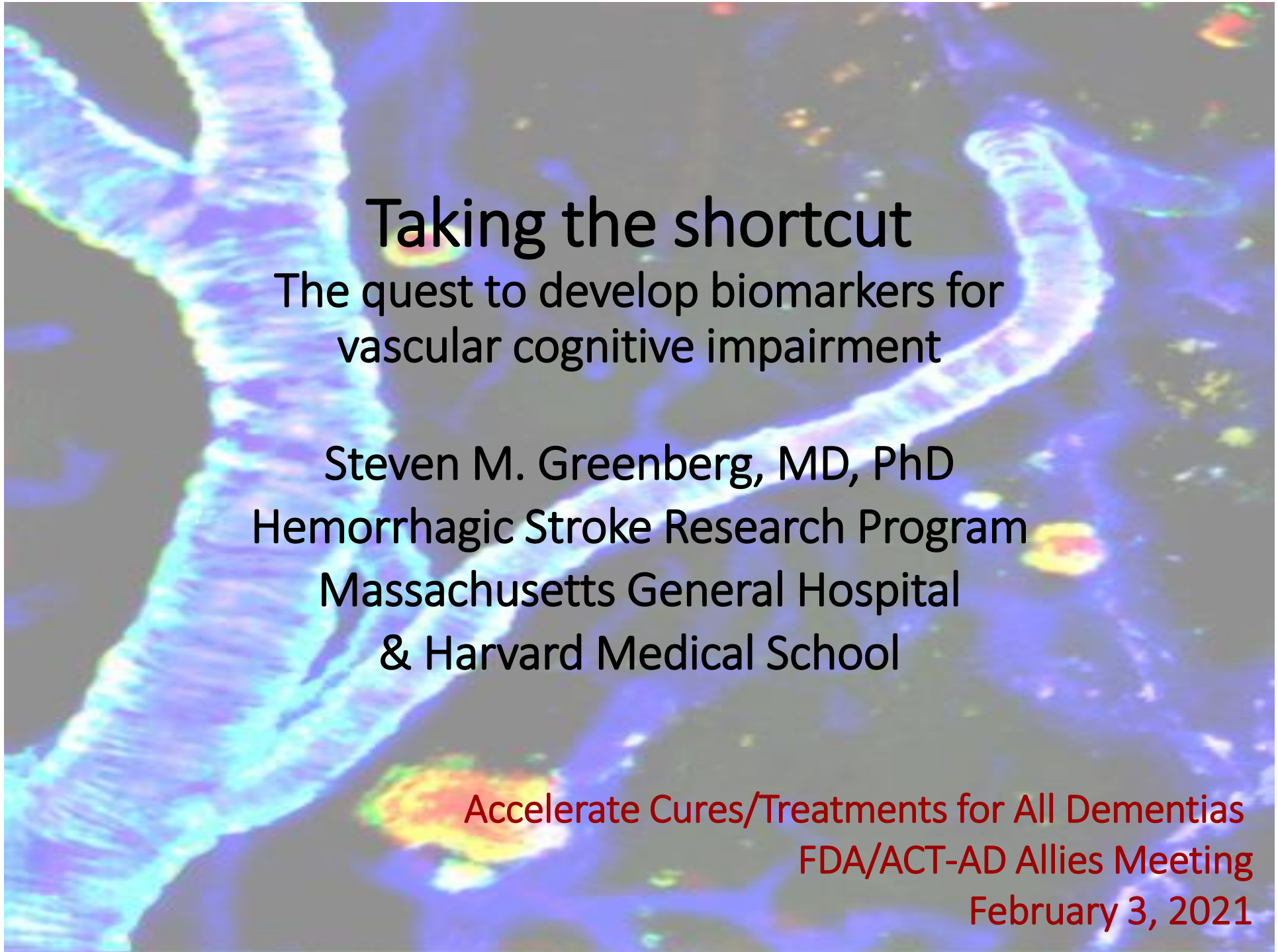
ACT-AD
Accelerate Cures/Treatments for ALL DEMENTIAS

Thank you for joining us today!

ACT-AD
Accelerate Cures/Treatments for ALL DEMENTIAS

Michael Ward
Vice President of Public Policy
Alliance for Aging Research
mward@agingresearch.org

Ryne Carney
Manager of Public Policy
Alliance for Aging Research
rcarney@agingresearch.org



Taking the shortcut

The quest to develop biomarkers for vascular cognitive impairment

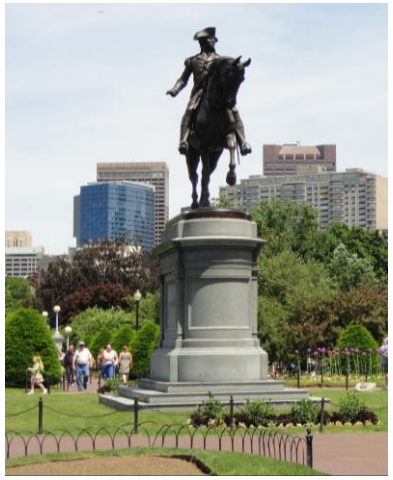
Steven M. Greenberg, MD, PhD
Hemorrhagic Stroke Research Program
Massachusetts General Hospital
& Harvard Medical School

Accelerate Cures/Treatments for All Dementias
FDA/ACT-AD Allies Meeting
February 3, 2021

Disclosure

Work supported by grants from the US National Institutes of Health (R01NS070834, R01AG26484, R01NS096730, U24NS100591)

Safety monitor for AD (DIAN-TU, Roche, Biogen), anticoagulant (Bayer) trials



Thanks to….

MarkVCID

Kristin Schwab Karl Helmer Pia Kivisakk-Webb Herpreet Singh
Rod Corriveau Hanzhang Lu Joel Kramer Gary Rosenberg
Julie Schneider Sudha Seshadri Danny Wang Donna Wilcock

Martinos Center/MGH Radiology

Keith Johnson Jon Polimeni
David Salat Bruce Fischl

Hemorrhage Research Program

Anand Viswanathan M. Edip Gurol
Andreas Charidimou Elif Gokcal
Kristin Schwab Vanessa Gonzalez Zora DiPucchio Mitchell Horn
Nicholas Raposo Yael Reijmer Grégoire Boulouis Marco Pasi

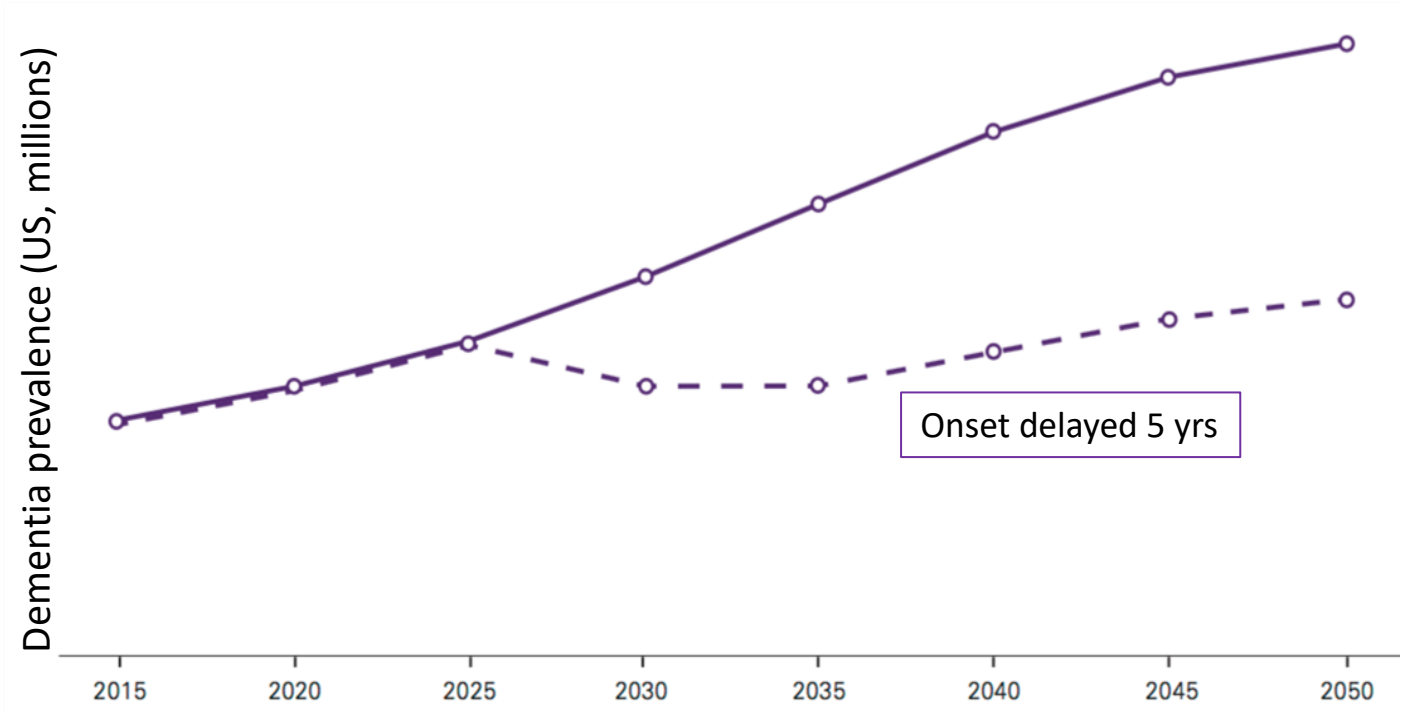
Center for Human Genetic Research

Jon Rosand
Chris Anderson
Alessandro Biffi

MassGeneral Institute for NeuroDegeneration

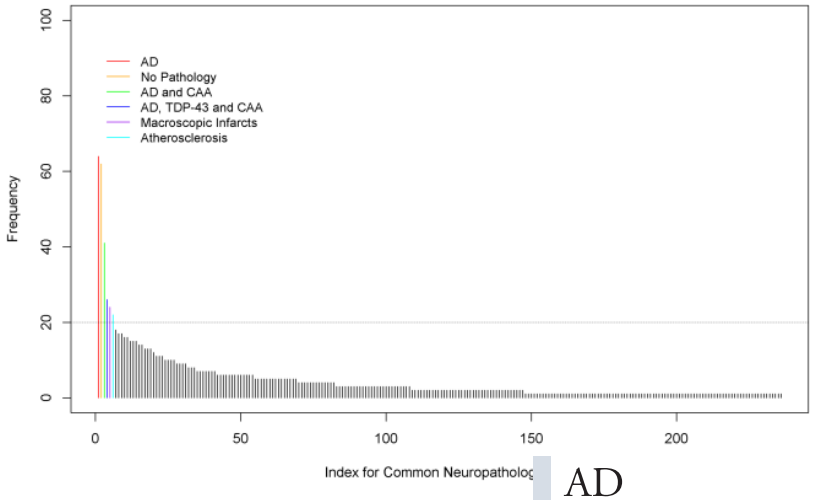
Susanne van Veluw Brian Bacskai
Brad Hyman Matthew Frosch

Dementia Burden
The coming storm



Data from Alzheimer's Association

Dementia Burden
Role of the AD-related dementias (ADRDs)



Boyle, Schneider Religious Orders/ Rush Memory and Aging
Ann Neurol 2018;83:74

	Path present (n=1079)	Proportion cog decline when present
AD	704	57.9%
Gross infarcts	388	28.8%
Cerebral amyloid angiopathy	386	20.6%
TDP-43	377	30.5%
Atherosclerosis	358	27.4%
Arteriolosclerosis	338	27.5%
Cortical Lewy bodies	143	45.1%
Hippocampal sclerosis	112	28.1%

ADRD Recommendations
Call for biomarkers

Table 1 Topic area 1: Research recommer

Focus area	Priority	Recommendation
Differential diagnosis	1	Develop clinical algori cognitive impairment and clinical algorithms consultations using n
	2	Develop imaging and expand their accessib
	3	Develop clinical, imag treatable dementias t
Epidemiology	1	Conduct population-b

Table 4 Topic area 4: Research re

Focus area	Priority	Recommendation
Basic science	1	Clarify the mechanism of tau pathogenesis and associated neurodegeneration
	2	Develop better FTD in vivo and cell-based model systems
	3	Determine the molecular basis for C9ORF72 expansion–related and GRN-related neurodegeneration
	4	Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity
Clinical science	1	Expand efforts to genotype patients with FTD and identify new genes
	2	Develop FTD biomarkers for diagnosis and disease progression
	3	Create an international FTD clinical trial network
	4	Understand phenotypic heterogeneity and natural history

Table 5 Topic area 5: Research recommendations for VaD—Small vessel disease and AD/vascular interactions

Focus area	Priority	Recommendation
Basic mechanisms and experimental models	1	Develop next-generation experimental models of VCI and VaD
	2	Encourage basic science research that investigates the impact of AD risk factors on cerebrovascular function
	3	Encourage basic science research that investigates the impact of cerebrovascular risk factors on AD-related neurodegeneration
Human-based studies	1	Develop and validate noninvasive markers of key vascular processes related to cognitive and neurologic impairment
	2	Determine interrelationships among cerebrovascular disease and risk factors, Aβ, and neurodegeneration
	3	Identify next-generation vascular interventions to treat or prevent VCI and VaD

iscover disease mechanisms through ain mapping and genetics	3	Using well-defined cohorts with DLB or PDD who have come to autopsy, systematically map disease-specific changes in the brain, spinal cord, and peripheral autonomic nervous system with state-of-the-art methods, including genomics, expression arrays, metabolomics, and proteomics to identify underlying disease mechanisms that will guide future biomarker and therapeutic approaches
	4	Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that affect the risk and clinical features of DLB and PDD
evelop and validate biological and aging biomarkers	5	Develop imaging approaches to enhance the diagnostic accuracy of DLB and PDD, detect latent and prodromal DLB and PDD, and monitor disease progression in natural history and treatment studies by integrating established and new imaging tools
	6	Use existing or new longitudinal case-control studies of individuals with DLB and PDD to develop biomarkers for Lewy-related pathologic changes, disease progression, and the relative amount of concurrent AD. As new markers of molecular disease mechanisms are discovered, incorporate them into biomarker studies for diagnosis of latent or prodromal disease and for monitoring molecular processes and their response to therapies
odel disease processes to develop erapies	7	Recognizing the importance of α-synuclein and AD pathophysiologic processes in DLB and PDD, new animal, cellular, and in vitro models are needed that recapitulate key features of these disorders with the ultimate goal of identifying strategies that can be carried forward into clinical trials
	8	Develop disease-modifying interventions based on research discoveries

Montine *Neurology* 2014;83:851

Taking the Shortcut
Biomarkers for vascular cognitive impairment

1. Validating SVD biomarkers: MarkVCID
2. Examples of biomarker applications: CAA

Taking the Shortcut
Biomarkers for vascular cognitive impairment

1. Validating SVD biomarkers: MarkVCID

Biomarker
/bīōˌmärkər/
noun: **biomarker**; plural noun: **biomarkers**
a measurable substance in an organism whose presence is indicative of some phenomenon

Taking the Shortcut
Biomarkers for vascular cognitive impairment

“Measurable”

- Accessible
- Reproducible across raters, timepoints, sites

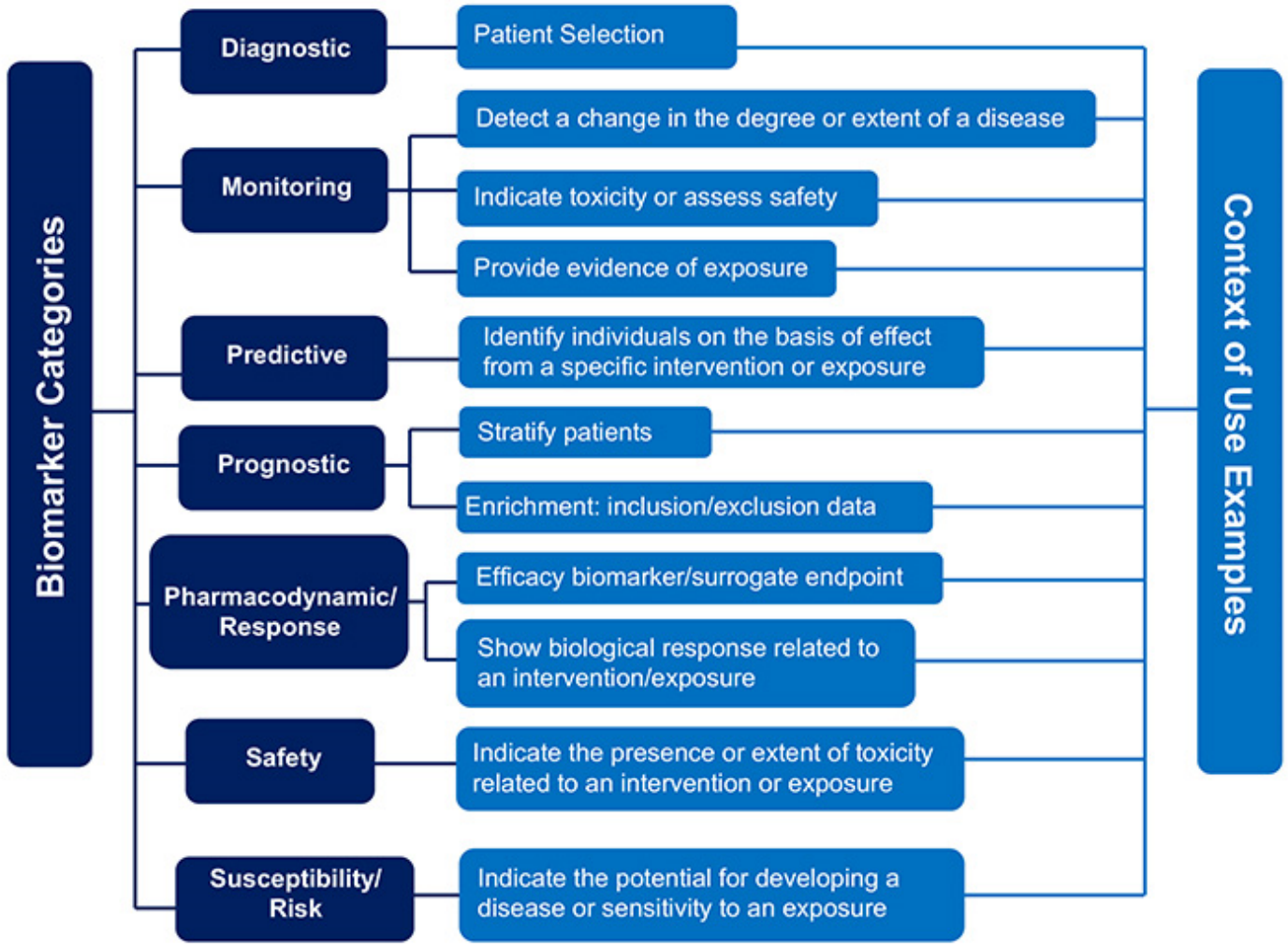
“Indicative of some phenomenon”

- Disease susceptibility/risk
- Diagnosis/subtype
- Prognosis/stratification
- Target engagement
- Mechanism of action
- Disease progression
- (Surrogate efficacy)

Subject characteristics

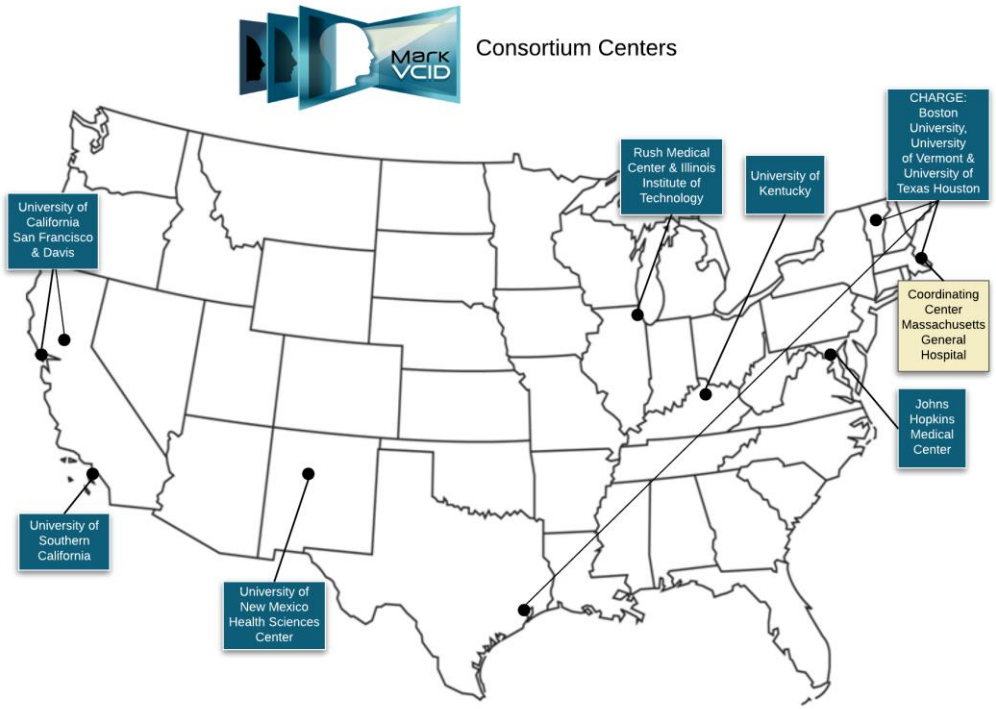
Response to intervention

FDA Biomarker Qualification Program
BEST Biomarker Category/Drug Development Uses



www.fda.gov/drugs/biomarker-qualification-program/context-use

MarkVCID Biomarkers Consortium



<u>MarkVCID</u> Consortium to identify and validate biomarkers for small vessel disease-related VCID "to the point of being fully ready for large scale multi-site clinical validation studies…and use in clinical trials."

<u>Coord Ctr</u>

S Greenberg

K Schwab K Helmer

<u>Site PIs</u>

J Schneider K Arfanakis

D Wang J Ringman

A Kashani

J Kramer, C DeCarli

H Lu, M Albert

G Rosenberg, A Caprihan

S Seshadri, M Fornage, R Tracy

D Wilcock, G Jicha

<u>NINDS</u>

Rod Corriveau

<u>External Advisory Committee</u>

R Gottesman, R Petersen

T Montine, GJ Biessels,

B Dunn

MarkVCID Biomarkers Consortium
Timeline

- Years 1-2 (UH2) Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

  -Clinical/cognitive data collection protocol

  -MRI and OCTA acquisition protocol

  -Fluid collection and handling best practices protocol

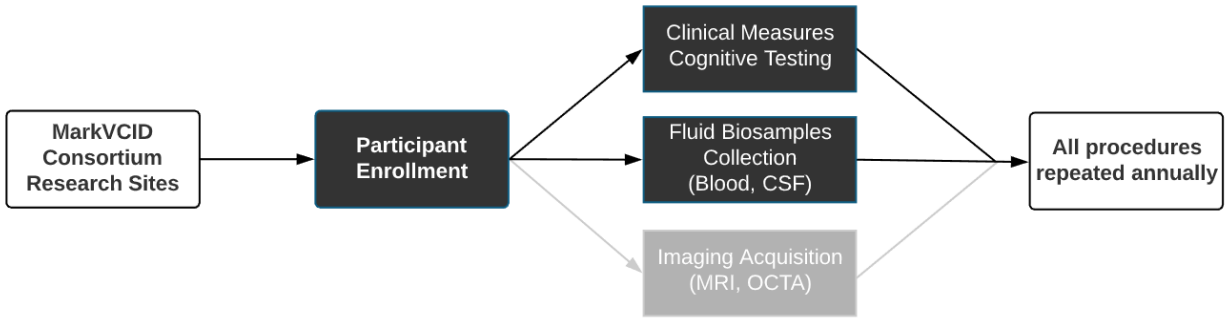
  -Broad IRB/consent language allowing unrestricted sharing and repurposing

Wilcock, Jicha, Blacker, Kivisakk, Greenberg et al *Alzheimers Dement* 2020; in press
Lu, Kashani, Arfanakis, Helmer, Greenberg et al *Alzheimers Dement* 2020; in press

MarkVCID Biomarkers Consortium Timeline

- Years 1-2 (UH2) Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

- Years 3-5 (UH3) Validate most promising biomarkers across consortium sites



MarkVCID Biomarkers Consortium Candidate Kits for Validation

MRI

WMH Volume
Lead site: UCSF/UCD/UCLA

WMH Growth/Regression
Lead site: Univ Kentucky

Peak Skeletonized Mean Diffusivity
Lead site: CHARGE

Free Water
Lead site: Univ New Mexico/UCSF

Arteriolosclerosis Score
Lead site: Rush

Cerebrovascular Reactivity to CO_2
Lead site: Johns Hopkins

Fluid

Plasma Endothelial Growth Factors
(VEGF-D, PlGF, bFGF)
Lead site: UCSF/UCD/UCLA

Exosome Endothelial Inflammatory Factors
(Complement Bb, C3b)
Lead site: UCSF/UCLA/UCLA

Plasma Neurofilament Light Chain
Lead site: CHARGE

CSF Placental Growth Factor
Lead site: Univ Kentucky

OCTA

Retinal Vessel Skeleton Density
Lead site: USC

MarkVCID Biomarkers Consortium Timeline

- Years 1-2 (UH2) Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

- Years 3-5 (UH3) Validate most promising biomarkers across consortium sites

  Instrumental validity

  Biological validity

MarkVCID Biomarkers Consortium
Timeline

- Years 1-2 (UH2) Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

- Years 3-5 (UH3) Validate most promising biomarkers across consortium sites

  Instrumental validity: Can the biomarker be accurately measured?

MarkVCID Biomarkers Kits
Instrumental Validation

Fluid-based kits

1. Intra- & inter-plate repeatability
2. Inter-site reproducibility

   40 plasma, 40 PPP, or 20 CSF samples (stratified by SVD severity)
3. Test-retest reproducibility

   Repeat blood samples from 10 participants/site (half non-controls) at 3 time points

Imaging-based kits

1. Inter-rater reliability

   30 MRI/OCTA scans (stratified by SVD severity)
2. Test-retest repeatability

   Repeat MRI/OCTA on 6 individuals/site at 2 time points
3. Inter-site reproducibility

   20 individuals (10 with SVD) traveling to 4 MRI scanner types in Boston & Baltimore

MarkVCID Biomarkers Consortium Timeline

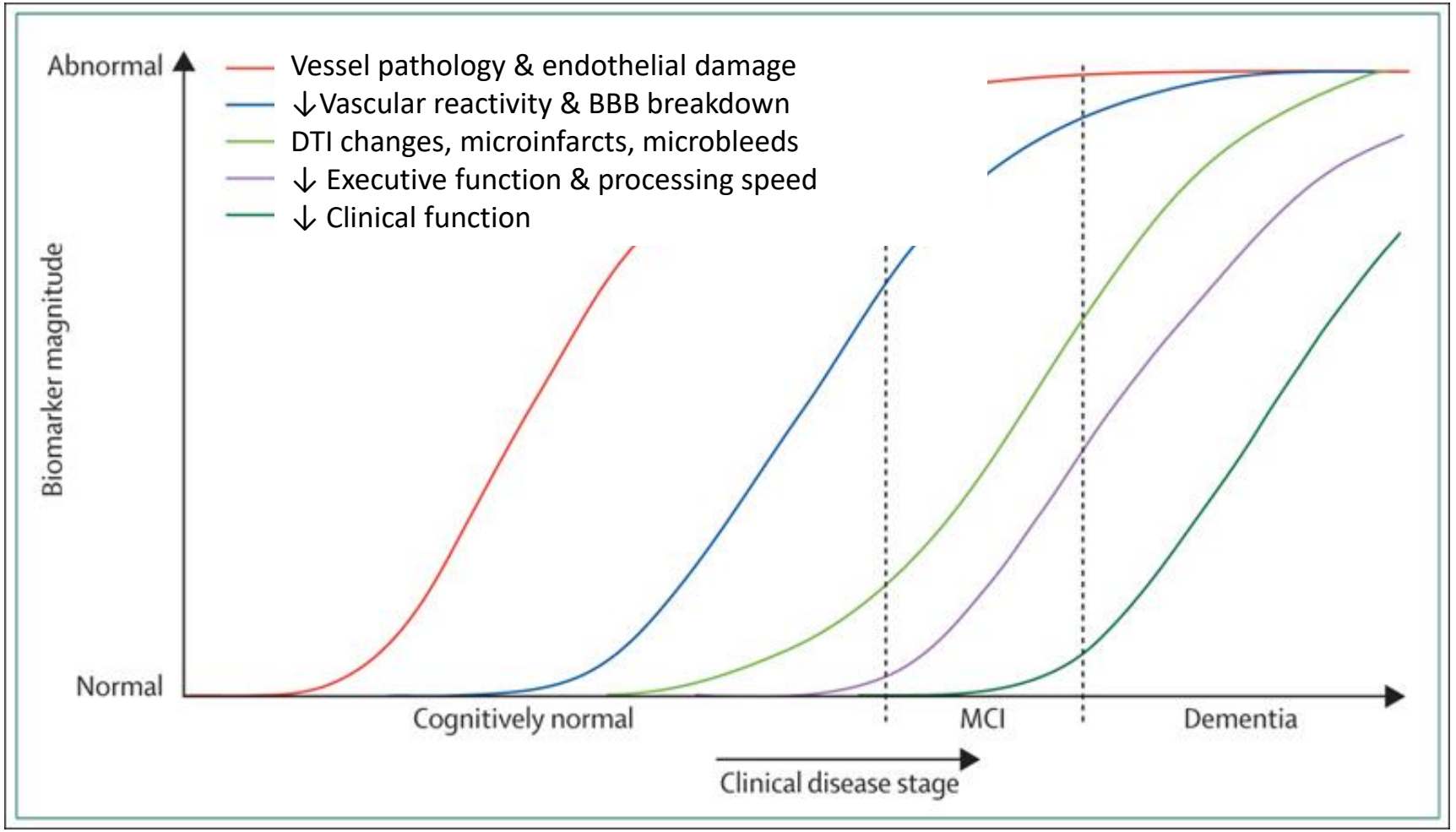
- Years 1-2 (UH2) Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

- Years 3-5 (UH3) Validate most promising biomarkers across consortium sites

  Instrumental validity

  Biological validity: Does the biomarker measure an important aspect of small vessel disease (generally operationalized as cognitive performance)?

MarkVCID Biomarkers Kits
Considerations for biological validation



Jack et al *Lancet Neurol* 2010;9:119

MarkVCID Biomarkers Kits
Potential applications to clinical trial

Subject selection/ stratification	Target engagement/ mechanism	Disease progression/ treatment effect
WMH	Free Water	WMH growth/regression
PSMD	CVR	PSMD
Arteriolosclerosis score		Free Water
Free Water		CVR
CVR		
Endothelial signaling	Endothelial signaling	NfL
Endothelial inflammation	Endothelial inflammation	
CSF PlGF	CSF PlGF	
OCTA VSD		OCTA VSD

MarkVCID Biomarkers Consortium Timeline

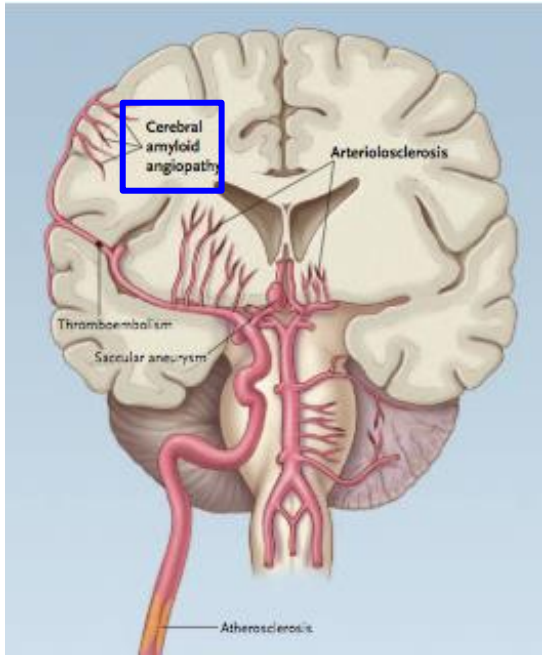
- Years 1-2 (UH2) Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures
- Years 3-5 (UH3) Validate most promising biomarkers across consortium sites
- Years 6-10 "This program is intended to fully prepare small vessel VCID biomarkers for integration into and widespread use in clinical trials (all phases) including in large-scale late phase clinical trials in general and diverse populations in the United States"

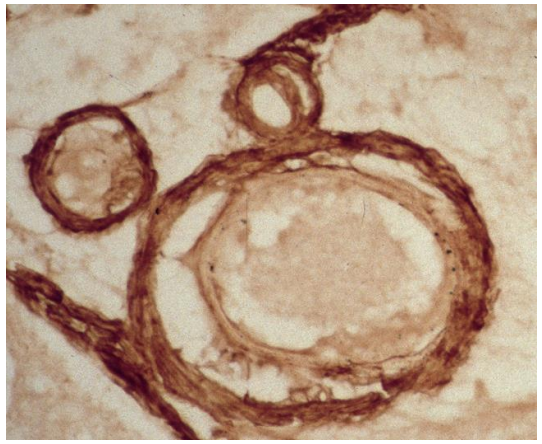
Funding Opportunity Title	Small Vessel VCID Biomarker Validation Consortium Sites (U01) (Clinical Trials Not Allowed)

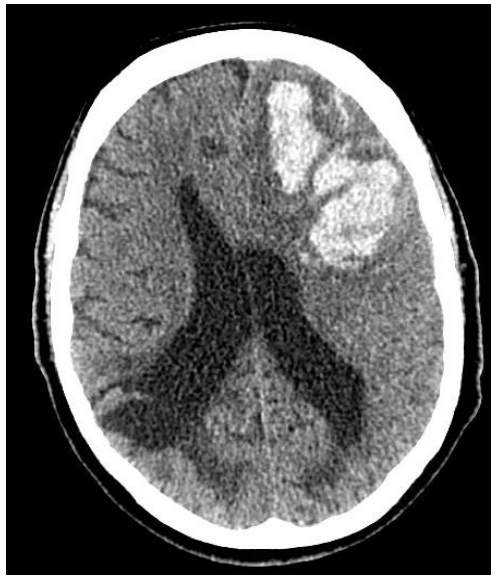
Taking the Shortcut
Biomarkers for vascular cognitive impairment

1. Validating SVD biomarkers: MarkVCID
2. Examples of biomarker applications: CAA

Cerebral amyloid angiopathy (CAA)



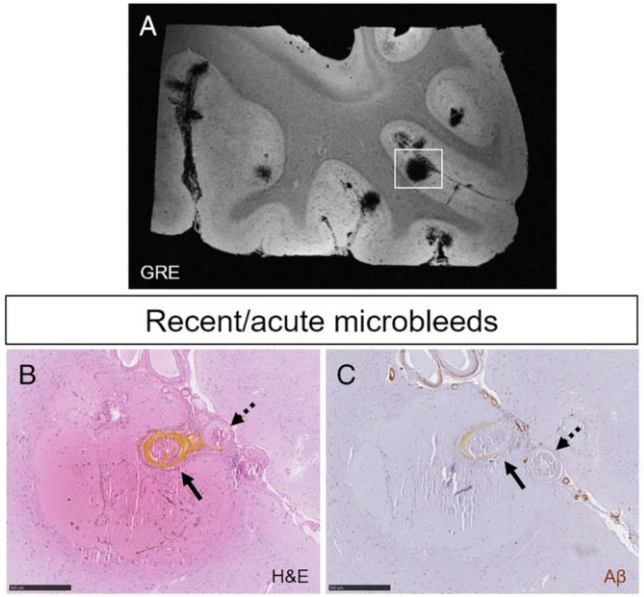




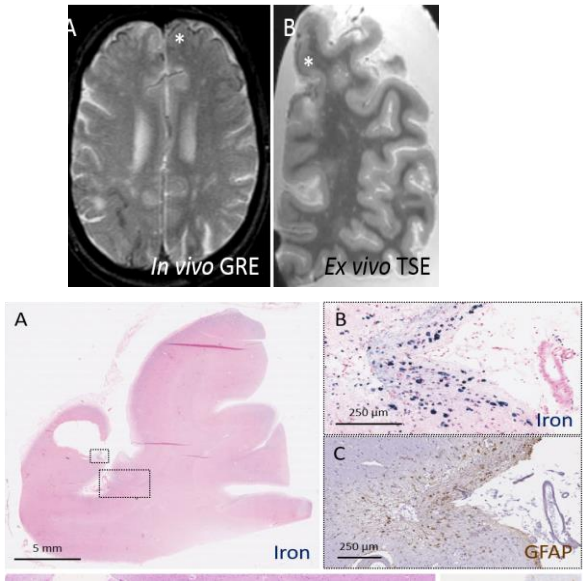
Imaging biomarkers for CAA

Diagnosis

- Cerebral microbleeds
- Cortical superficial siderosis



van Veluw *Ann Neurol* 2019;86:279



Charidimou, van Veluw *Brain* 2020;143:3343

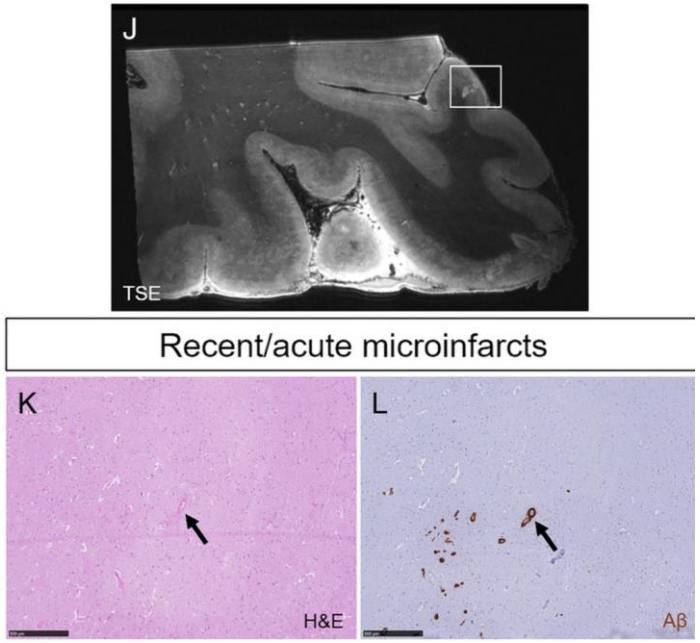
Imaging biomarkers for CAA

Diagnosis

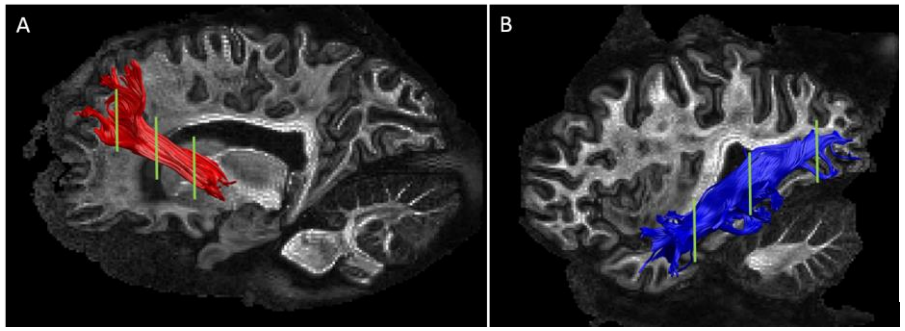
- Cerebral microbleeds
- Cortical superficial siderosis

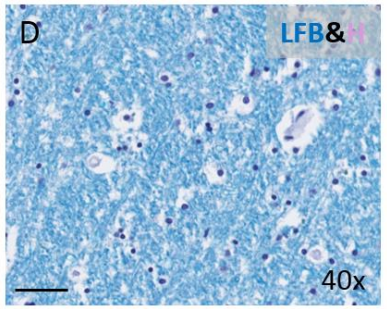
Markers of clinical brain injury

- Microinfarcts
- Altered structural connectivity



van Veluw *Ann Neurol* 2019;86:279





van Veluw, Reijmer *Neurology* 2019;92:e933

Imaging biomarkers for CAA

Diagnosis

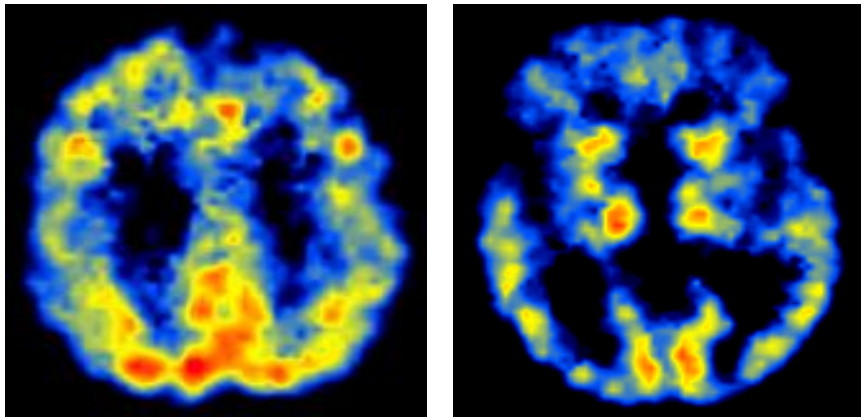
- Cerebral microbleeds
- Cortical superficial siderosis

Markers of clinical brain injury

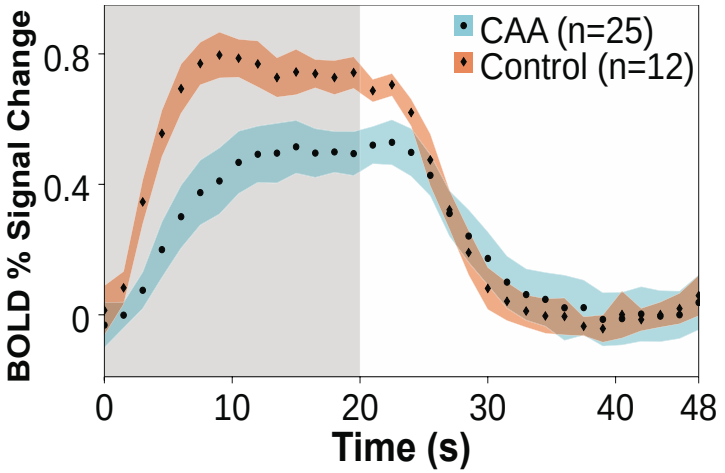
- Microinfarcts
- Altered structural connectivity

Markers of pathophysiologic pathways

- Amyloid deposition
- Vascular reactivity



Johnson *Ann Neurol* 2007;62:229



Dumas *Ann Neurol* 2012;72:76

Taking the Shortcut
Biomarkers for cerebral small vessel disease

- Wide range of strong candidate VCID biomarkers addressing different aspects of VCID presence, pathogenesis and progression

- …but lots of important caveats re instrumental properties, specificity, disease stage, pathophysiologic basis, pathogenic vs bystander role

- A buffet of validated biomarkers will allow marker selection tailored to goals and stage of future trials

MarkVCID Biomarkers Consortium

Open for business!

markvcid.org sgreenberg@partners.org

MarkVCID Biomarkers Consortium
Harmonized MRI Protocol

Common core protocol (<45 mins)

- 3D Multi-echo MPRAGE
- 3D FLAIR
- DTI
- 3D GRE
- T2-w FSE

Optional

- Cerebrovascular reactivity
- 3D pCASL
- Resting-state fMRI

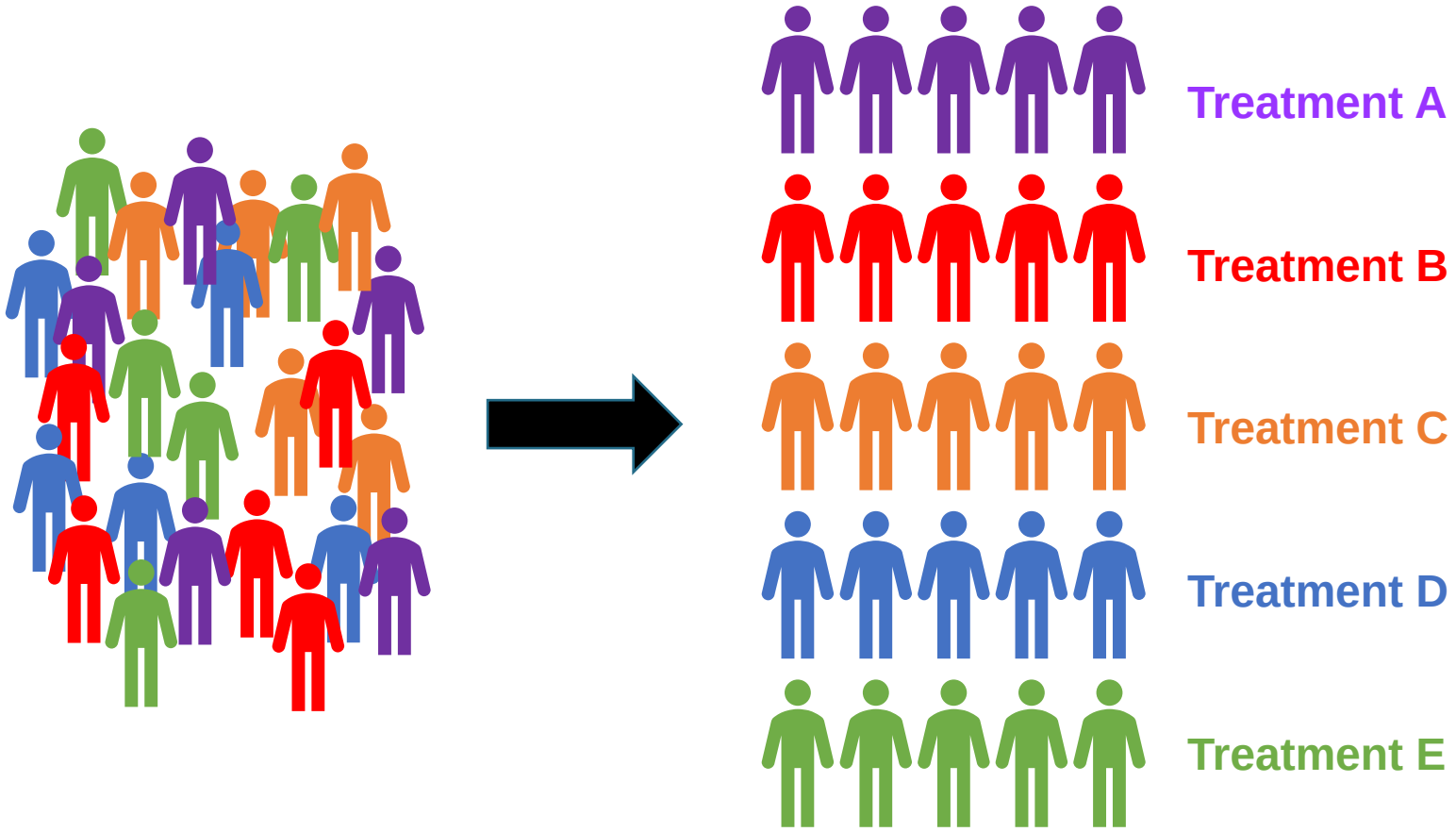
Accelerating Therapy Development for Alzheimer's and Related Dementias
-Enabling Infrastructure and Initiatives-

Laurie Ryan, PhD
Chief, Clinical Interventions and Diagnostics Branch,
Program Director, Pharmacological Interventions

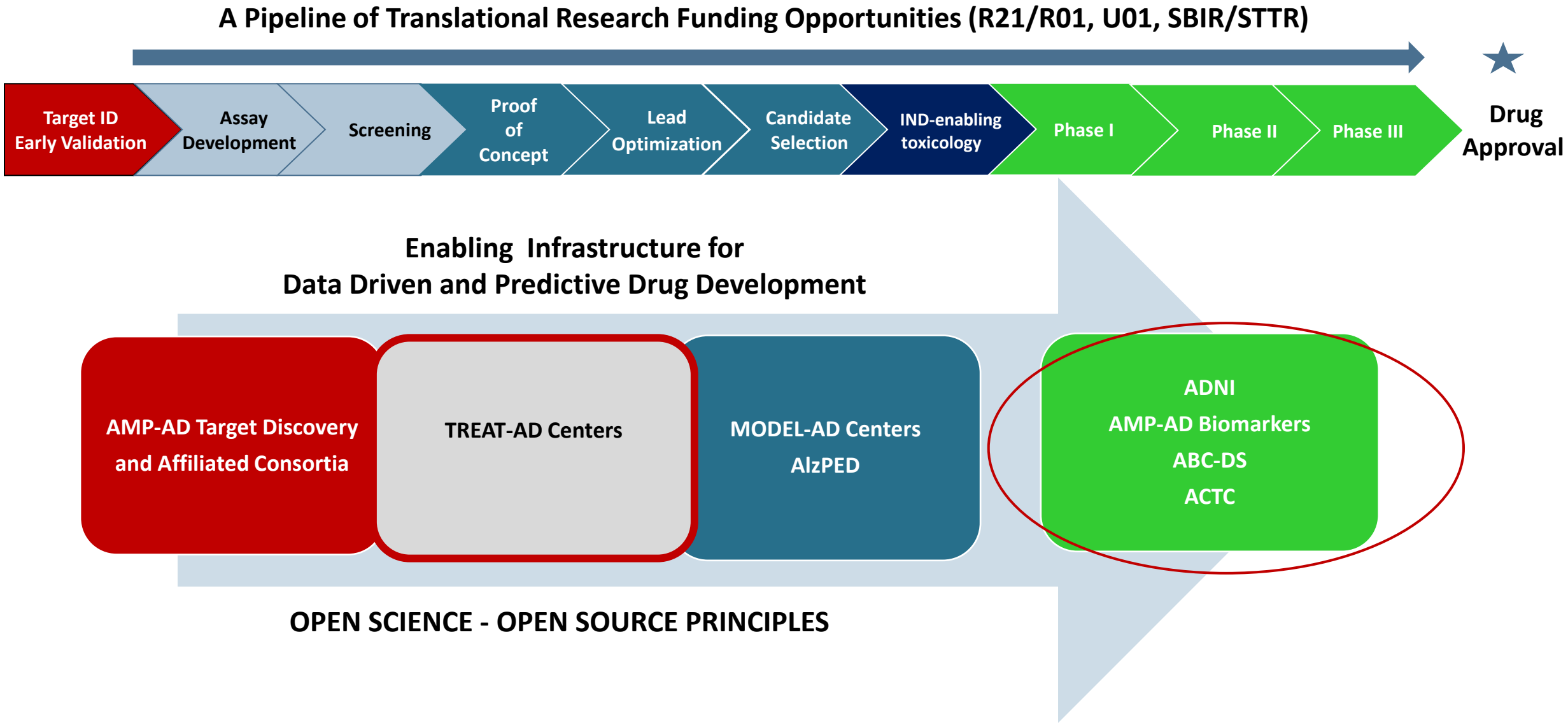
13th Annual FDA/ACT-AD Allies Meeting

Precision Medicine Approach

Right Pathway/Target, Therapeutic Agent, and Dose
for the Right Patient at the Appropriate Stage of Disease



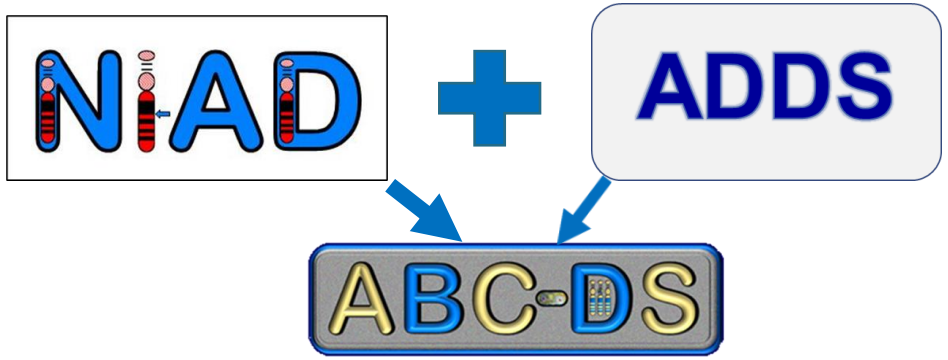
NIA AD Translational Research Program: Diversifying the Therapeutic Pipeline



Alzheimer's Biomarkers Consortium — Down Syndrome (ABC-DS)

Exploring the Connection Between Down Syndrome and Alzheimer's Disease

- Initiated in 2015 by the National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) with the funding of two groups of research collaborators:
  - Neurodegeneration in Aging Down Syndrome (NiAD, PIs: Ben Handen, Brad Christian, Bill Klunk U01AG051406)
  - Alzheimer's Disease in Down Syndrome (ADDS, PIs: Nicol Schupf, Ira Lott, Wayne Silverman, U01AG051412)



Down syndrome (DS) provides unique platform for understanding the temporal and age-dependent development of AD

Goals:

- Develop valid assessment procedures for tracking clinical progression in adults with DS
- Determine blood- and CSF-based biomarker profiles associated with clinical profiles
- Identify neuroimaging profiles (MRI & PET) associated with AD progression
- Identify genetic signatures influencing AD risk
- Compare findings with other populations having high and low risk for AD
- Compare findings with studies of sporadic AD to determine common and distinct profiles that can aid in identifying pathways and mechanisms determining risk
- Make data and bio-samples available to the research community
- Employ findings as a foundation to design and implement clinical trials focused on both treatment and prevention

- Next iteration of ABC-DS was funded by the NIA, NICHD and the Trans-NIH INCLUDE Project (U19AG068054, PIs: Ben Handen, Brad Christian, Elizabeth Head, Mark Mapstone) in September 2020

- Follow the cohort of people with Down syndrome to conduct three projects:
  - 1. Investigating how Alzheimer's disease in Down syndrome parallels and differs from sporadic Alzheimer's within an amyloid, tau, neurodegeneration framework and to identify modifiers of risk of conversion/progression
  - 2. Identifying genetic modifiers of the development of AD in DS
  - 3. Translating outcomes to a precision medicine framework and expedite clinical trials

- Includes an emphasis on the increasing the diversity of individuals in the cohort of adults with DS
  - The Alzheimer's Disease/Down Syndrome Outreach, Recruitment, and Engagement (ADDORE) Core will rapidly disseminate information to Down syndrome communities and engage underrepresented ethnic groups

Available ABC-DS Data and Biosamples

Data are managed by the University of Southern California Laboratory of Neuro Imaging (LONI)

Biospecimen samples are managed by the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD)

Requesting Data

1. Complete and submit the data/sample request form (ABC-DS Data or Biospecimen Request Form)
2. Review and sign the ABC-DS Data Use Agreement

Any questions about ABC-DS data and/or biospecimens should be directed to: Joni Vander Bilt (Email Joni Vander Bilt)

Publication and Ancillary Studies Committee Co-Chairs

Brad Christian (Email Brad Christian)

Mark Mapstone (Email Mark Mapstone)

Sid O'Bryant (Email Sid O'Bryant)

Biospecimen

- Plasma in 0.25 mL (250 uL) aliquots
- Serum in 0.25 mL (250 uL) aliquots
- Buffy coat in 1 mL aliquots
- CSF in 15-20 mL aliquots

Clinical data

- Demographic
- Medical and psychiatric history
- Physical and neurological exam results
- Caregiver assessment tools on adaptive functioning (Vineland 3), AD symptoms (DLD and NTG-EDSD), and psychiatric symptoms (Reiss)

Cognitive data

- Neuropsychological battery results (DSMSE, Block Design, Tinetti Gait, Modified Cats & Dogs Task, Cued Recall, Purdue Pegboard, Rivermead)
- Consensus diagnosis

Neuroimaging data

The neuroimaging data are selected to mirror the ADNI protocols

- PET – amyloid, tau, and FDG
- MRI – T1-weighted structural, T2 FSE, T2-FLAIR, T2*, ASL, DTI and rs-fMRI.

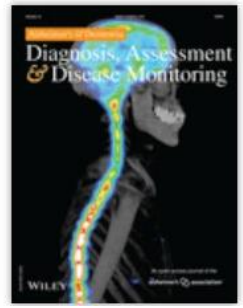
Genetic data

- APOE genotype
- Karyotyping
- GWAS (~760K SNPs)

Sibling controls

- Data on over 40 sibling controls of participants with Down syndrome
- Primarily biospecimens and neuroimaging data

https://www.nia.nih.gov/research/abc-ds#data



Volume 12, Issue 1

2020

Open Access

Down syndrome: Distribution of brain amyloid in mild cognitive impairment

David B. Keator, Michael J. Phelan, Lisa Taylor, Eric Doran, Sharon Krinsky-McHale, Julie Price, Erin E. Ballard, William C. Kreisl, Christy Hom, Dana Nguyen, Margaret Pulsifer, Florence Lai, Diana H. Rosas, Adam M. Brickman, Nicole Schupf, Michael A. Yassa, Wayne Silverman, Ira T. Lott

e12013 | First Published: 17 April 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Amyloid accumulation in Down syndrome measured with amyloid load

Matthew D. Zammit, Charles M. Laymon, Tobey J. Betthauser, Karly A. Cody, Dana L. Tudorascu, Davneet S. Minhas, Marwan N. Sabbagh, Sterling C. Johnson, Shahid H. Zaman, Chester A. Mathis, William E. Klunk, Benjamin L. Handen, Ann D. Cohen, Bradley T. Christian

e12020 | First Published: 16 April 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Metabolic correlates of prevalent mild cognitive impairment and Alzheimer's disease in adults with Down syndrome

Mark Mapstone, Thomas J Gross, Fabio Macciardi, Amrita K Cheema, Melissa Petersen, Elizabeth Head, Benjamin L Handen, William E Klunk, Bradley T Christian, Wayne Silverman, Ira T Lott, Nicole Schupf, for the Alzheimer's Biomarkers Consortium–Down Syndrome (ABC-DS) Investigators

e12028 | First Published: 05 April 2020

Abstract | Full text | PDF | References | Request permissions

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Proteomic profiles of incident mild cognitive impairment and Alzheimer's disease among adults with Down syndrome

Sid E. O'Bryant, Fan Zhang, Wayne Silverman, Joseph H. Lee, Sharon J. Krinsky-McHale, Deborah Pang, James Hall, Nicole Schupf

e12033 | First Published: 21 May 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Proteomic profiles of prevalent mild cognitive impairment and Alzheimer's disease among adults with Down syndrome

Melissa Petersen, Fan Zhang, Sharon J. Krinsky-McHale, Wayne Silverman, Joseph H. Lee, Deborah Pang, James Hall, Nicole Schupf, Sid E. O'Bryant

e12023 | First Published: 17 April 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Proteomic profiles for Alzheimer's disease and mild cognitive impairment among adults with Down syndrome spanning serum and plasma: An Alzheimer's Biomarker Consortium–Down Syndrome (ABC–DS) study

Melissa E. Petersen, Fan Zhang, Nicole Schupf, Sharon J. Krinsky-McHale, James Hall, Mark Mapstone, Amrita Cheema, Wayne Silverman, Ira Lott, Michael S. Rafii, Benjamin Handen, William Klunk, Elizabeth Head, Brad Christian, Tatiana Foroud, Florence Lai, H. Diana Rosas, Shahid Zaman, Beau M. Ances, Mei-Cheng Wang, Benjamin Tycko, Joseph H. Lee, Sid O'Bryant, the Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS)

e12039 | First Published: 30 June 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Alzheimer-related altered white matter microstructural integrity in Down syndrome: A model for sporadic AD?

H. Diana Rosas, Eugene Hsu, Nathaniel D. Mercaldo, Florence Lai, Margaret Pulsifer, David Keator, Adam M. Brickman, Julie Price, Michael Yassa, Christy Hom, Sharon J. Krinsky-McHale, Wayne Silverman, Ira Lott, Nicole Schupf

e12040 | First Published: 07 November 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Promising outcome measures of early Alzheimer's dementia in adults with Down syndrome

Sharon J Krinsky-McHale, Warren B. Zigman, Joseph H. Lee, Nicole Schupf, Deborah Pang, Tracy Listwan, Cynthia Kovacs, Wayne Silverman

e12044 | First Published: 05 July 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Diagnosis of prodromal and Alzheimer's disease dementia in adults with Down syndrome using neuropsychological tests

Bessy Benejam, Laura Videla, Eduard Vilaplana, Isabel Barroeta, Maria Carmona-Iragui, Miren Altuna, Silvia Valldeneu, Susana Fernandez, Sandra Giménez, Florencia Iulita, Diana Garzón, Alexandre Bejanin, David Bartrés-Faz, Sebastià Videla, Daniel Alcolea, Rafael Blesa, Alberto Lleó, Juan Fortea

e12047 | First Published: 28 June 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

The AT(N) framework for Alzheimer's disease in adults with Down syndrome

Michael S. Rafii, Beau M. Ances, Nicole Schupf, Sharon J. Krinsky-McHale, Mark Mapstone, Wayne Silverman, Ira Lott, William Klunk, Elizabeth Head, Brad Christian, Florence Lai, H. Diana Rosas, Shahid Zaman, Melissa E. Petersen, Andre Strydom, Juan Fortea, Benjamin Handen, Sid O'Bryant

e12062 | First Published: 27 October 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Sex differences in risk of Alzheimer's disease in adults with Down syndrome

Florence Lai, Pooja G. Mhatre, Yuchen Yang, Mei-Cheng Wang, Nicole Schupf, H. Diana Rosas

e12084 | First Published: 13 September 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Feasibility of dual-task gait to estimate Alzheimer's related cognitive decline in Down syndrome

Kathryn L. Van Pelt, Lisa Koehl, Allison Caban-Holt, Amelia Anderson-Mooney, Elizabeth Head, Frederick A. Schmitt

e12092 | First Published: 25 August 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Cognitive indicators of transition to preclinical and prodromal stages of Alzheimer's disease in Down syndrome

Sigan L. Hartley, Benjamin L. Handen, Darlynne Devenny, Dana Tudorascu, Brianna Piro-Gambetti, Matthew D. Zammit, Charles M. Laymon, William E. Klunk, Shahid Zaman, Annie Cohen, Bradley T. Christian

e12096 | First Published: 13 September 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Distribution of microglial phenotypes as a function of age and Alzheimer's disease neuropathology in the brains of people with Down syndrome

Alessandra C. Martini, Alex M. Helman, Katie L. McCarty, Ira T. Lott, Eric Doran, Frederick A. Schmitt, Elizabeth Head

e12113 | First Published: 14 October 2020

Abstract | Full text | PDF | References | Request permissions

Open Access

Brain amyloid and the transition to dementia in Down syndrome

David B. Keator, Eric Doran, Lisa Taylor, Michael J. Phelan, Christy Hom, Katherine Tseung, Theo G. M. van Erp, Steven G. Potkin, Adam M. Brickman, Diana H. Rosas, Michael A. Yassa, Wayne Silverman, Ira T. Lott

e12126 | First Published: 11 November 2020

Abstract | Full text | PDF | References | Request permissions

U01 AG057195(PIs: Liana Apostolova, Maria Carrillo, Brad Dickerson, Gil Rabinovici)

LEADS
Longitudinal Early-Onset Alzheimer's Disease Study

Observational study

Enroll 500 amyloid positive APP/PSEN1/PSEN2 mutation negative EOAD and 100 age-matched controls ages 40 to 64 at ~15 sites across US

Collect longitudinal detailed clinical, cognitive, imaging, biomarker and genetics

Imaging and biomarker collection, data sharing aligned with ADNI, Biosamples at NCRAD

Available Data

LEADS uses a standard set of protocols and procedures to collect several types of data. Data is shared for free with authorized investigators through the LONI Image and Data Archive (IDA).

Clinical: Demographic, vitals, general medical and neurologic examinations, past medical history, medications, clinical diagnosis and diagnostic subtype

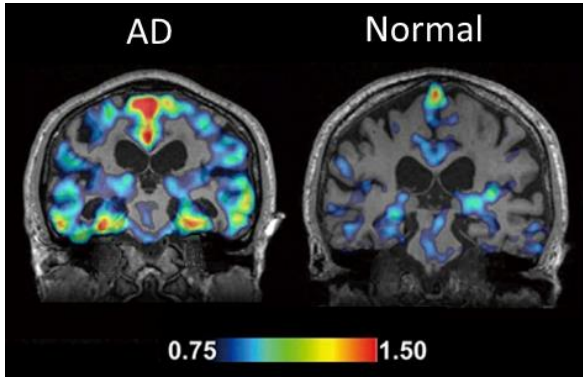
Cognitive/behavioral: NACC UDS cognitive and FTD batteries, AVLT, Digit symbol, ADAS-Cog, TabCat, FAQ, GDS, NPI-Q, Amsterdam IADL

Imaging: Magnetic resonance, amyloid (florbetaben) and tau (flortaucipir) PET images, Imaging summary measures

Biosamples: peripheral blood (plasma, serum, PBMC) and CSF

Genetic: DNA and RNA

AMP-AD (Biomarkers): Supplement NIA-supported Phase II/III secondary prevention trials testing several anti-amyloid therapies with tau PET imaging (AV1451)



Distribution of tau across brain with AD

Data sharing under AMP-AD includes making the screening data and biosamples available after enrollment completion and making post-randomization data and biosamples available as soon as possible after completion without compromising trial integrity.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease Trial (A4 Trial) has achieved the first milestone:

- Making screening data and biosamples available (via the Laboratory of Neuroimaging, LONI) on 6,763 screened participants
- This is the first registration trial to ever do so and the first paper using the screening data from A4 was published in 2020
- Enrollment complete; open label extension ongoing
- First screening data paper published in *JAMA Neurology*

The A4 Study
NOW IS THE TIME

› JAMA Neurol. 2020 Jun 1;77(6):735-745. doi: 10.1001/jamaneurol.2020.0387.

Association of Factors With Elevated Amyloid Burden in Clinically Normal Older Individuals

Reisa A Sperling [1 2], Michael C Donohue [3], Rema Raman [3], Chung-Kai Sun [3], Roy Yaari [4], Karen Holdridge [4], Eric Siemers [4 5], Keith A Johnson [1 2], Paul S Aisen [3], A4 Study Team

Affiliations + expand

PMID: 32250387 PMCID: PMC7136861 (available on 2021-04-06)
DOI: 10.1001/jamaneurol.2020.0387

NINDS Dementia Research Initiatives: Different Forms and Cross-Cutting Themes

- **MarkVCID**, national VCID Biomarkers Consortium
- **Tau Center Without Walls** to study molecular mechanisms that lead to tau toxicity in FTD
- **FTD Sequencing Consortium** to discover FTD-causing gene mutations
- **Lewy Body Center Without Walls** to characterize α-synuclein and β-amyloid subtypes in LBD
- **LBD biomarker discovery research**
- **DetectCID** to develop paradigms to increase detection of cognitive impairment/dementia in primary care settings and in populations that experience health disparities
- **ALLFTD Natural History Study in FTLD**, together with the NIA
- **DISCOVERY** and **Diverse VCID** to determine types of stroke and white matter lesions and comorbidities that cause **VCID** including in populations that experience health disparities
- **PET Ligand Development Proteinopathy Structural Biology for ADRD Center Without Walls**
- Establish **CARD** with NIA, intramural Center for the Study of Alzheimer's & Related Dementias

Tau Center Without Walls

Mark VCID

detectCID

Lewy Body Dementias Biomarkers Research

Tauopathy and TDP-43 Proteinopathy Structural Biology Using Cryo-EM & Mass Spectrometry

Boston Children's Hospital
Until every child is well

Columbia University

Mayo Clinic

CTE/TBI Center Without Walls

Boston University

Penn
University of Pennsylvania

DIVERSE VCID

NINDS ADRD FY 2021 Funding Opportunities

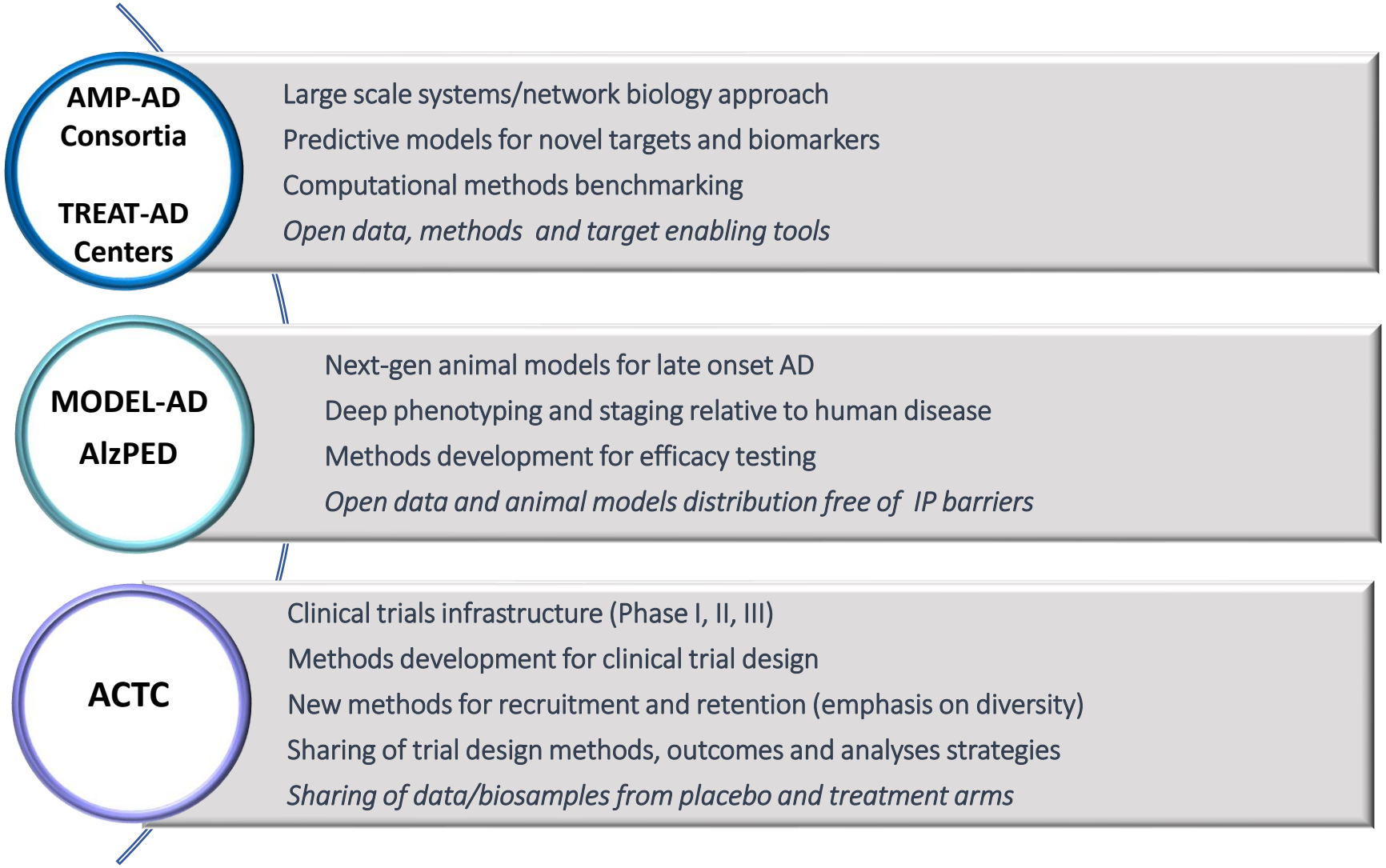
- **Center Without Walls (CWOW) for Molecular Mechanisms of Neurodegeneration in FTD** – to continue support for interdisciplinary team science on molecular mechanisms of neurodegeneration in FTD, with a focus tau, TDP-43 or FUS pathogenesis, and specific genetic causes and risks factors. **RFA-NS-21-003**
- **Mechanisms of Selective Vulnerability in LBD and FTD** – why certain brain regions are more vulnerable to abnormal protein accumulation and damage. **RFA-NS-21-007**

https://go.usa.gov/xwN8f

- **Mechanisms of Pathological Spread of Abnormal Proteins in LBD and FTD** –how abnormal proteins spread in the nervous system of LBD and FTD patients. **RFA-NS-21-006**
- **Connecting Pre-mortem Clinical Information with Post-Mortem Brain Analysis in LBD** – linking comprehensive pre-mortem clinical information with gold standard post-mortem diagnostic analysis in LBD patients. **RFA-NS-21-001**
- **Treatments for LBD-Exploratory Clinical Trial** – to encourage exploratory clinical trials (Phase I or II) testing either new or repurposed drugs or devices to treat patients with LBD. **RFA-NS-21-008**
- **Small Vessel VCID Biomarker Validation for Clinical Trials and Coordinating Center** – to continue support for a consortium (currently implemented as MarkVCID) to develop and validate high-quality small vessel VCID biomarkers ready for use in clinical trials, and for generating scientific breakthroughs in the understanding and treatment of VCID. **RFA-NS-21-004, RFA-NS-21-005**

ENABLING INFRASTRUCTURE PROGRAMS FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

OPEN SCIENCE/OPEN SOURCE
FROM TARGETS TO TRIALS



ACTC
ALZHEIMER'S
CLINICAL TRIALS CONSORTIUM

Submit a Proposal | About Us | Projects | Sites | News | Alzheimer's Information | Contact Us

Alzheimer's Clinical Trials Consortium

To provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer's disease and related disorders.

About Us

actcinfo.org

ACTC

- Initiated in December 2017
- PIs: Paul Aisen, Alzheimer's Therapeutic Research Institute (ATRI), San Diego; Reisa Sperling, Brigham and Women's Hospital and Massachusetts General Hospital, Boston; Ronald Petersen, Mayo Clinic, Rochester, Minnesota (U24AG057437)
- Next generation infrastructure - collaboration between NIA and ACTC investigators
- Includes multiple clinical trial sites with dedicated support
- A separate NIA Funding Opportunity Announcement (FOA) is soliciting applications for clinical trials to be managed and supported by the ACTC (PAR-20-309)

ACTC GOALS

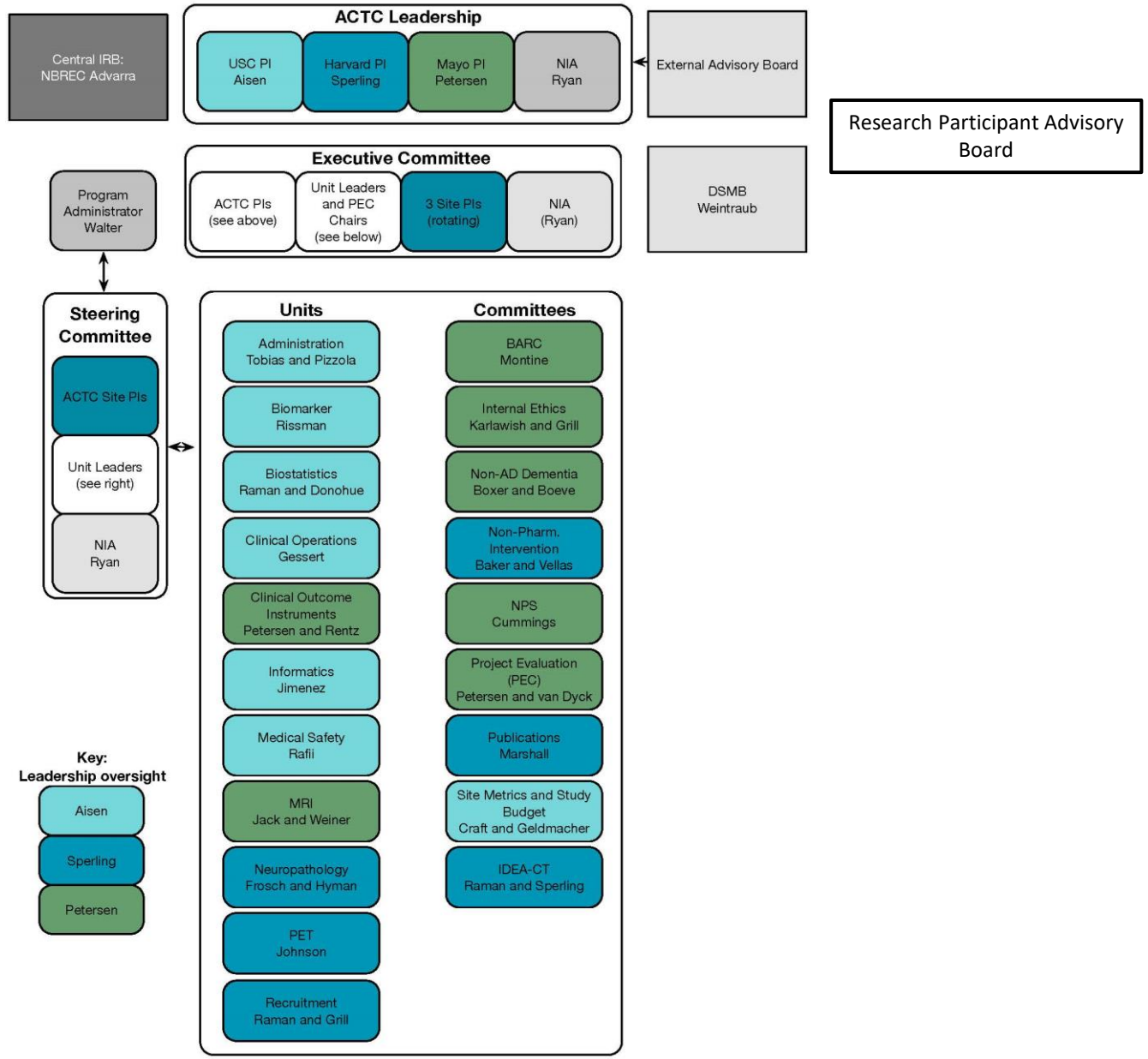
- Conduct clinical trials (phase 1b to 3) of promising pharmacological and non-pharmacological interventions for
  - cognitive and neuropsychiatric symptoms in individuals with AD and other age-related dementias
  - across the spectrum from pre-symptomatic to more severe stages of disease
- Provide a state-of-the-art clinical trial infrastructure to facilitate rapid development and implementation of protocols
- Provide leadership in innovative trial design methods, outcomes and analyses as well as recruitment strategies, particularly in diverse/underrepresented populations
- Enable broad sharing of procedures and methods, as well as trial data and biosamples

KEY ELEMENTS OF THE ACTC

- Novel approaches to recruitment and assessment, including innovations in technology:
  - The Minority Outreach and Recruitment Team is developing central and local partnerships with diverse communities to enhance representation of these underrepresented groups in AD/ADRD trials
- Streamlined implementation of trials from start-up to publication, e.g., use of master trial agreements, efficient contracting and centralized IRB
- Track site performance; maximize protocol adherence and data quality
- Centralized tissue banking/sharing for biosamples
- Centralized biostatistics, bioinformatics and data management support
- Meeting and communication coordination among clinical trial sites of ACTC
- Provide guidance to investigators developing interventions for AD/ADRD

THE ACTC INFRASTRUCTURE IS WELCOMING OF:

- Academic and industry applicants; Public-Private Partnerships
- Both pharmacological and non-pharmacological interventions
- Applications are encouraged that propose:
  - Testing candidate therapeutic compounds against novel therapeutic targets
  - Testing repurposed drugs and combination therapies from data driven approaches, including candidates coming from NIA's translational bioinformatics FOA (PAR-20-156)


Central IRB:
NBREC Advarra
ACTC Leadership
USC PI
Aisen
Harvard PI
Sperling
Mayo PI
Petersen
NIA
Ryan
External Advisory Board
Research Participant Advisory Board
Executive Committee
ACTC PIs
(see above)
Unit Leaders
and PEC
Chairs
(see below)
3 Site PIs
(rotating)
NIA
(Ryan)
DSMB
Weintraub
Program
Administrator
Walter
Steering
Committee
ACTC Site PIs
Unit Leaders
(see right)
NIA
Ryan
Units
Administration
Tobias and Pizzola
Biomarker
Rissman
Biostatistics
Raman and Donohue
Clinical Operations
Gessert
Clinical Outcome
Instruments
Petersen and Rentz
Informatics
Jimenez
Medical Safety
Rafii
MRI
Jack and Weiner
Neuropathology
Frosch and Hyman
PET
Johnson
Recruitment
Raman and Grill
Committees
BARC
Montine
Internal Ethics
Karlawish and Grill
Non-AD Dementia
Boxer and Boeve
Non-Pharm.
Intervention
Baker and Vellas
NPS
Cummings
Project Evaluation
(PEC)
Petersen and van Dyck
Publications
Marshall
Site Metrics and Study
Budget
Craft and Geldmacher
IDEA-CT
Raman and Sperling
Key:
Leadership oversight
Aisen
Sperling
Petersen

- Non-AD Dementia Committee (Chairs: Brad Boeve, Adam Boxer)
  - Advises on trial design for studies where the population is non-AD age-related dementia

- Neuropsychiatric Symptoms (NPS, Chair: Jeff Cummings)
  - Advises on trial design for studies of agents, devices, or non-pharmacologic interventions targeting NPS such as agitation, psychosis, depression, apathy, and sleep disorders

- Non-Pharmacological Intervention Committee (Chairs: Laura Baker, Bruno Vellas)
  - Provides expertise and guidance in the development and management of trials involving non-pharmacological approaches in clinical trials

- Inclusion, Diversity, and Education in Alzheimer's disease Clinical Trials (IDEA-CT) Committee (Chairs: Rema Raman, Reisa Sperling)
  - Developing goals, formulating strategic plan, and providing oversight for ACTC's core values of inclusion, diversity and training in ADRD clinical trials and the ADRD clinical research community at large
- Research Participant Advisory Board (Chair: Sarah Walter)
  - Provides guidance to the consortium to help ensure that the outcomes of ACTC work are meaningful to the public.
  - Focus on inclusion of individuals from underrepresented populations as well as from across the disease spectrum.

ACTC
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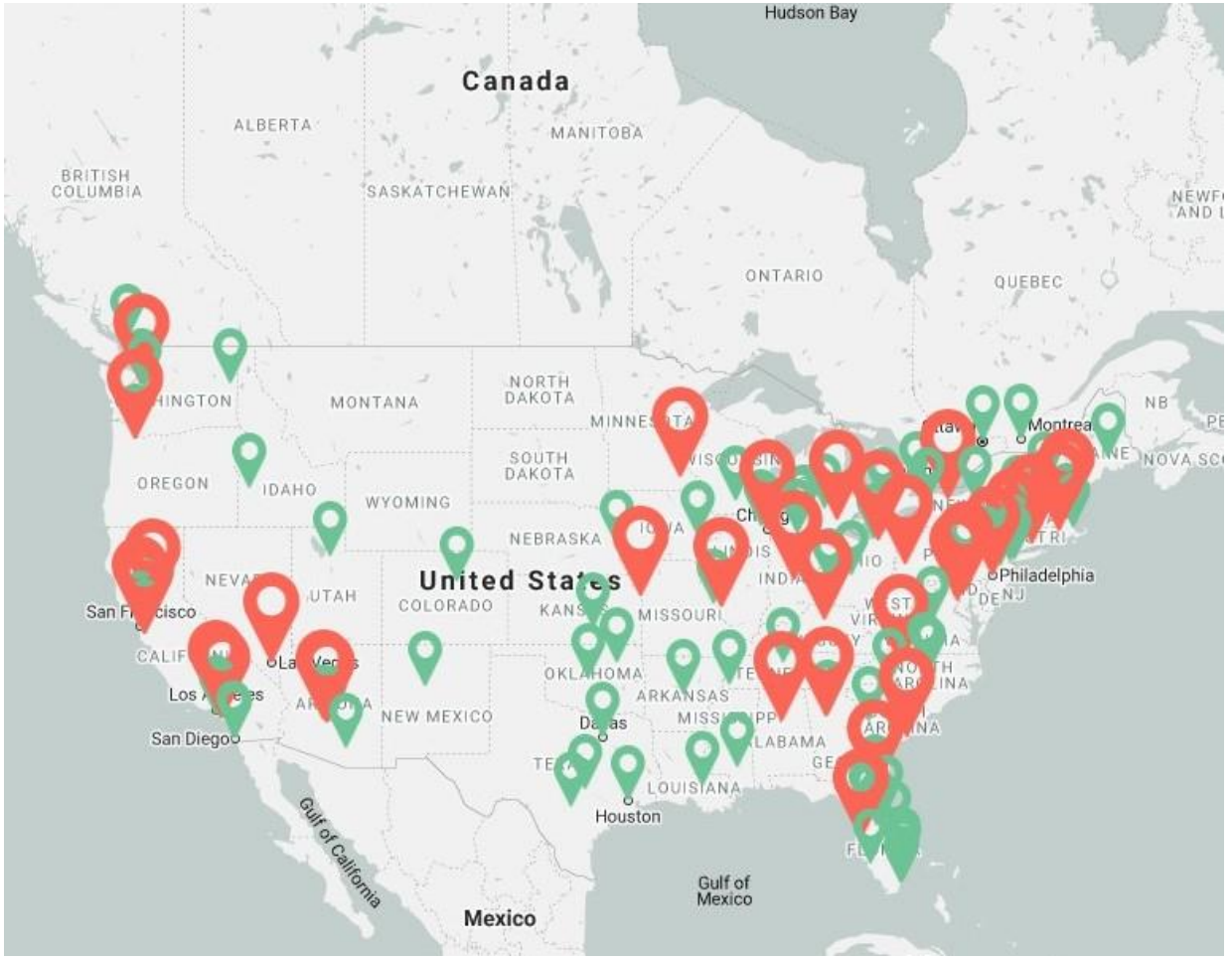
CLINICAL TRIALS CONSORTIUM

Sites

Member Site Participating Site



DATA, IMAGES AND BIOSPECIMEN SHARING POLICY

- Primary goal of this policy is to make available project research data, images and biospecimens from ACTC clinical trials to the scientific community in a timely manner, while safeguarding the safety and privacy of trial participants and protecting confidential and proprietary data.
- Follow the Collaboration for Alzheimer's Prevention (CAP) principles as well as NIA/NIH guidelines and policies

- Data, images and biospecimens will be shared at two time-points for each project:

1. Pre-randomization data, images and biospecimens will be shared within twelve (12) months of the final participant randomization.
2. Project data, images and biospecimens will be shared with the scientific community after the earlier of either regulatory approval of the tested treatment, at time of publication of top line results, or nine (9) months after the completion or early termination of the trial.

ACTC
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Alzheimer's Clinical Trials Consortium (ACTC)

Mission: To provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer's disease and related disorders.

Apply for an ACTC project

Eligibility: Anyone (academic or industry)

Studies: Phase 1b-III, non-pharmacological and novel approaches encouraged

Contact: Sarah Walter waltersa@usc.edu

- We work in collaboration with proposers to develop idea and submit grant to NIA
- Infrastructure includes expertise in study design and conduct, full clinical trial management capability at coordinating center and network of trial sites
- Learn more at: **www.actcinfo.org**

ACTC
ALZHEIMER'S
CLINICAL TRIALS CONSORTIUM

CURRENT ACTC TRIALS

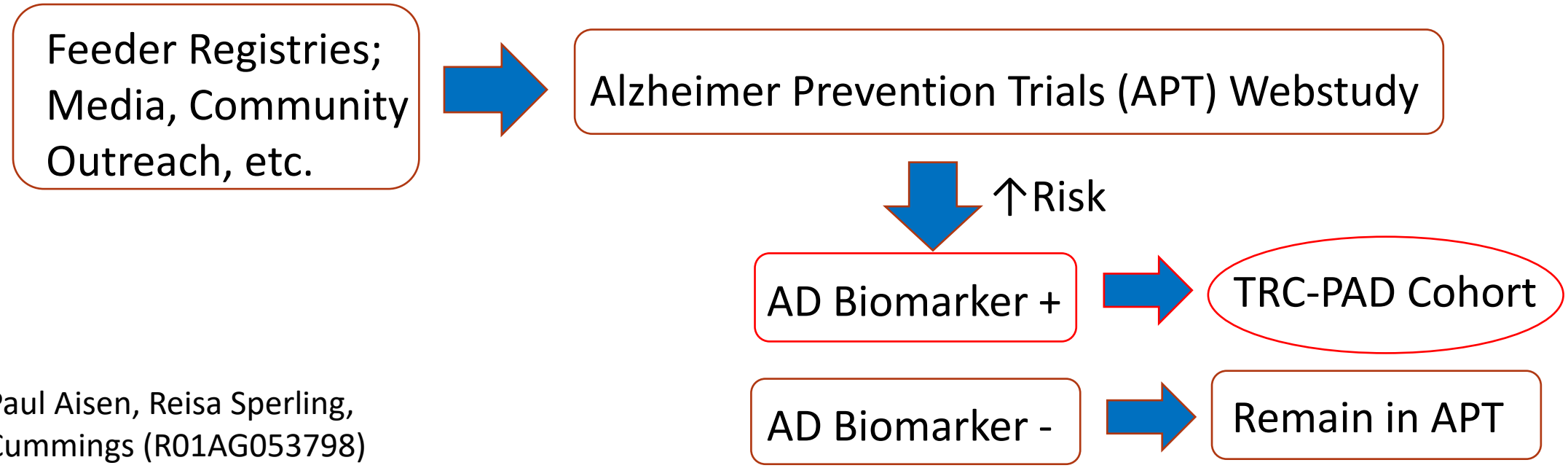
- Enrolling
  - AHEAD A3-45 (BAN2401)
    - A3: cognitively normal, below threshold amyloid PET, at risk
    - A45: clinically normal, elevated amyloid PET, high risk
- Enrollment Complete – Ongoing
  - A4 Open Label Extension
- Launching in 2021
  - CT1812
    - Phase 2, prodromal or mild AD
  - Life's End Benefits of Cannabidiol and Tetrahydrocannabinol (LiBBY)
    - Phase 2, sever dementia with agitation
    - oral combination of tetrahydrocannabinol (THC) and cannabidiol (CBD)

ACTC
ALZHEIMER'S
CLINICAL TRIALS CONSORTIUM

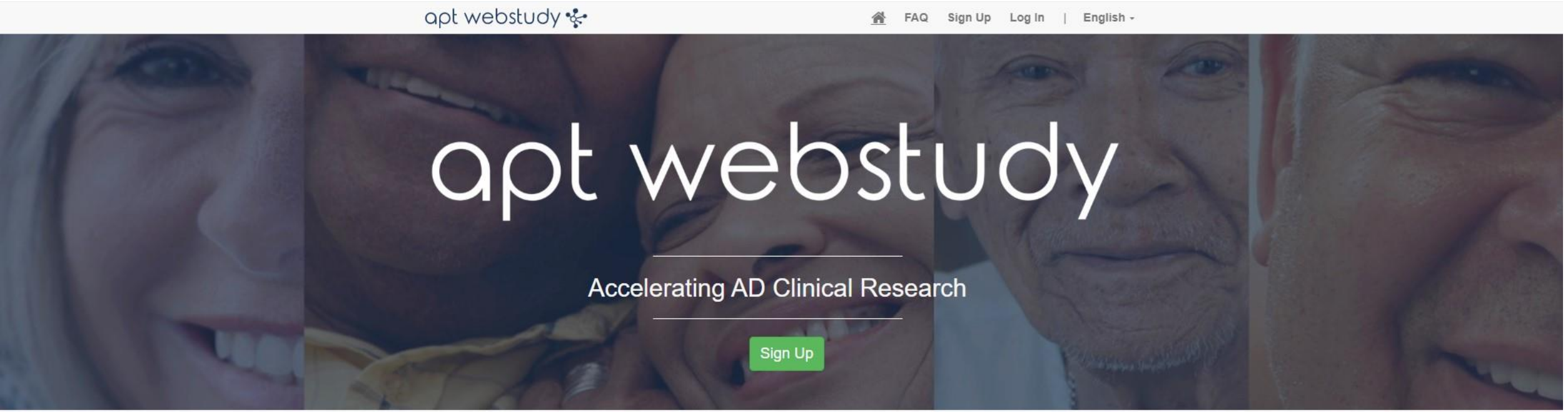
ACTC Affiliated Clinical Trial Enabling Projects

Trial Ready Cohort for the Prevention of Alzheimer's Dementia

- Establish a trial-ready, AD biomarker positive cohort, i.e., a pool of well-characterized participants, for trials at multiple sites across North America to facilitate recruitment
- Enrolling



PIs: Paul Aisen, Reisa Sperling, Jeff Cummings (R01AG053798)

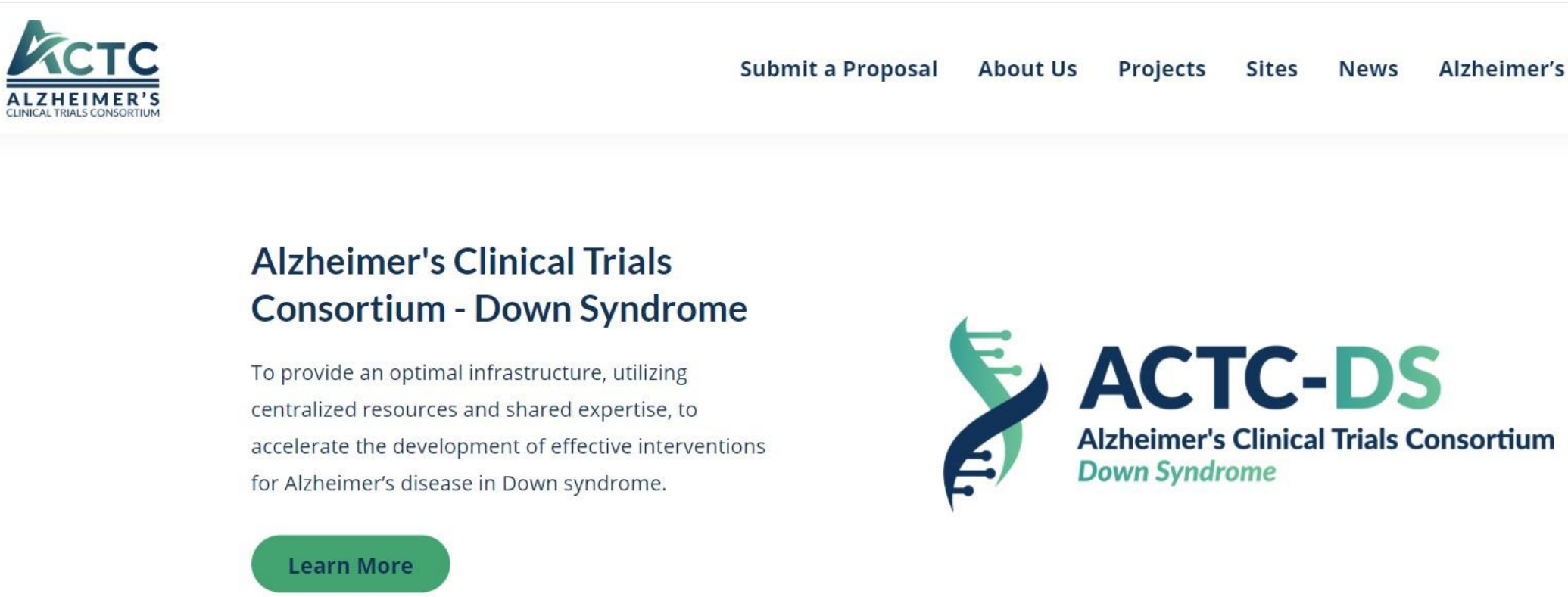


Alzheimer Prevention Trials Webstudy

If you are at least 50 years of age and interested in Alzheimer's research, please join!

www.aptwebstudy.org

Low barriers: 10-15 min per visit, flexible schedule
Engagement: feedback on progress, testing
Education: news and updates on trials



- ACTC-DS will leverage the experience and expertise of the ACTC, as well as the NIH-funded Alzheimer's Biomarker Consortium - Down Syndrome (ABC-DS) groups to build a trial-ready cohort of adults with DS and then design and conduct clinical trials in this cohort.

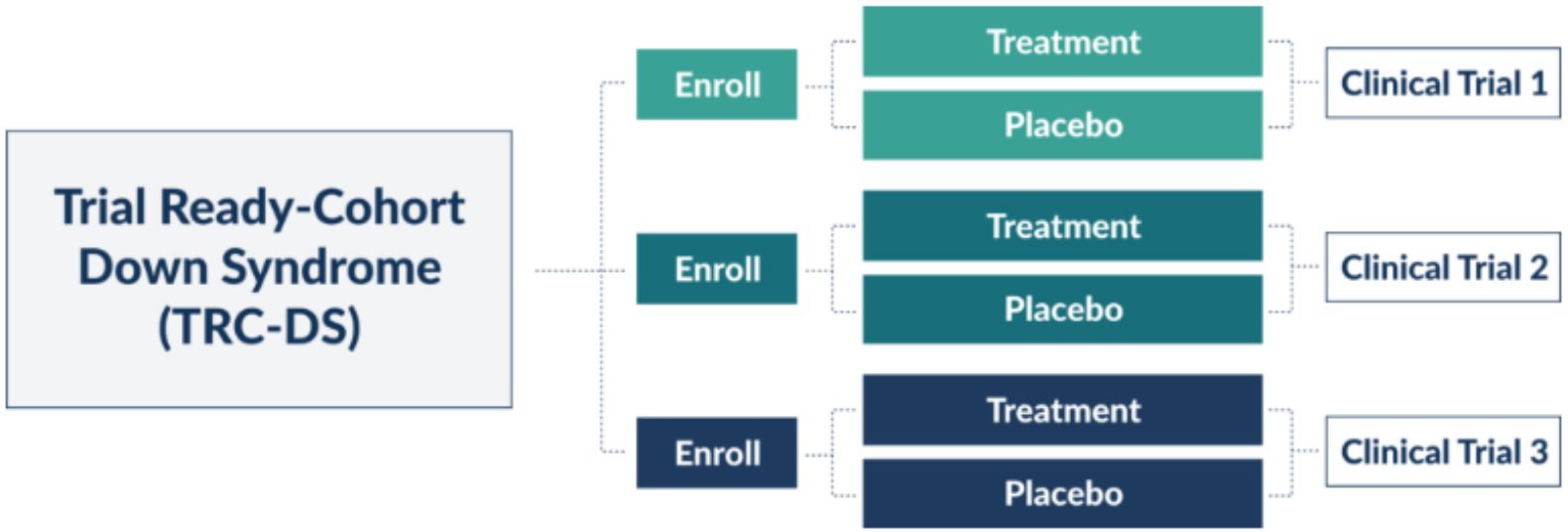
- ACTC-DS will serve as a platform for bringing the latest and most innovative AD therapies to the DS population.

actc-ds.org

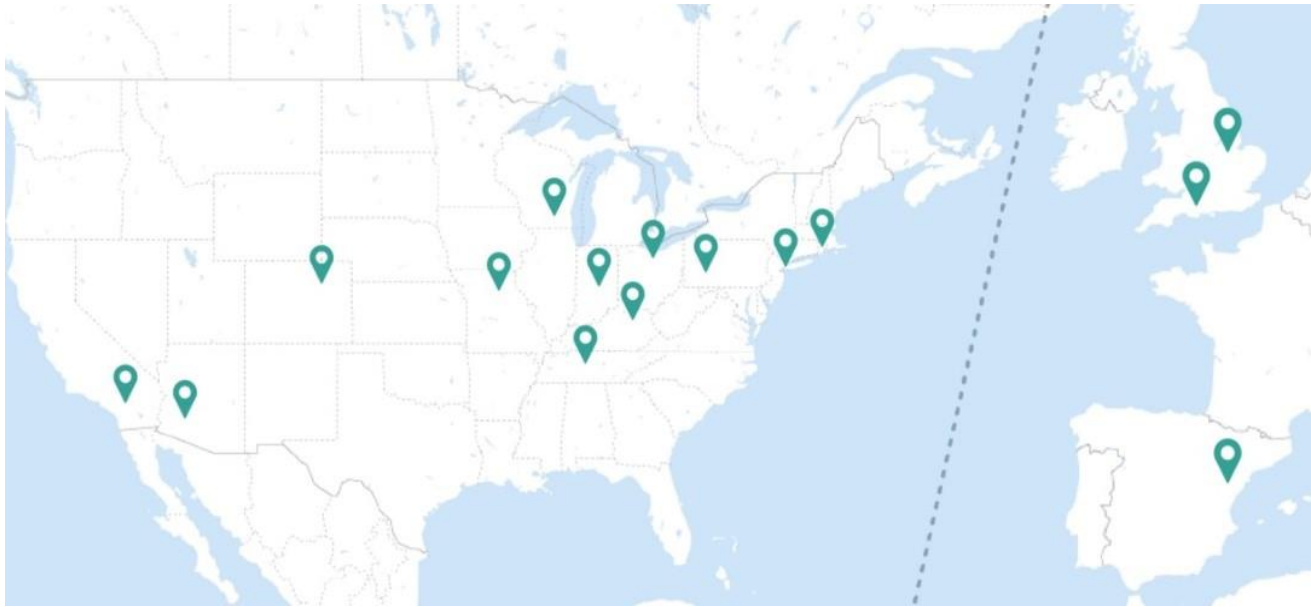
Trial Ready Cohort – Down Syndrome

PI: Mike Rafii (AG066543)

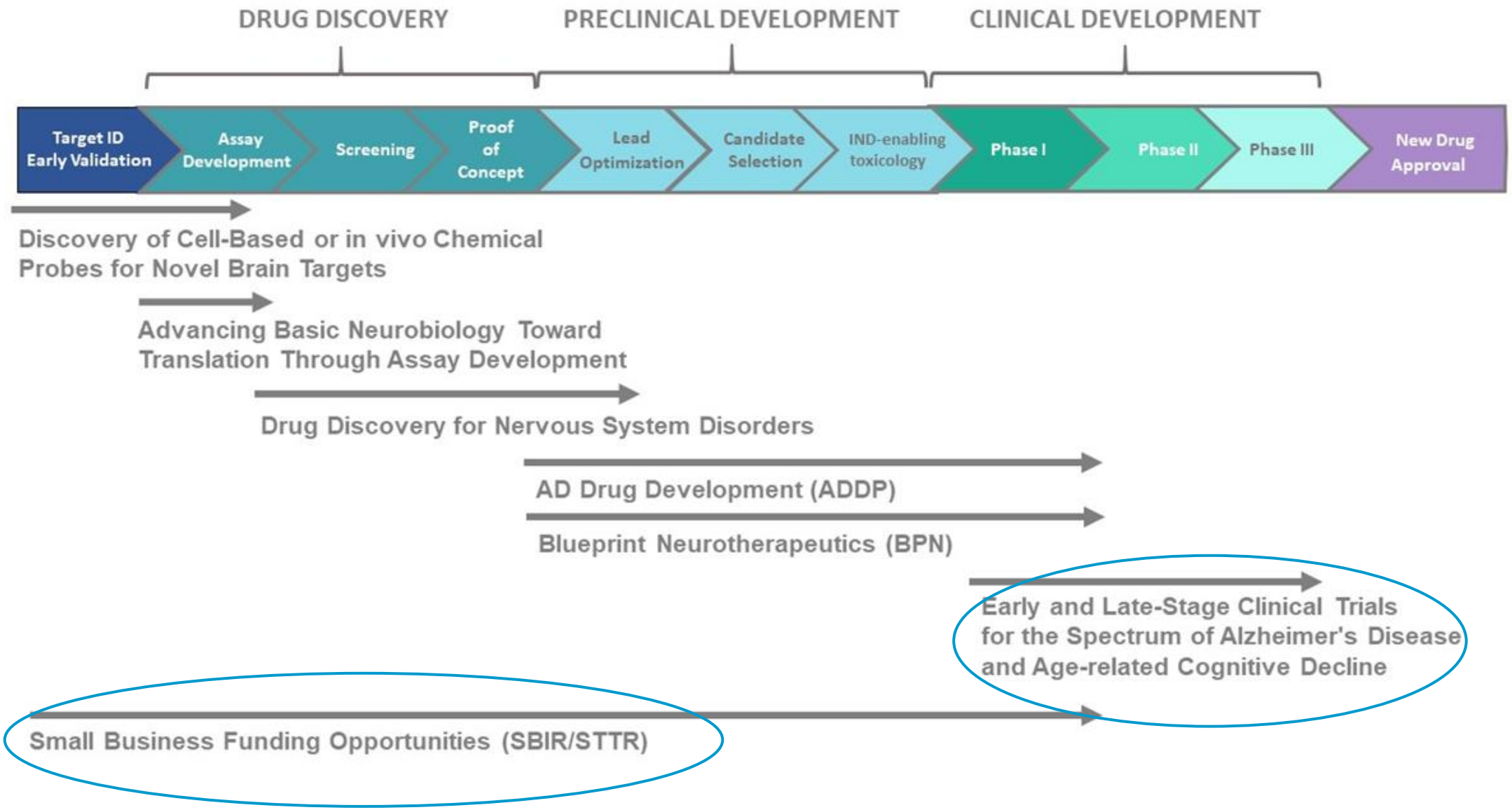
- Establish a trial-ready pool of well-characterized adults with Down Syndrome (DS) to participate in AD trials
- Launching in 2021




Participants and Families
Executive Commitee
ACTC Research Units
Funding Partners
Research Collaborators
Industry Partners
Clinical Sites
Advocacy Groups
ACTC-DS
Alzheimer's Clinical Trial Consortium
Down Syndrome



Pipeline of NIA and Trans-NIH Translational Research Funding Opportunities



Clinical Therapy Development

PAR-18-877:

Early Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01)

- **Phase 1 and Phase 2 Clinical Trials (Pharm and Non-Pharm)**
- **Studies to enhance trial design and methods**

PAR-18-878:

Late Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01)

- **Phase 2/3 and 3 Clinical Trials (Pharm and Non-Pharm)**

*Early and late-stage clinical trials for the spectrum of AD/ADRD and age-related cognitive decline 2021 Re-issue: planning to combine these FOAs into a single FOA covering Phases I-III pharm/non-pharm clinical trials, as well as clinical trial design/methods

Data Sharing Requirements for NIA AD/ADRD Clinical Trials

- Sharing of data and biosamples is expected at the time of publication of the primary results or within 9 months of data lock, whichever comes first

- Pivotal trials are expected to follow **Collaboration for Alzheimer's Prevention (CAP)** data and sample sharing principles:
  - make screening/pre-randomization baseline data available within 12 months of enrollment completion
  - post-randomization data and biosamples should be made available as soon as possible without compromising trial integrity, i.e., after regulatory approval or trial completion/termination or 18 months whichever comes first

*Weninger, et al. *Alzheimers Dement*. 2016

Clinical Therapy Development

PAS-19-316:

Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD) (R43/R44)

- **SBIR: Clinical trials allowed**

PAS-19-317:

Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD) (R41/R42)

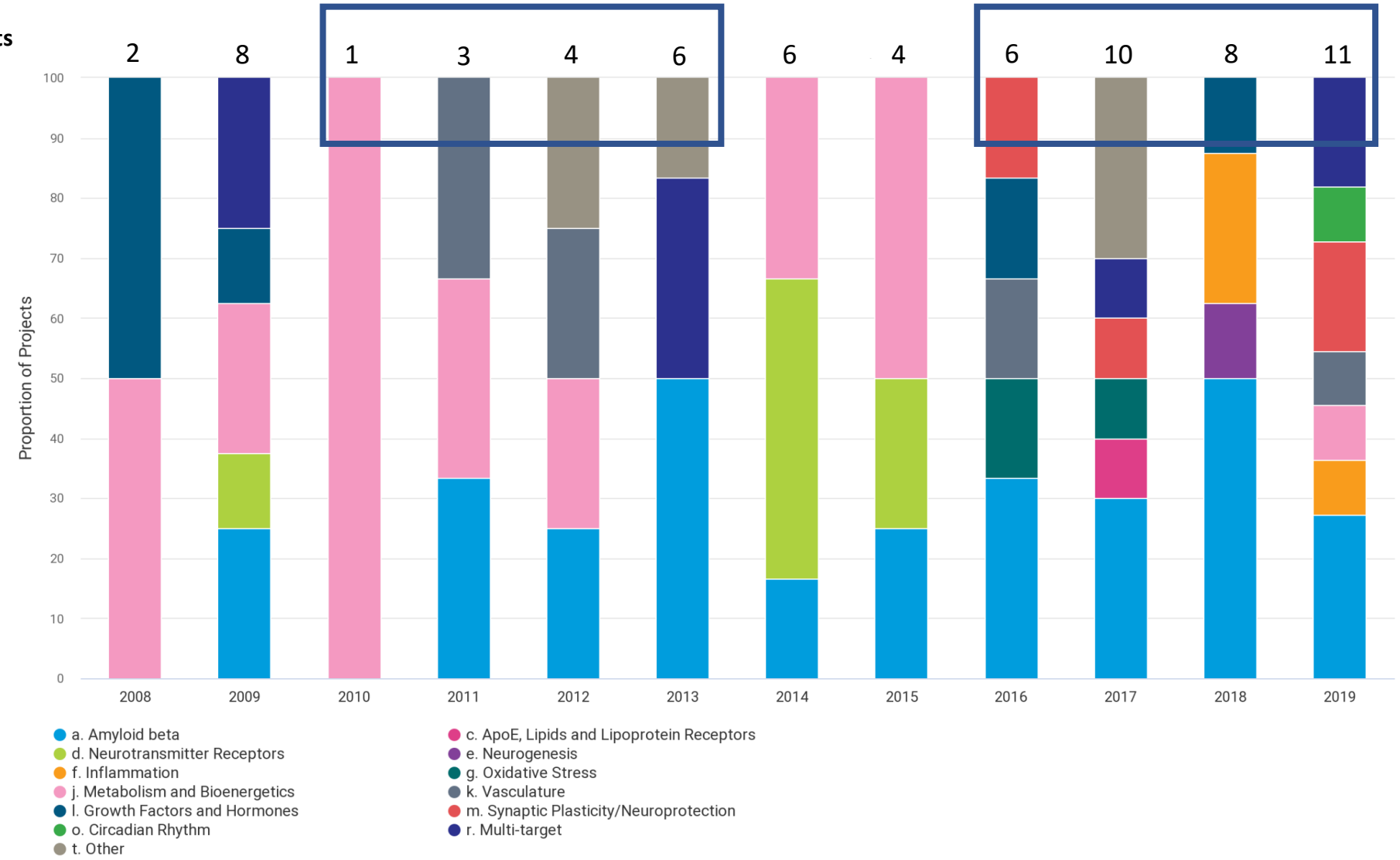
- **STTR: Clinical trials allowed**

Trends in NIA-funded Early Stage Clinical Trials for AD/ADRD

(Phase 1 & 2) 2008-2019

-by therapeutic target/disease mechanism-

# of newly funded projects



IADRP International Alzheimer's and Related Dementias Research Portfolio

iadrp.nia.nih.gov

Drug Candidates Supported by NIA through the Drug Development Funding Initiatives ADDP and BPN: Currently in Clinical Development

Targeted Disease Process	Therapeutic Agent	Stage of Development	Investigator	Organization
Amyloid b-related mechanisms	**CT1812**	**Phase 2 Clinical Trial**	CATALANO, SUSAN M	COGNITION THERAPEUTICS INC.
Growth Factors/Growth Factor Receptors	**LM11A-31**	**Phase 2 Clinical Trial**	LONGO, FRANK M	PHARMATROPIX, STANFORD UNIVERSITY
Synaptic Plasticity	**BPN14770**	**Phase 2 Clinical Trial**	GURNEY, MARK	TETRA THERAPEUTICS/SHIONOGI
Proteostasis	**PU-AD**	**Phase 2 Clinical Trial**	CHIOSIS, GABRIELA	SLOAN-KETTERING INSTITUTE/SAMUS THERAPEUTICS Inc.
Multi-target	**Allopregnanolone**	**Phase 2 Clinical Trial**	BRINTON, ROBERTA EILEEN	UNIVERSITY OF SOUTHERN CALIFORNIA
Growth Factors/Growth Factor Receptors	**AAV2-BDNF****	**Phase 1 Clinical Trial**	TUSZYNSKI, MARK H.	UNIVERSITY OF CALIFORNIA SAN DIEGO
Immune mechanisms/Inflammation	**MW150**	**Phase 1 Clinical Trial**	WATTERSON, DANIEL MARTIN	NORTHWESTERN UNIVERSITY AT CHICAGO
Immune mechanisms/Inflammation	**MW151**	**Phase 1 Clinical Trial**	WATTERSON, DANIEL MARTIN	NORTHWESTERN UNIVERSITY AT CHICAGO
Neurogenesis	**NNI-362**	**Phase 1 Clinical Trial**	KELLEHER-ANDERSSON, JUDITH A	NEURONASCENT INC.
Amyloid b-related mechanisms	**AV-1959***	**Phase 1 Clinical Trial**	AGADJANYAN, MICHAEL G	INSTITUTE FOR MOLECULAR MEDICINE

*Vaccine **Gene therapy

Expanding the Alzheimer's and Related Dementias Clinical Trials Workforce

The Need

- With increased federal funding for research in Alzheimer's Disease and related dementias and a goal of the National Plan to Address Alzheimer's to identify interventions to treat or cure ADRD by 2025, the number of clinical trials has significantly increased over the last few years

- There is a critical need to expand the AD/ADRD clinical trials workforce to meet this demand overall and in particular with regards to the inclusion of individuals from diverse backgrounds

- Clinical trials struggle to recruit individuals from diverse racial, ethnic, socioeconomic backgrounds. One of the potential barriers to participation is the lack of cultural sensitivity and ethic similarity to staff participants

IMPACT-AD

Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD

Alzheimer’s Disease and related disorders (ADRD) course that aims to educate and promote diversity among research professionals and future principal investigators in the field of ADRD research

Joshua Grill, PhD

University of California, Irvine
Course Co-Director

Rema Raman, PhD

University of Southern California
Course Co-Director

Goals of the Course

To provide junior investigators with a unique, comprehensive, and active learning experience in ADRD trials.

This will be accomplished by leveraging the full infrastructure and expertise of the Alzheimer’s Clinical Trials Consortium (ACTC) to enable a diverse range of clinicians, scientists and researchers to receive modern and robust training on ADRD clinical trials.

Supported by:
National Institute on Aging (NIA) U13 AG067696, Alzheimer’s Association
Alzheimer's Clinical Trials Consortium (ACTC), UCI MIND, USC ATRI

Key Elements

- Provide education and tools to establish a national cohort of qualified investigators to guide the field toward improved therapies

- Focused on diversifying the ADRD trial workforce:
  - Demographic characteristics (age, race, ethnicity, etc.)
  - Specialties (physicians, psychologists, statisticians, etc.)
  - Backgrounds (rural, urban, etc.)
  - Career stage or current position

IMPACT-AD
Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD

IMPACT-AD
Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD

Course Tracks

Professionals Track

Individuals selected to this track have at least 2 years of experience in ADRD research and/or clinical trials (in a broad variety of roles including, but not limited to clinicians, study coordinators, psychometricians, and other study professionals) and will be trained to further their knowledge and advance their careers in ADRD trials.

Fellowship Track

Individuals selected to this track will be trained to serve as Principal Investigators in ADRD trials and offered mentored training in protocol development.

First Class held online, September 14-17, 2020

2021 NIA Initiative: AD/ADRD Clinical Trials Short Courses (R25)

- Designed to encourage applications for intensive short courses that will develop, implement, and evaluate creative and innovative short courses to provide education in state-of-the-art clinical research skills in AD/ADRD
- Courses may vary in duration from one-week or less up to a maximum of 12-weeks. Courses will include graduate/medical students, post docs, and/or early career faculty
- Diversify the AD/ADRD clinical trials workforce
- This type of training is necessary to thrive in a team science environment and is rarely provided through the traditional course of medical and graduate education.
- With this proposed concept, we hope to expand AD/ADRD clinical trials training and strengthen the pipeline of promising new trialists

ACKNOWLEDGMENTS

DIVISION OF NEUROSCIENCE

Director: Eliezer Masliah
Deputy Director: Jennie Larkin

Population Studies and Genetics
Acting Chief – Eliezer Masliah
Dallas Anderson
Marilyn Miller
Damali Martin
Ananya Paria
Sharna Tingle
Alison Yao

Office for Strategic Development and Partnerships
Director - Suzana Petanceska
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Nadezda Radoja
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Alvin McKelvy

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Cerise Elliot
John Hsiao
Yuan Luo
Akanni Clarke
Grayson Donley
Alvin McKelvy

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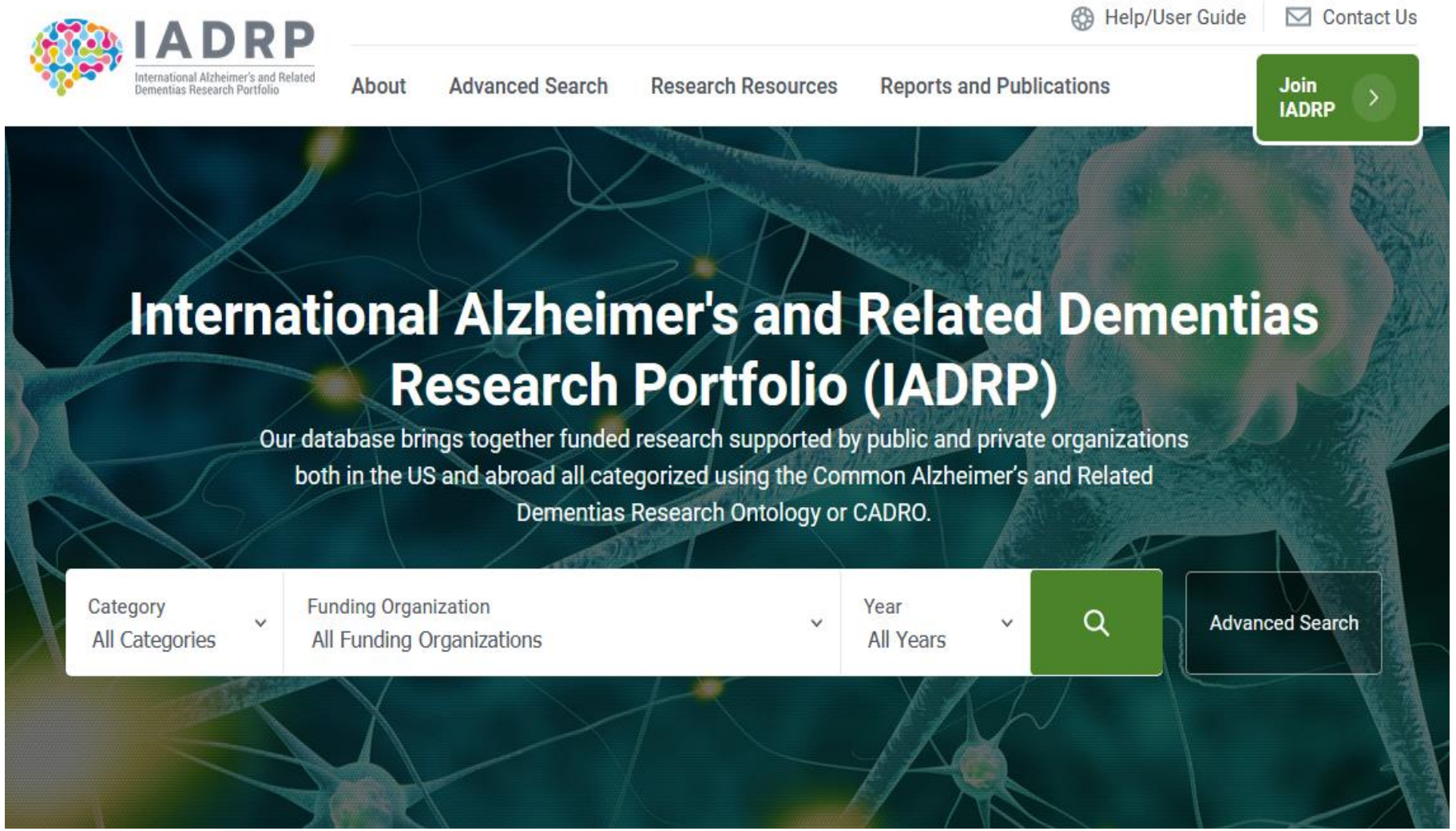
Shreaya Chakroborty
Zane Martin
Suzana Petanceska
Ali Sharma
Jean Yuan

Behavioral and Systems Neuroscience
Chief – Molly Wagster
Dave Frankowski
Coryse St. Hillaire-Clarke
Devon Oskvig
Luci Roberts
Matt J Sutterer

Thank You!



https://iadrp.nia.nih.gov/

Accelerating Therapy Development for Alzheimer's and Related Dementias -from Open Science to Open Drug Discovery-

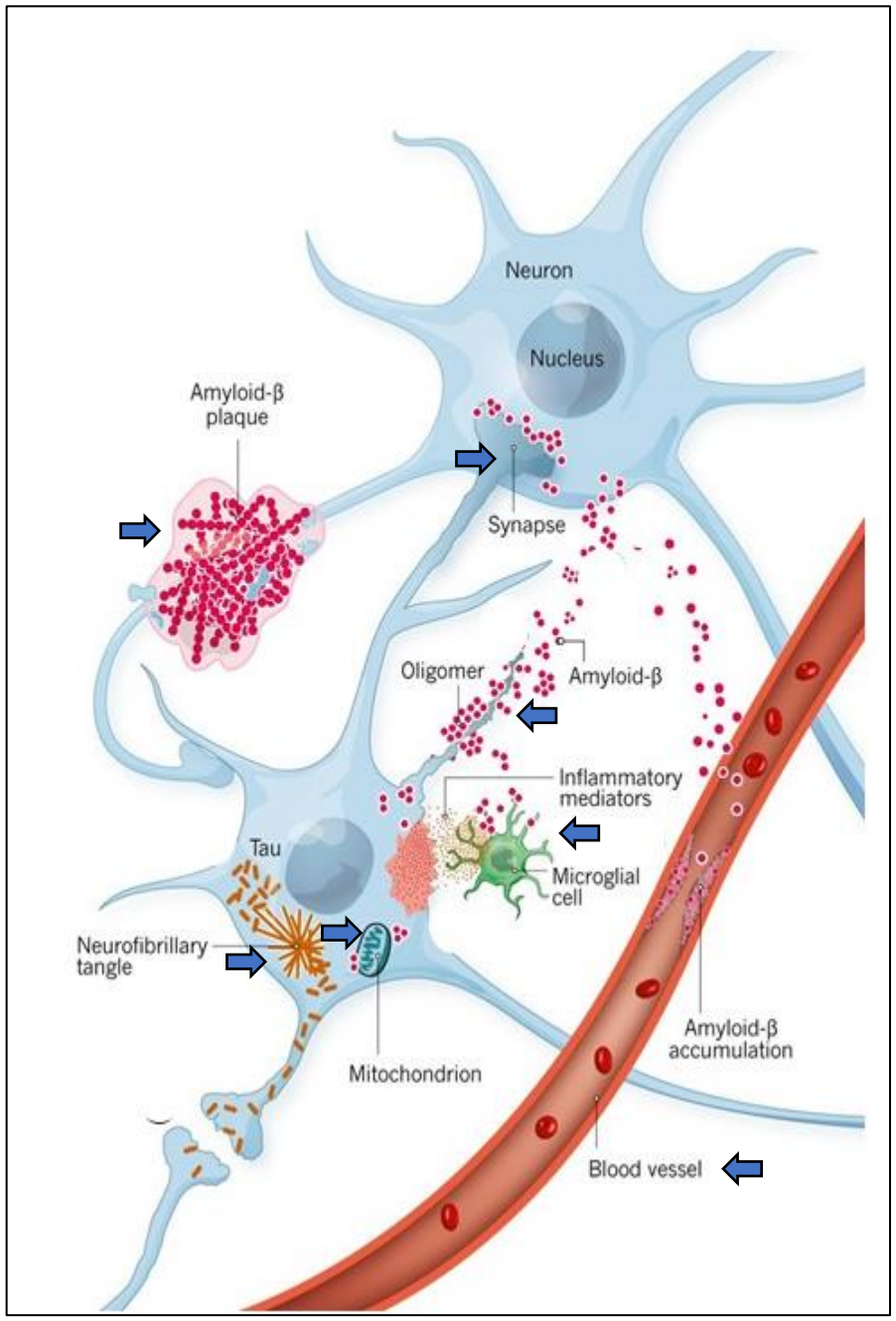
Suzana Petanceska PhD
Director – Strategic Development and Partnerships
Division of Neuroscience

NIH National Institute on Aging

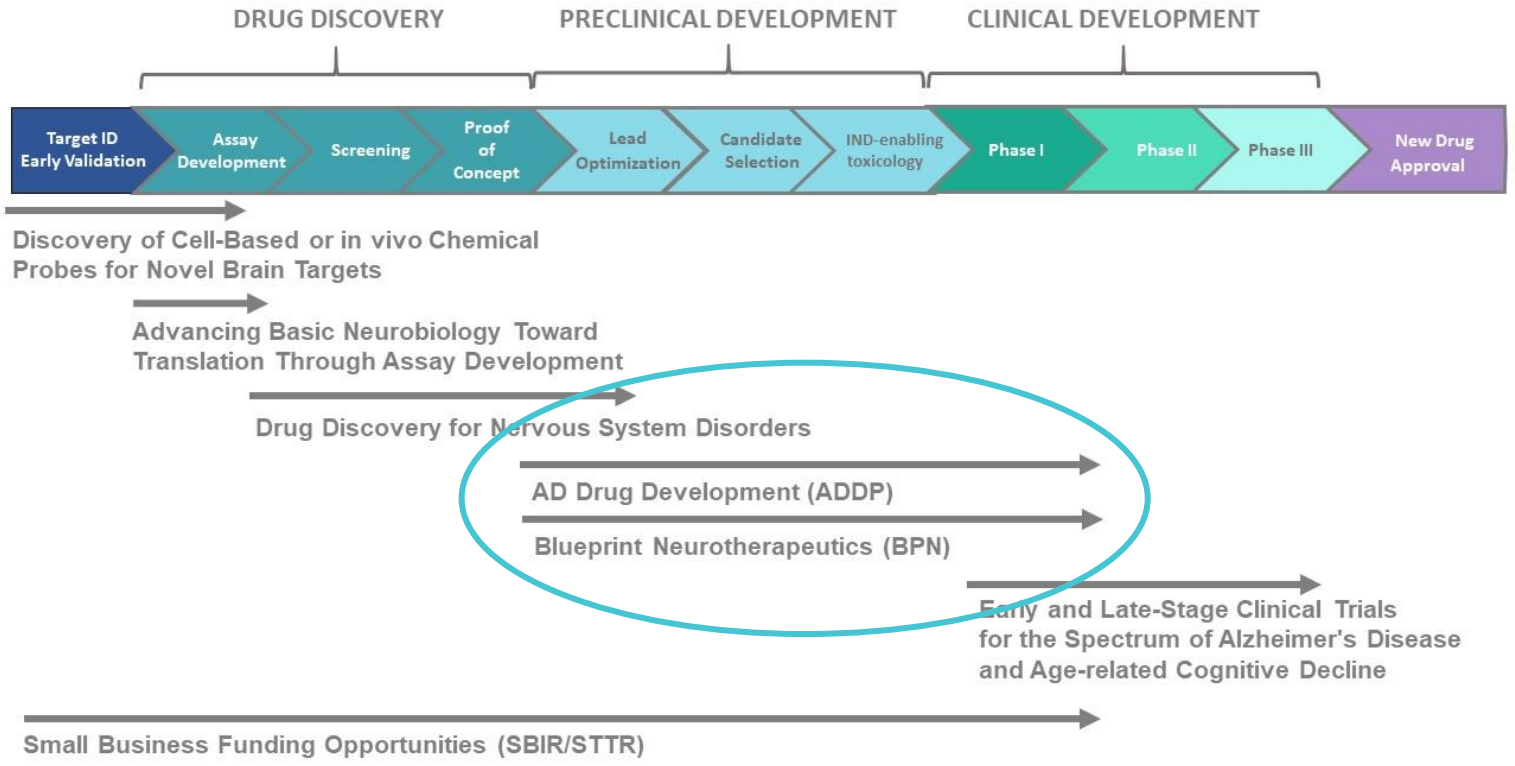
13th Annual FDA/ACT-AD Allies Meeting

Outline:

- NIA AD Translational Research Program: New Drug Candidates
- AMP-AD and Affiliated Consortia: Systems-based Approaches to Novel Target and Biomarker Discovery
- TREAT-AD Centers: Advancing Novel Targets into Drug Discovery
- MODEL-AD Consortium: Resources for Rigorous Preclinical Efficacy Testing
- Accelerating Therapy Development through Data-Driven Drug Repurposing
- Understanding the Impact of Sex Differences on AD Risk and Responsiveness to Treatment
- Training the New Translational Workforce



NIA's Alzheimer's Translational Research Program provides a pipeline of funding opportunities that support the discovery and development of new drugs for a diverse portfolio of therapeutic targets.



PAR-18-820:

NIA Alzheimer's Drug Development Program, ADDP (U01)

- Small molecules and biologics
- Two Entry Points: Hits Optimization through IND/Lead Selection through Phase I
- Milestone driven (Go/No-Go decision points)
- Budget capped at $1M Direct Cost per year for up to 5 years

PAR-20-122 and PAR-20-111:

Blueprint Neurotherapeutics Network, BPN (UG3/UH3) (U44)

- Small molecules only
- Two Entry Points: Hits Optimization through IND/Lead Selection through Phase I
- Milestone driven (Go/No-Go decision points)
- Funding up to 5 years
- *Virtual Pharma Model: PIs Collaborate with NIH-funded consultants and NIH CROs*

10 Therapeutic Programs Supported by NIA through ADDP or BPN are in Clinical Development

Targeted Disease Process	Therapeutic Agent	Current Stage of Development	Investigator	Organization
Amyloid b-related mechanisms	**CT1812**	**Phase 2 Clinical Trial**	CATALANO, SUSAN M	COGNITION THERAPEUTICS INC.
Growth Factors/Growth Factor Receptors	**LM11A-31**	**Phase 2 Clinical Trial**	LONGO, FRANK M	PHARMATROPIX/STANFORD UNIVERSITY
Synaptic Plasticity	**BPN14770*** **	**Phase 2 Clinical Trial**	GURNEY, MARK	TETRA THERAPEUTICS/SHIONOGI
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Amyloid b-related mechanisms	**AV-1959***	**Phase 1 Clinical Trial**	AGADJANYAN, MICHAEL G	INSTITUTE FOR MOLECULAR MEDICINE

*Vaccine **Gene therapy ***Supported through BPN

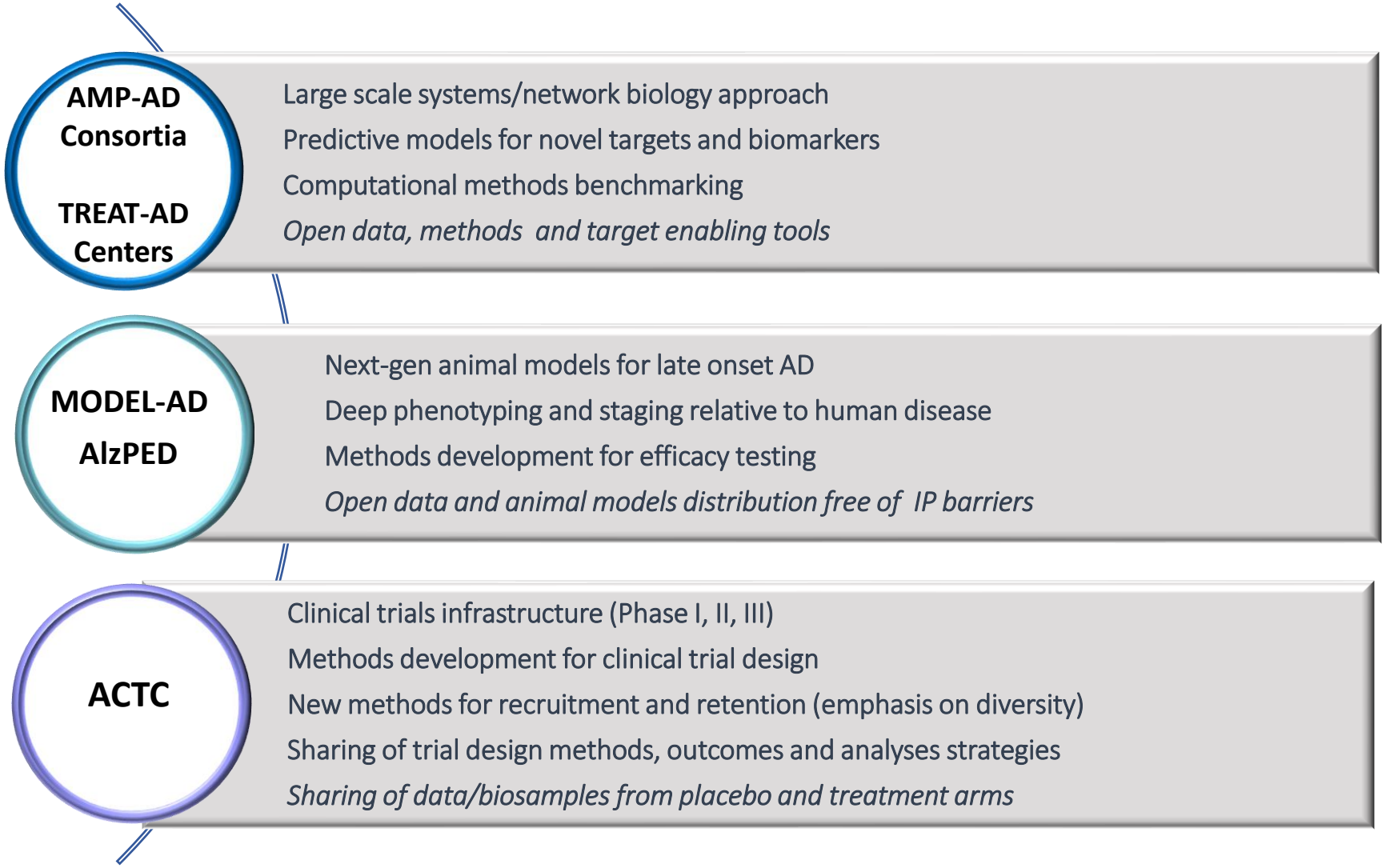
Additional Therapeutic Programs Supported by NIA through ADDP or BPN

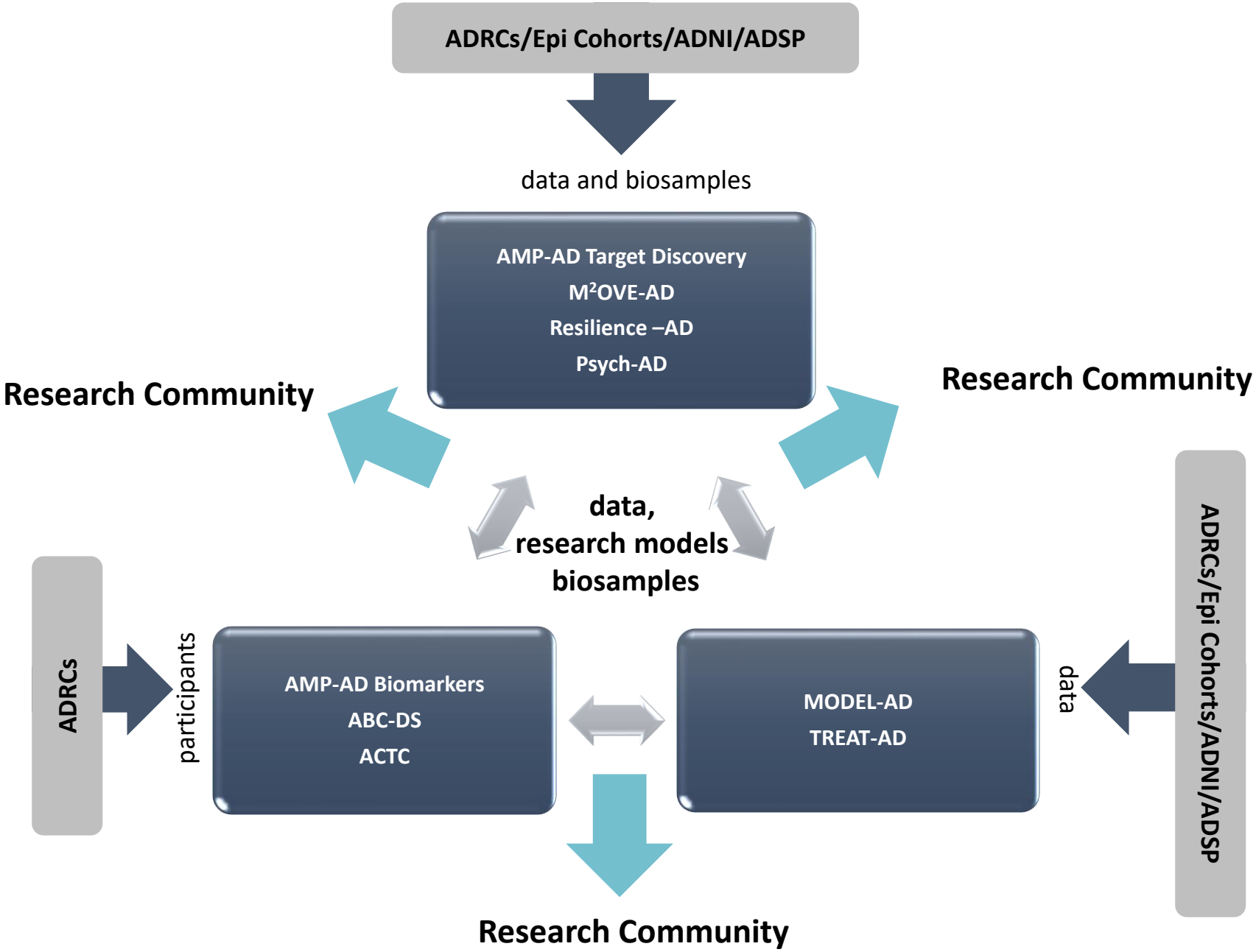
Targeted Disease Process	Therapeutic Agent	Stage of Development	Investigator	Organization
Amyloid b-related mechanisms	ACU193	Preclinical Drug Development	SIEMERS, ERIC	ACUMEN PHARMACEUTICALS, INC.
Amyloid b-related mechanisms	UCSD 776890	Preclinical Drug Development	WAGNER, STEVEN LEE	UNIVERSITY OF CALIFORNIA SAN DIEGO
Amyloid b-related mechanisms	Anti-abeta IgV	Preclinical Drug Development	PAUL, SUDHIR	UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER
Amyloid b-related mechanisms	SMApBAs	Preclinical Drug Development	KLUNK, WILLIAM E	UNIVERSITY OF PITTSBURGH
Amyloid b-related mechanisms	BPN15606 ***	Preclinical Drug Development	WAGNER, STEVEN LEE	UNIVERSITY OF CALIFORNIA SAN DIEGO
ApoE, Lipids and Lipoprotein Receptors	PY-101	Preclinical Drug Development	MAHLEY, ROBERT W	J. DAVID GLADSTONE INSTITUTES
Immune mechanisms/Inflammation	EP2 receptor antagonist	Preclinical Drug Development	GANESH THOTA	EMORY UNIVERSITY
Immune mechanisms/Inflammation	Curcumin	Preclinical Drug Development	FRAUTSCHY, SALLY ANN	SEPULVEDA RESEARCH CORPORATION
Immune mechanisms/Inflammation	PU.1 Inhibitors	Preclinical Drug Development	TSAI, LI-HUEI	MASSACHUSETS INSTITUTE OF TECHNOLOGY
Immune mechanisms/Inflammation	Epoxide Hydrolase Inhibitors	Preclinical Drug Development	WANG, JIN	BAYLOR COLLEGE OF MEDICINE
Multi-target	GT-1061	Preclinical Drug Development	THATCHER, GREGORY R. J	UNIVERSITY OF ILLINOIS CHICAGO
Neurogenesis	Neural stem cells	Preclinical Drug Development	FELDMAN, EVA LUCILLE	UNIVERSITY OF MICHIGAN
Neurotransmitter Receptors	MW071 and MW109	Preclinical Drug Development	WATTERSON, DANIEL MARTIN	NORTHWESTERN UNIVERSITY AT CHICAGO
Neurotransmitter Receptors	mGluR6 Modulators	Preclinical Drug Development	STRITTMATTER, STEPHEN M	YALE UNIVERSITY
Neurotransmitter Receptors	BPN-27473 ***	Preclinical Drug Development	ROSENZWEIG-LIPSON, SHARON	AGENEBIO, INC.
Neurotransmitter Receptors	522-054	Preclinical Drug Development	GEE, KELVIN W	UNIVERSITY OF CALIFORNIA IRVINE
Neurotransmitter Receptors	YF012403	Preclinical Drug Development	ARANCIO, OTTAVIO	COLUMBIA UNIVERSITY
Proteostasis	ANVS401	Preclinical Drug Development	MACCECCHINI, MARIA	ANNOVIS
Proteostasis	KU32 and A4	Preclinical Drug Development	MICHAELIS, MARY L.	UNIVERSITY OF KANSAS LAWRENCE
Synaptic Plasticity	EAAT2 activators	Preclinical Drug Development	LIN, CHIEN-LIANG GLENN	OHIO STATE UNIVERSITY
Synaptic Plasticity	E64 and BDA-410	Preclinical Drug Development	ARANCIO, OTTAVIO	COLUMBIA UNIVERSITY
Synaptic Plasticity	M3	Preclinical Drug Development	LIN, CHIEN-LIANG GLENN	OHIO STATE UNIVERSITY
Tau	AV-1980R/A	Preclinical Drug Development	AGADJANYAN, MICHAEL G	INSTITUTE FOR MOLECULAR MEDICINE
Tau	Triazolopyrimidines	Preclinical Drug Development	BRUNDEN, KURT R.	UNIVERSITY OF PENNSYLVANIA
Tau	Epothilones	Preclinical Drug Development	SMITH, AMOS B	UNIVERSITY OF PENNSYLVANIA
Vascular mechanisms	RASRx 1902	Preclinical Drug Development	RODGERS, KATHLEEN E.	UNIVERSITY OF ARIZONA
Vascular mechanisms	PNA5	Preclinical Drug Development	HAY, MEREDITH	UNIVERSITY OF ARIZONA
Vascular mechanisms	Carvedilol	Preclinical Drug Development	PASINETTI, GIULIO MARIA	ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

***Supported through BPN

NIA Alzheimer's Translational Research Program: ENABLING INFRASTRUCTURE PROGRAMS FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

OPEN SCIENCE/OPEN SOURCE
FROM TARGETS TO TRIALS

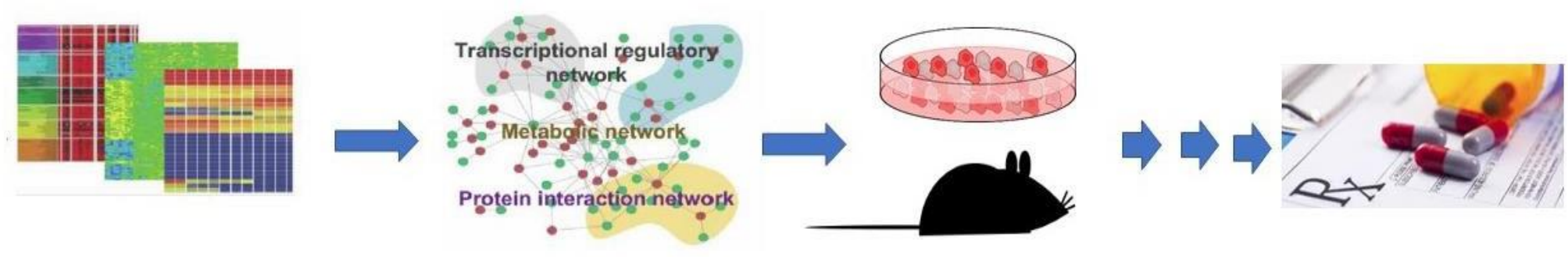



ADRCs/Epi Cohorts/ADNI/ADSP
data and biosamples
AMP-AD Target Discovery
M2OVE-AD
Resilience –AD
Psych-AD
Research Community
Research Community
data,
research models
biosamples
ADRCs
participants
AMP-AD Biomarkers
ABC-DS
ACTC
MODEL-AD
TREAT-AD
data
ADRCs/Epi Cohorts/ADNI/ADSP
Research Community

ACCELERATING MEDICINES PARTNERSHIP FOR ALZHEIMER'S DISEASE (AMP-AD)

TARGET DISCOVERY AND PRECLINICAL VALIDATION PROJECT

Launched in 2014



Genomic, proteomic, metabolomic data from human brain and peripheral fluid samples

Computational modeling /network biology

Experimental validation in cell-based and animal models

Drug Discovery

AMP-AD 1.0 Partners

GOVERNMENT MEMBERS

NIH National Institute on Aging

NIH National Institute of Neurological Disorders and Stroke

FDA U.S. FOOD & DRUG ADMINISTRATION

INDUSTRY MEMBERS

abbvie Biogen gsk Lilly

NOT-FOR-PROFIT MEMBERS

FNIH Foundation for the National Institutes of Health

alzheimer's association

GEOFFREY BEENE FOUNDATION

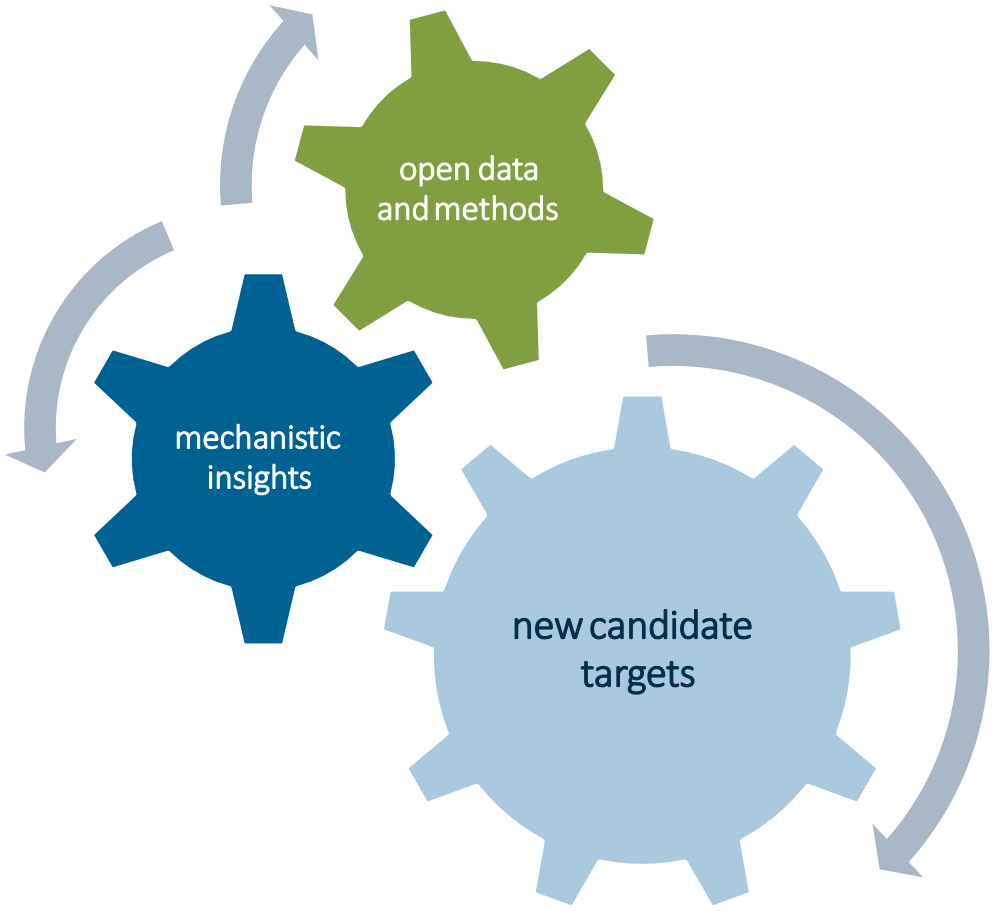
UsAgainst Alzheimer's we can stop it by 2020

Alzheimer's Drug Discovery Foundation

- Systems biology approach to target discovery and validation.
- Large-scale, cross-disciplinary, team science.
- Open science research model: rapid sharing of data, methods and results through centralized data infrastructure: AD Knowledge Portal

AMP AD 1.0 delivered multi-omic data and analytical resources, mechanistic insights, and a systems-based, data-driven process for target discovery and validation

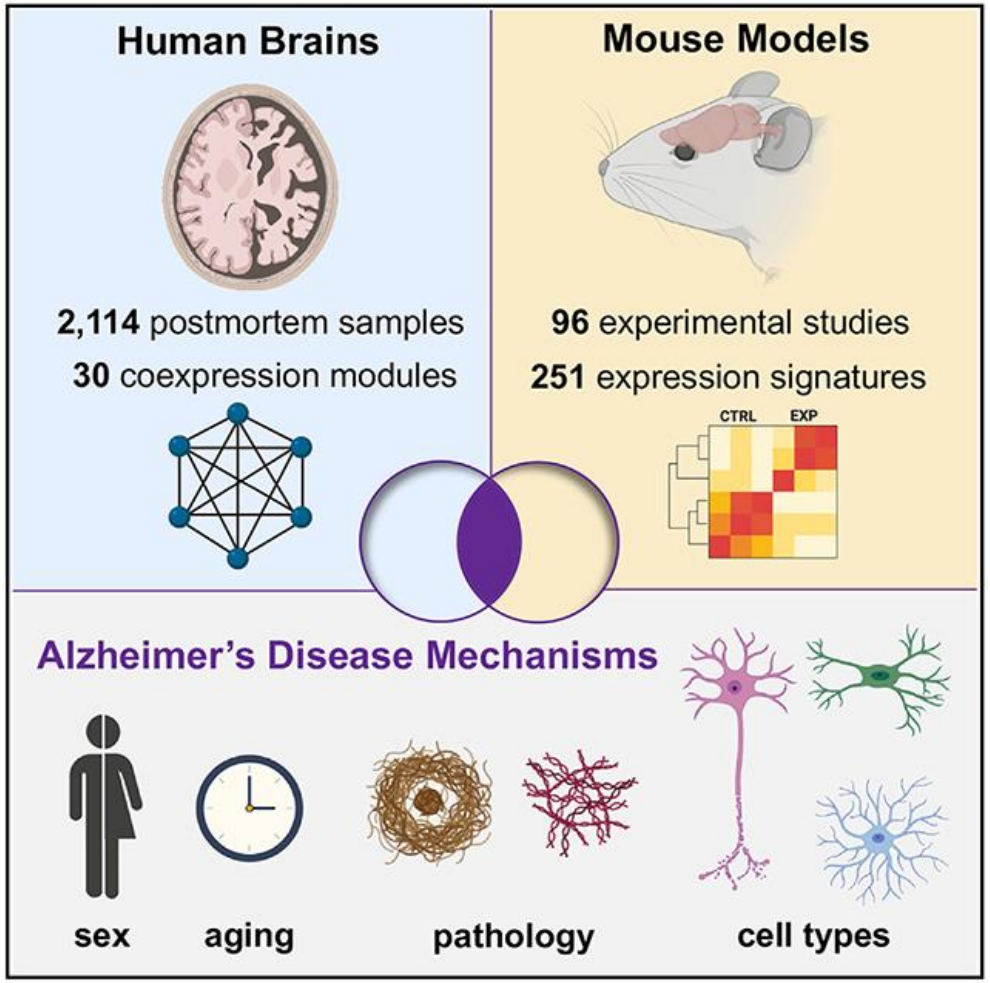
- Centralized FAIR data repository and knowledgebase - AD Knowledge Portal
- Rich, human, multi-omic data generated and made available;>3000 users to date (60% academia / 40% industry)
- Molecular network models of disease made available
- Animal models phenotyped and evaluated relative to human molecular networks
- New mechanistic disease insights on role of genome, proteome, metabolome and microbiome
- Agora, open-source platform, featuring AMP-AD nominated targets and verified systems biology analyses for any gene of interest
- 542 unique targets made available through Agora along with the supporting evidence and extensive druggability information
- Early experimental validation completed for over 20 candidate targets



Meta-Analysis of the Alzheimer's Disease Human Brain Transcriptome and Functional Dissection in Mouse Models

Ying-Wooi Wan [1], Rami Al-Ouran [2], Carl G Mangleburg [1], Thanneer M Perumal [3], Tom V Lee [4], Katherine Allison [4], Vivek Swarup [5], Cory C Funk [6], Chris Gaiteri [7], Mariet Allen [8], Minghui Wang [9], Sarah M Neuner [10], Catherine C Kaczorowski [10], Vivek M Philip [10], Gareth R Howell [10], Heidi Martini-Stoica [11], Hui Zheng [12], Hongkang Mei [13], Xiaoyan Zhong [13], Jungwoo Wren Kim [14], Valina L Dawson [15], Ted M Dawson [16], Ping-Chieh Pao [17], Li-Huei Tsai [17], Jean-Vianney Haure-Mirande [18], Michelle E Ehrlich [19], Paramita Chakrabarty [20], Yona Levites [20], Xue Wang [21], Eric B Dammer [22], Gyan Srivastava [23], Sumit Mukherjee [3], Solveig K Sieberts [3], Larsson Omberg [3], Kristen D Dang [3], James A Eddy [3], Phil Snyder [3], Yooree Chae [3], Sandeep Amberkar [24], Wenbin Wei [25], Winston Hide [26], Christoph Preuss [10], Ayla Ergun [27], Phillip J Ebert [28], David C Airey [28], Sara Mostafavi [29], Lei Yu [7], Hans-Ulrich Klein [30], Accelerating Medicines Partnership-Alzheimer's Disease Consortium; Gregory W Carter [10], David A Collier [31], Todd E Golde [20], Allan I Levey [32], David A Bennett [7], Karol Estrada [27], T Matthew Townsend [33], Bin Zhang [9], Eric Schadt [9], Philip L De Jager [30], Nathan D Price [6], Nilüfer Ertekin-Taner [34], Zhandong Liu [35], Joshua M Shulman [36], Lara M Mangravite [37], Benjamin A Logsdon [38]

A consensus atlas of the human brain transcriptome in Alzheimer's disease



Cell Rep 2020 Jul 14;32(2):107908.
https://pubmed.ncbi.nlm.nih.gov/32668255/

NIA-supported Grants Provide a Foundation for AMP-AD 2.0

RFA-AG18-013 (U01) / RFA-AG18-014 (U24)

- AMP AD Data Coordinating Center: Lara Mangravite, Sage Bionetworks
- Multi-omic network-directed proteoform discovery, dissection and functional validation to prioritize novel AD therapeutic targets : Phil De Jager, Columbia U
- AMP AD Brain proteomic network enhancement, validation, and translation into CSF biomarkers: Allan Levey, Emory University
- Integrative network biology approaches to identify, characterize and validate molecular subtypes in Alzheimer's Disease : Bin Zhang, ISMMS
- Metabolomic signatures for disease sub-classification and target prioritization in AMP AD: Rima Kaddurah-Daouk, Duke University
- A systems approach to targeting innate immunity in AD : Nilufer Ertekin-Taner, Mayo Clinic
- Identification of the genetic and transcriptomic networks of cognitive and neuropathological resilience to Alzheimer's Disease associated viruses: Ben Readhead, Arizona State University

Research Scope of Foundational Grants

1. Sustain and expand the capabilities of the AMP AD Knowledge Portal and the AGORA platform
2. Maximize the use of existing data and generate additional molecular profiling data (human and mouse) for use in target and biomarker discovery
3. Increase the bandwidth and develop new methods for functional validation of novel targets
4. Develop methods for integrative network analyses to discover patient stratification biomarkers and to enable disease sub-classification

Opportunity to renew and expand the public private partnership

FNIH Coordinated the Effort to Develop the Second Phase of AMP-AD

FNIH convened discussions among NIA, existing and potential new private partners (industry and non-profit organizations) to identify key areas for strategic partnering that can leverage the NIA foundational grants investment:

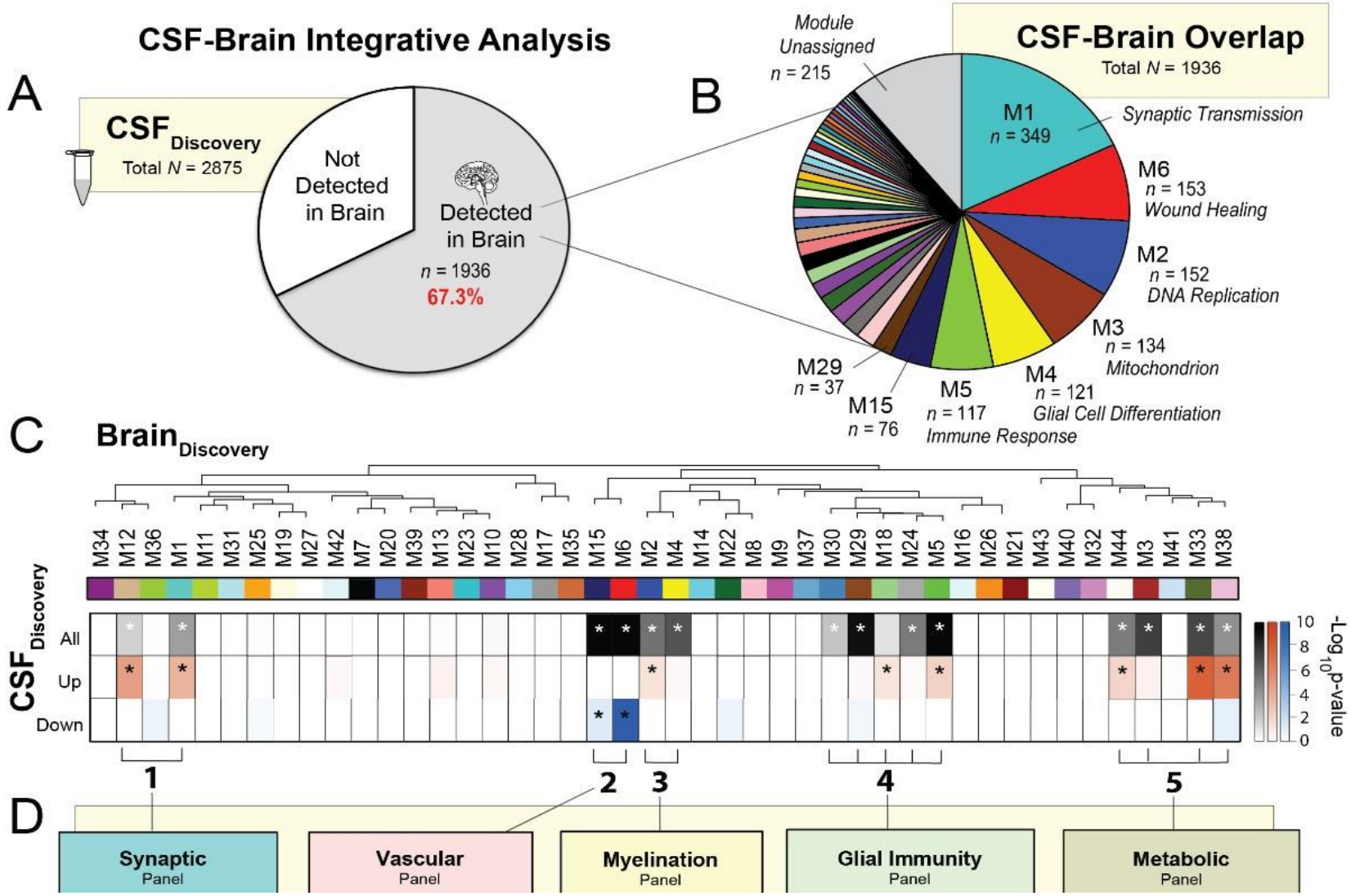
- Expand the multi-omic profiling in samples from diverse cohorts (brain, CSF, plasma)
- Generate longitudinal immunologic profiling data in diverse cohorts
- Expand the existing sn/sc molecular profiling efforts to develop a molecular atlas of AD

Deconstruct Disease Heterogeneity and Enable a Precision Medicine Approach to Target and Biomarker Discovery

FNIH Contact: Eline Appelmans, Scientific Program Manager in Neuroscience, Research Partnerships
eappelmans@fnih.org

Integrated Proteomics Reveals Brain-based Cerebrospinal Fluid biomarkers in Asymptomatic and Symptomatic Alzheimer's Disease

- Multiplex mass spectrometry of brain (~12,000 proteins) and CSF ~3500 proteins).
- 15 overlapping CSF-Brain protein network modules map to five pathophysiological processes.
- Synaptic, vascular, and metabolic panels demonstrate divergent expression trends in the brain and CSF.
- Replication experiments demonstrate that the CSF signatures are disease specific of and reproducible.



Higginbotham et al. Science Advances 2020
https://advances.sciencemag.org/content/6/43/eaaz9360

Recent AMP-AD Manuscripts

Transcriptomic maps of the disease

- Meta-Analysis of the Alzheimer's Disease Human Brain Transcriptome and Functional Dissection in Mouse Models – *Cell Reports*
- Molecular Subtyping of Alzheimer's Disease Using RNA-Sequencing Data Reveals Novel Mechanisms and Targets – *Science Advances*
- Molecular estimation of neurodegeneration pseudotime in older brains – *Nature Communications*

Integrative proteomics

- Integrated proteomics reveals brain-based cerebrospinal fluid biomarkers in asymptomatic and symptomatic Alzheimer's disease – *Science Advances*
- Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation – *Nature Medicine*

Integrative metabolomics/lipidomics

- Sex and APOE ε4 genotype modify the Alzheimer's disease serum metabolome – *Nature Communications*
- Concordant peripheral lipidome signatures in two large clinical studies of Alzheimer's disease – *Nature Communications*
- Metabolic Network Analysis Reveals Altered Bile Acid Synthesis and Metabolism in Alzheimer's Disease – *Cell Reports*

Cellular resolution modeling

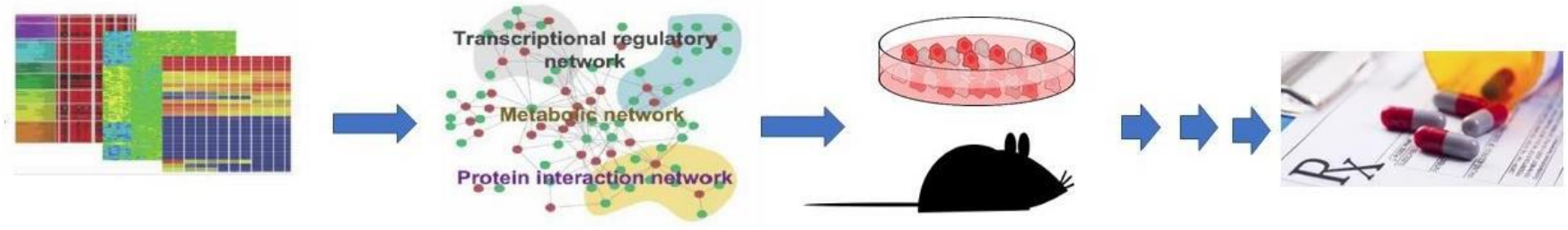
- Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease – *Nature Communications*
- Deciphering cellular transcriptional alterations in Alzheimer's disease brains - *Molecular Neurodegeneration*

Target ID and Experimental Validation

- Multiscale causal networks identify VGF as a key regulator of Alzheimer's disease – *Nature Communications*
- Transformative Network Modeling of Multi-Omics Data Reveals Detailed Circuits, Key Regulators, and Potential Therapeutics for AD – *Neuron*

AMP-AD and Affiliated Consortia

Harnessing the Power of Big Data and Open Science to Understand the Complex Biology of Disease Risk and Resilience and Discover New Therapeutic Targets and Biomarkers

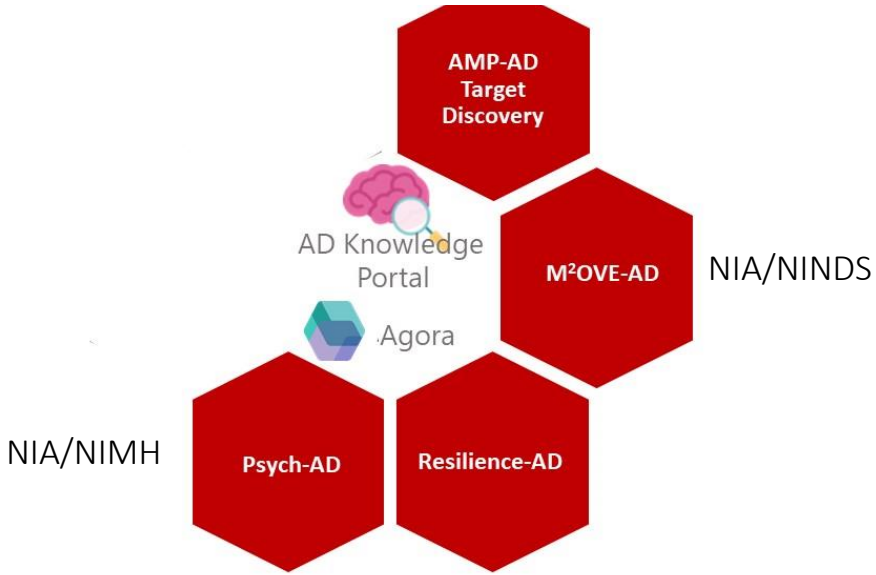


Genomic, proteomic, metabolomic data from human brain and peripheral fluid samples

Computational modeling /network biology

Experimental validation in cell-based and animal models

Drug Discovery



M²OVE-AD – Molecular Mechanisms of the Vascular Etiology of AD
Psych-AD - Molecular Mechanisms of the Neuropsychiatric Symptoms in AD

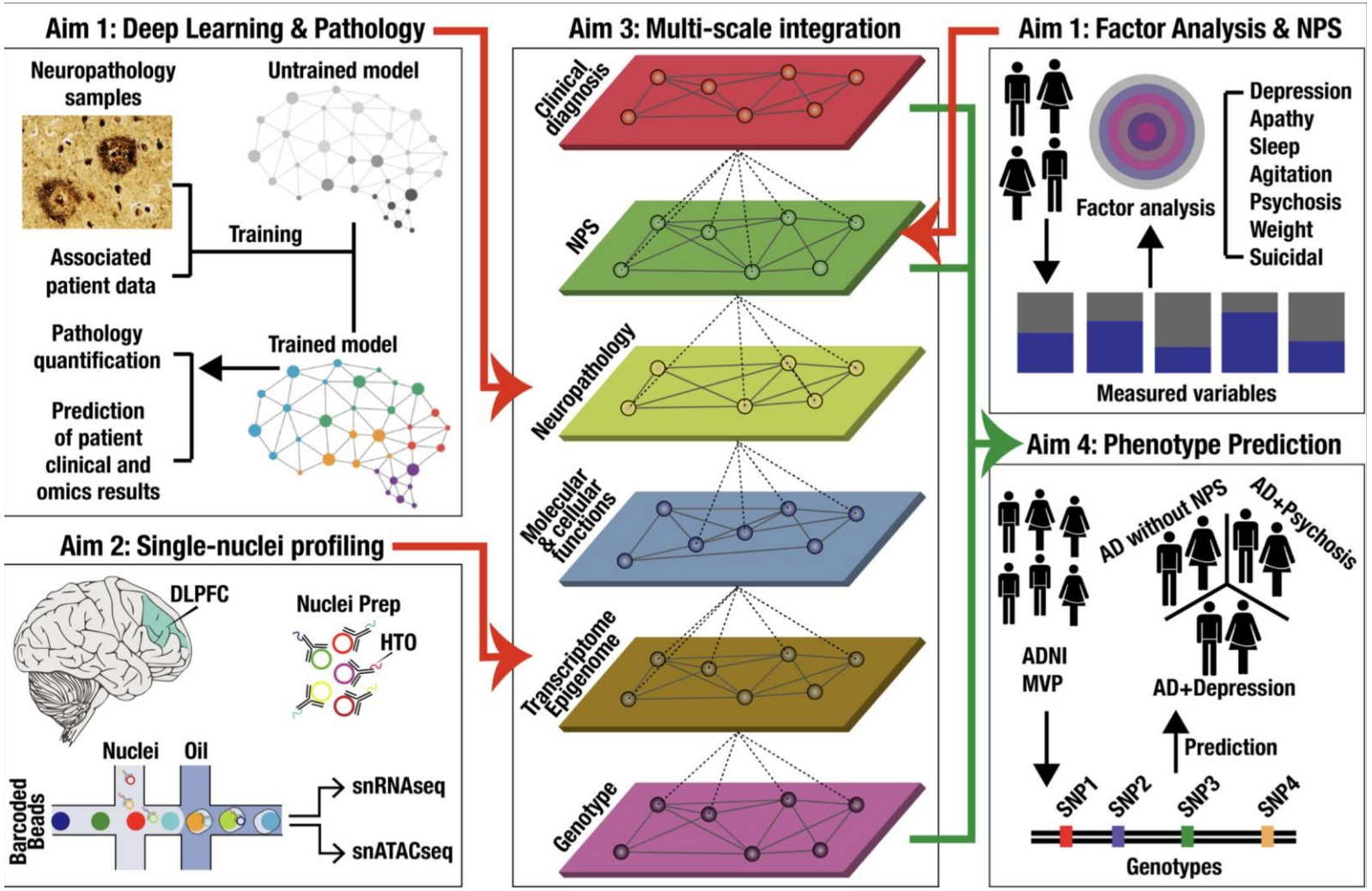
Psych-AD Program

Funded projects:

R56AG062302	LUTZ, MICHAEL WILLIAM (contact); CHIBA-FALEK, ORNIT ; LUO, SHENG ; WILLIAMSON, DOUGLAS E	Shared genetic, epigenetic, and transcriptomic profiles between AD and PTSD: molecular insights into the heterogeneity of neuropsychiatric symptoms in Alzheimers Disease
R01AG062249	DONG, HONGXIN (contact); WILSON, ROBERT S	Molecular Mechanisms Underlying Behavioral and Psychological Symptoms in Alzheimers Disease
R01AG062268	HUEY, EDWARD D	Neuroanatomical associations with the factor structure underlying neuropsychiatric symptoms in Alzheimers disease
R01AG062335	KELLIS, MANOLIS (contact); TSAI, LI-HUEI	Elucidating the Molecular Mechanisms of Neuropsychiatric Symptoms in Alzheimers Disease
R01AG062355	SALTON, STEPHEN R (contact); EHRLICH, MICHELLE E; ZHANG, BIN	Systems modeling of shared and distinct molecular mechanisms underlying comorbid Major Depressive Disorder and Alzheimers disease
R56AG062272	XU, RONG	Construct large-scale phenomes of disease and drugs and develop data-driven systems approaches to understand genetic links between Alzheimers disease and Neuropsychiatric symptoms
R01AG067015	LUNNON, KATIE (contact); KOFLER, JULIA K	A multi-omic approach to elucidate novel disease mechanisms and biomarkers for psychosis in Alzheimer’s disease
R01AG067025	ROUSSOS, PANAGIOTIS (contact); FINKBEINER, STEVEN M; HAROUTUNIAN, VAHRAM ; WANG, DAIFENG	Understanding the molecular mechanisms that contribute to neuropsychiatric symptoms in Alzheimer Disease

R01AG067025 Understanding the Molecular Mechanisms that Contribute to Neuropsychiatric Symptoms in AD

Multi-PIs: Roussos, Haroutunian (ISMMS) Smibert (NYGC), Wang (UWM), Finkbeiner (UCSF/Gladstone)



<u>Aim 1:</u> Derive additional phenomics data including severity of NPS and cellular features from neuropathological slides by deep learning approaches.

<u>Aim 2:</u> snRNAseq and snATACseq in 1,300 cases from Mount Sinai Brain Bank.

<u>Aim 3:</u> Integrate all data layers with deep learning approaches to identify markers that can predict NPS in AD.

<u>Aim 4:</u> Validate the predictive power of the models using independent genotype and phenomics datasets (ADNI and Million Veteran Program).

Novel Mechanism Research on Neuropsychiatric Symptoms (NPS) in Alzheimer's Dementia

PAR 20-157 (R01)/PAR 20-159 (R21)

(NIMH/NIA, active through May 2023)

NIA's Areas of Interest

- ❑ Integrate epidemiologic, genomic and mechanistic research to understand the **dynamic relationship between NPS and AD/ADRD pathogenesis across diverse populations**
- ❑ Examine the role of the **gut-brain axis and the microbiome in the emergence of NPS in AD** and as a **mediator of responsiveness** to interventions targeting NPS
- ❑ Generate **multi-omic data using biosamples from existing as well as legacy clinical trials targeting NPS in AD/ADRD** to interrogate disease mechanisms and molecular determinants of responsiveness to treatment
- ❑ **Preclinical validation of novel candidate targets** nominated by the AMP-AD Target Discovery Program, to test their utility as therapeutic targets **for NPS in AD/ADRD**

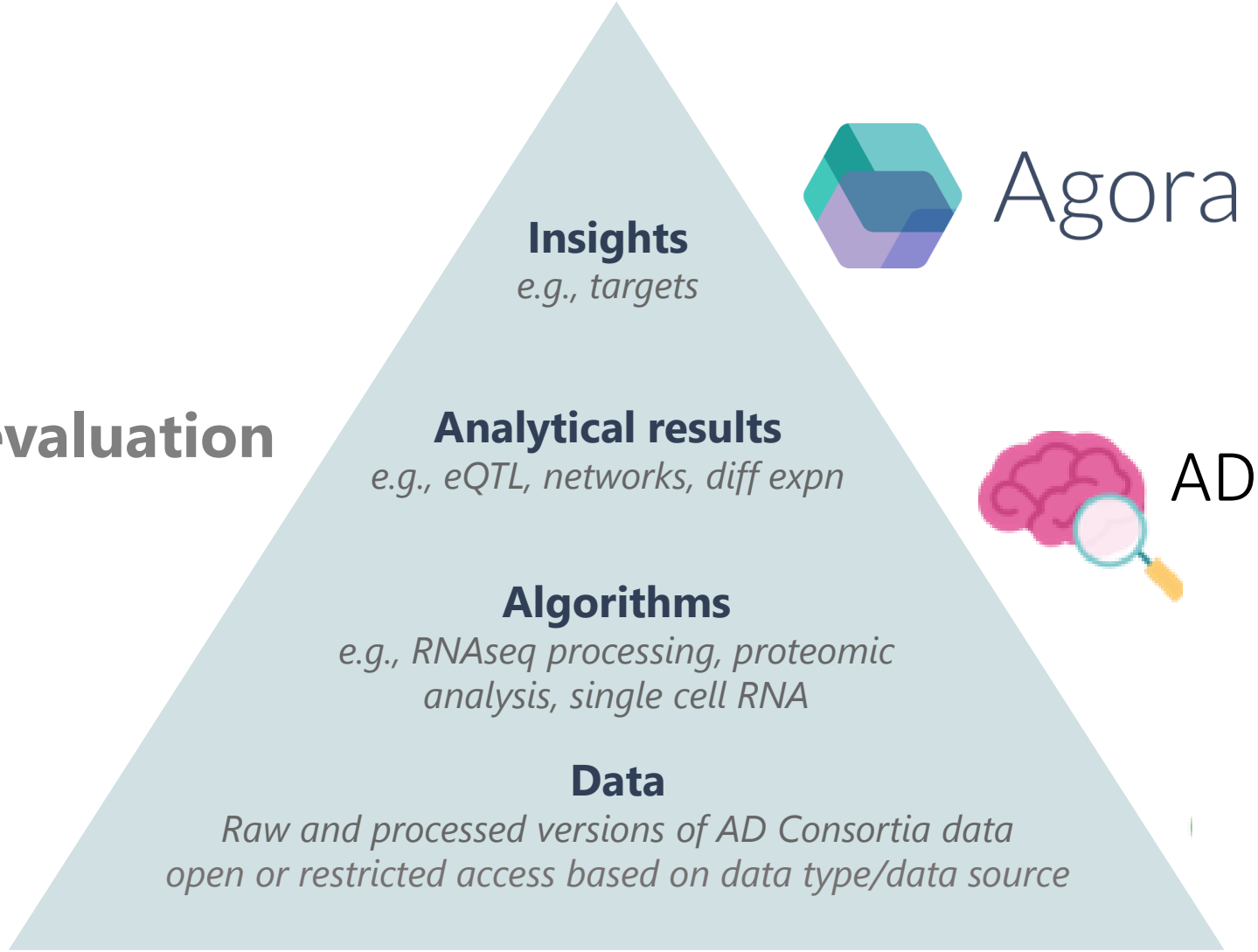
Academic-industry collaborations are strongly encouraged

Expectations for **rapid and broad sharing of data, analytical methods and research tools** prior to publication via the NIA-supported AD Knowledge Portal and/or other NIA/NIH designated data repositories

AD Knowledge Portal – an Open Science Discovery Engine

Launched - March 4, 2015

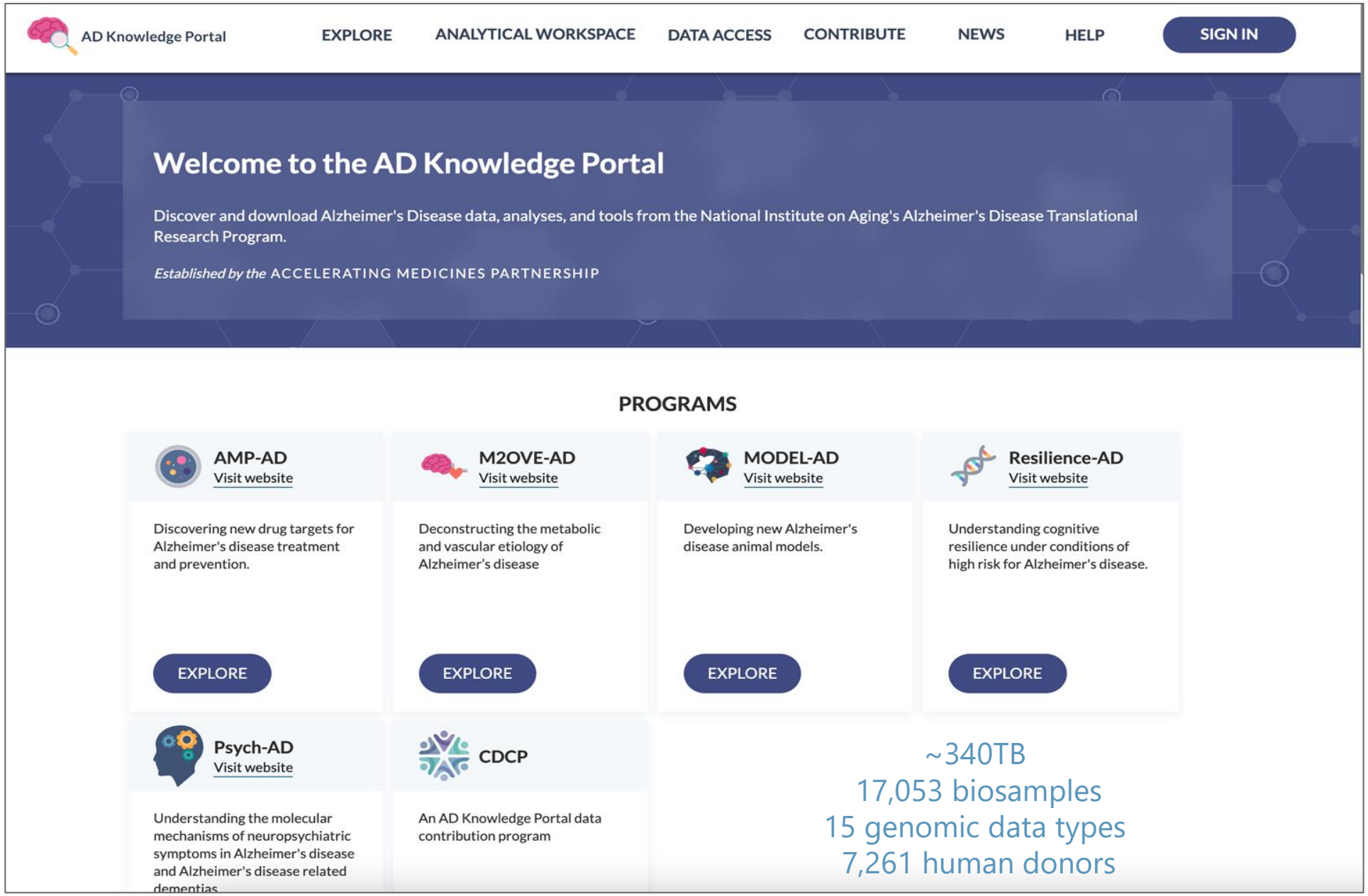
1. **Data Reuse**
2. **Transparency**
3. **Independent evaluation**
4. **Attribution**



Agora

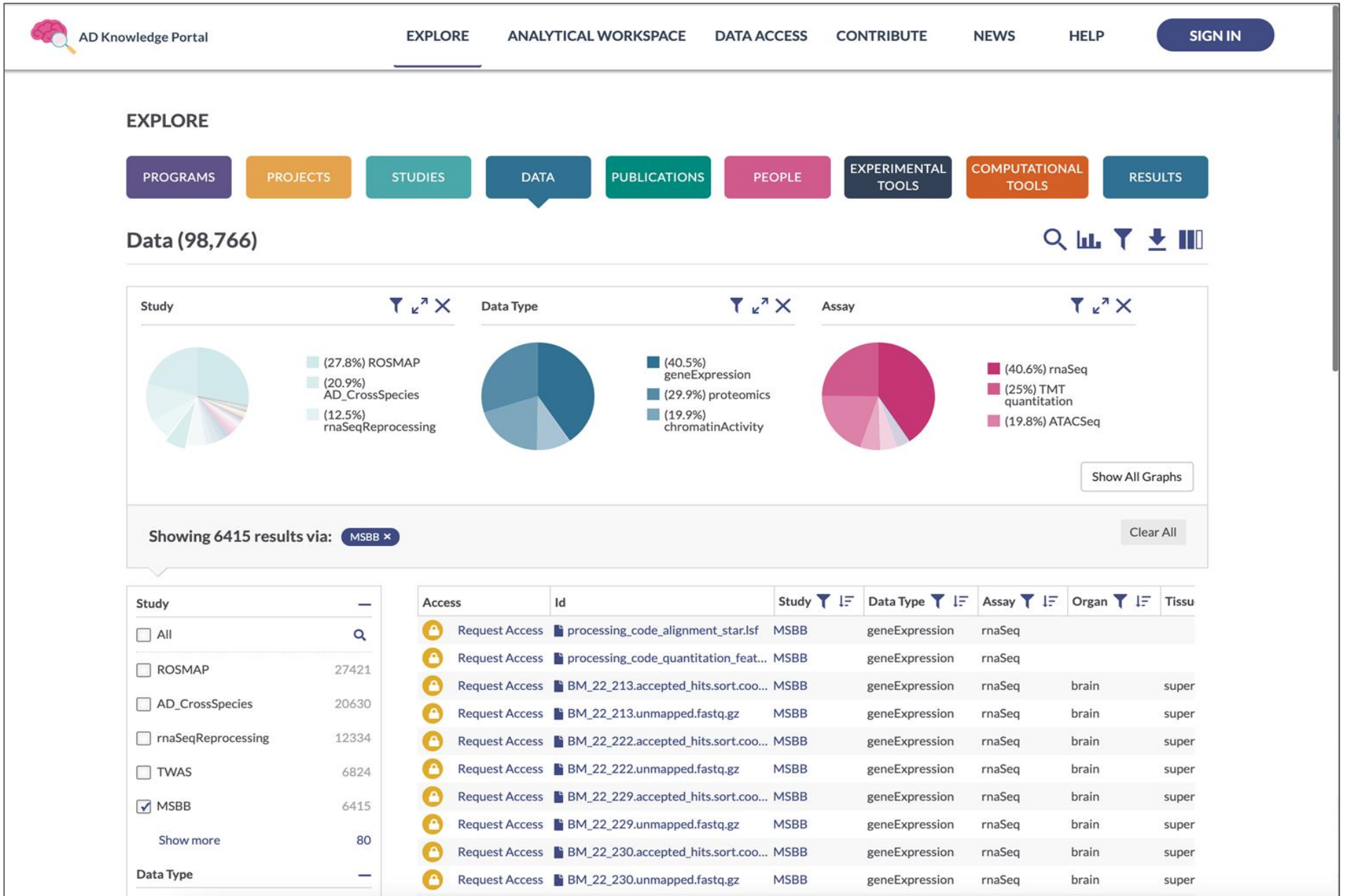
AD Knowledge Portal

SageBionetworks

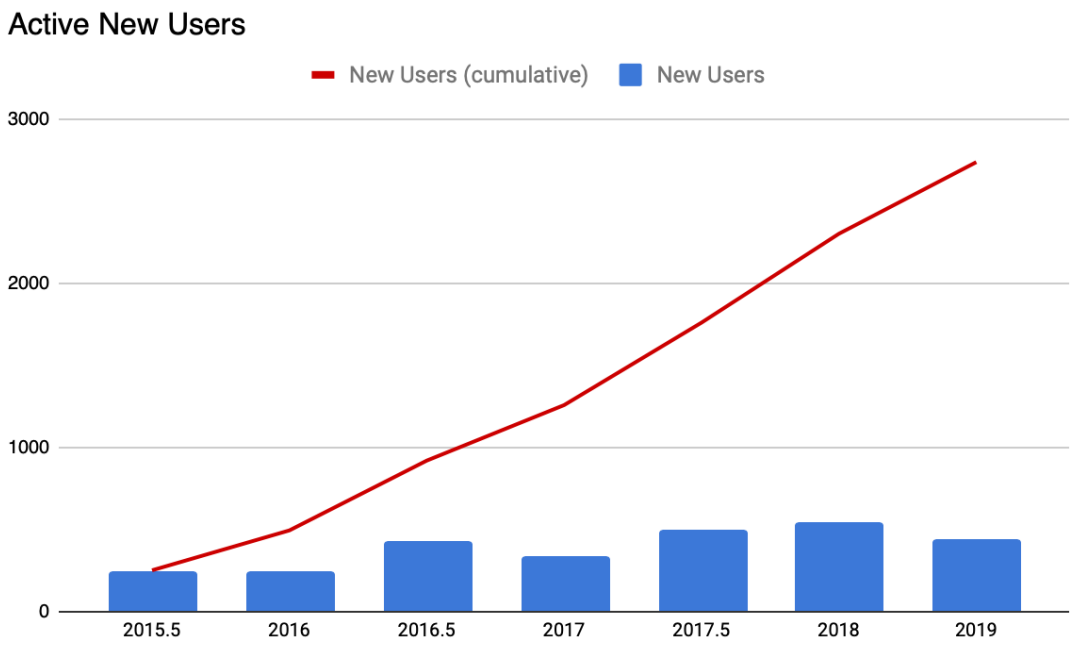


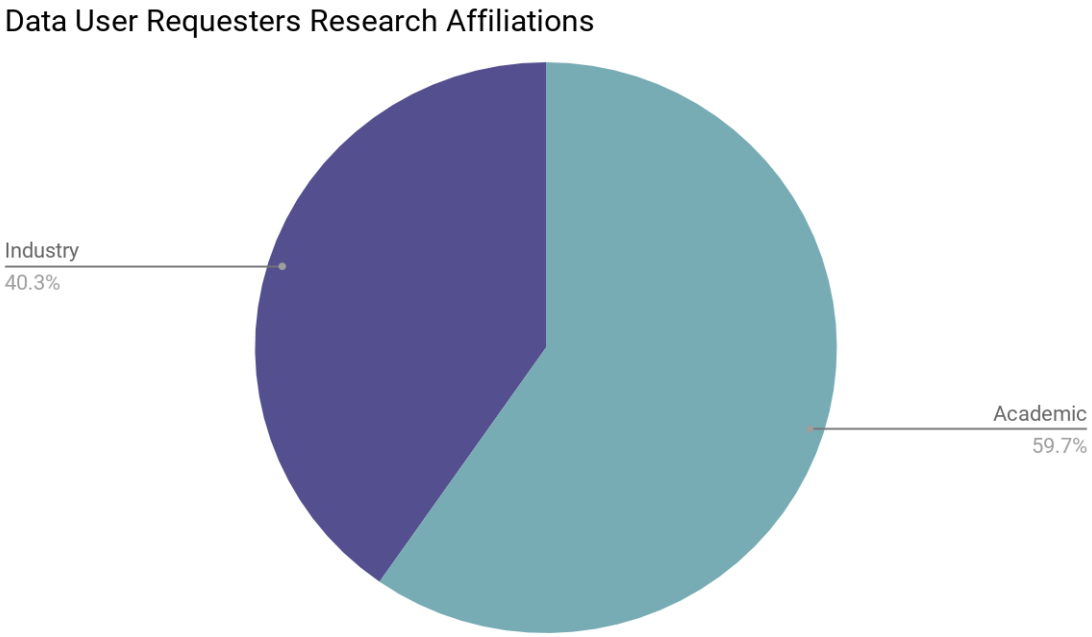
adknowledgeportal.org

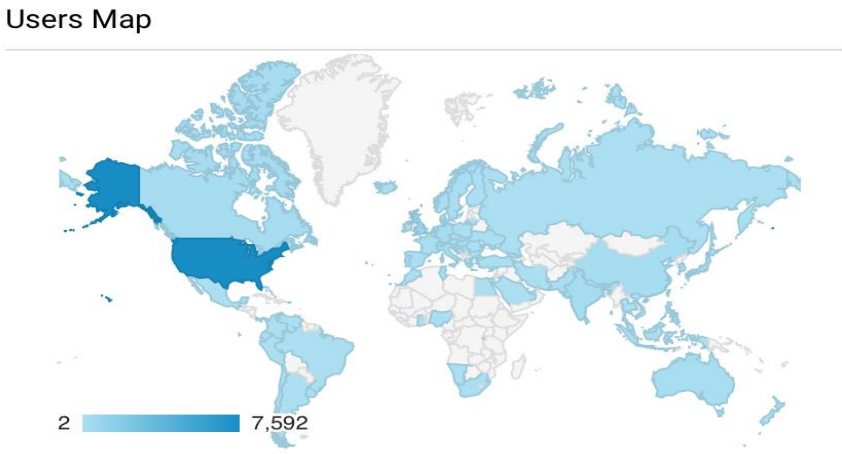
New search features to improve data discoverability



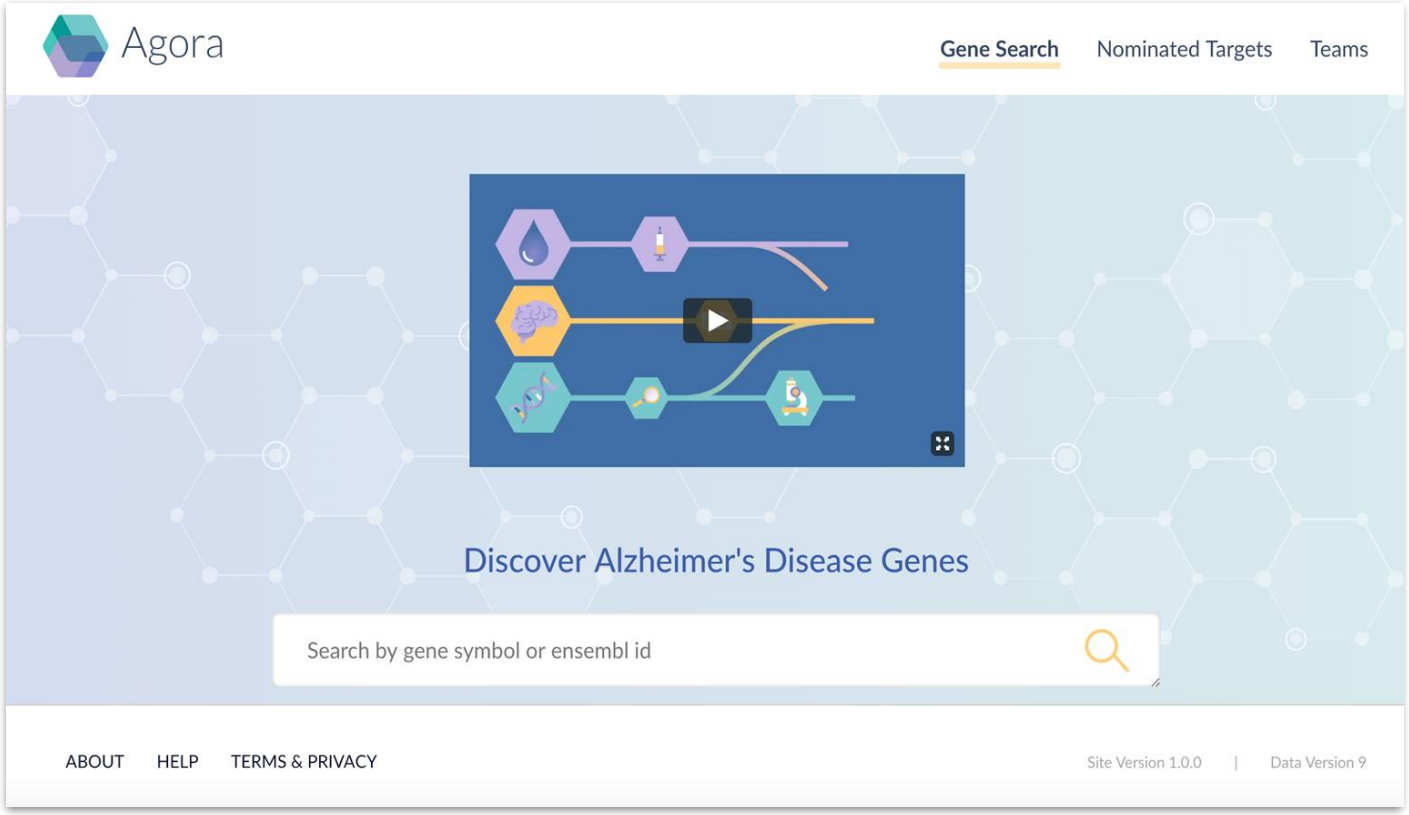
Use of AD Knowledge Portal Resources







Agora: Sharing Analytical Results and Insights



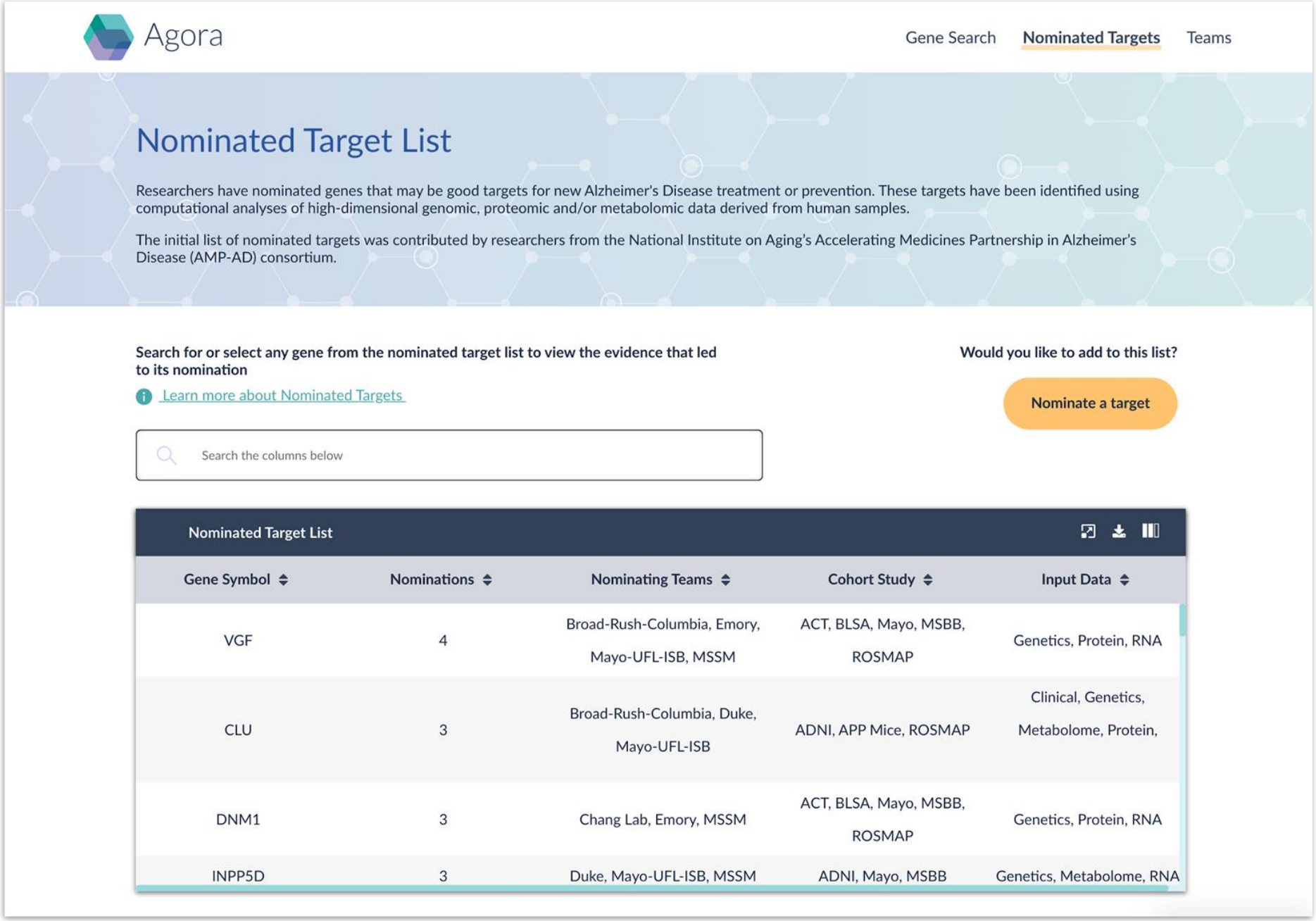
https://agora.ampadportal.org/

Open-source platform providing curated, AMP-AD verified, systems biology analyses for any gene of interest.

Enables researchers at large to discover and evaluate the evidence behind the AMP-AD nominated targets as well as to nominate new targets.

542 unique targets currently available, derived from unbiased, computational analyses of high-dimensional human omic data along with supporting evidence and extensive druggability information.

Building Confidence in Targets through Independent Converging Lines of Evidence



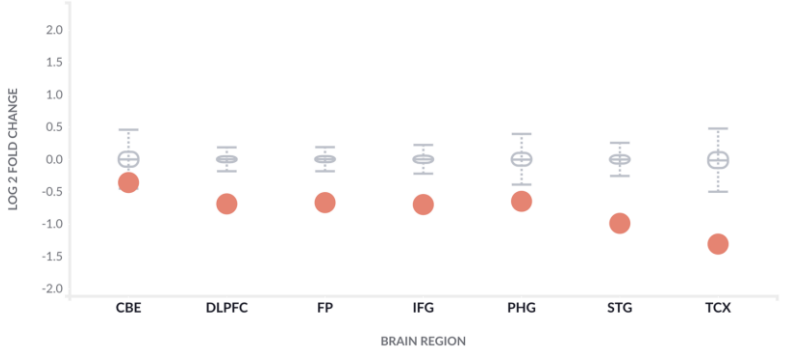
Agora Targets – Systems Biology Evidence

VGF

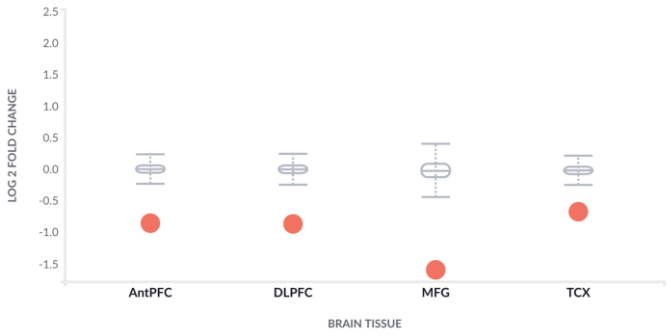
VGF nerve growth factor inducible

NOMINATION DETAILS | SUMMARY | **EVIDENCE** | DRUGGABILITY

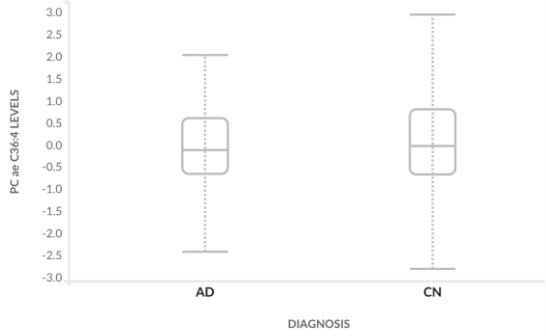
RNA

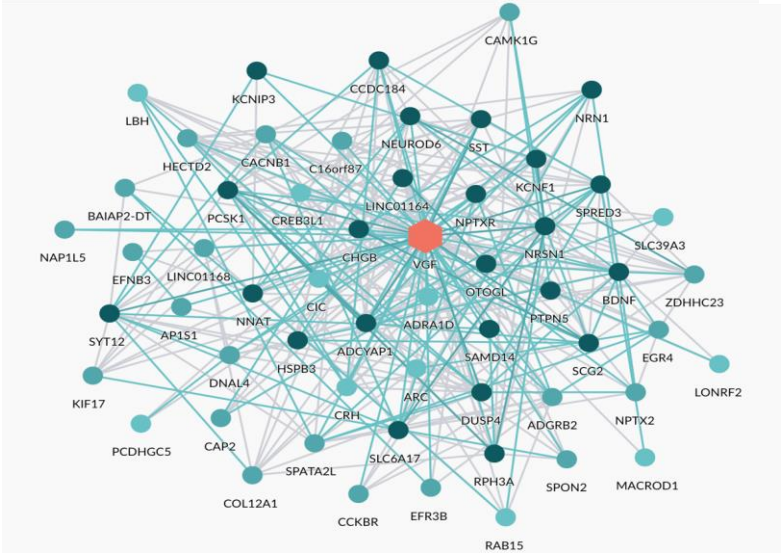


Protein



Metabolites





Druggability

Small Molecule Modality	13	Unknown: There is no information on ligands or structure in any of the categories above. +
Antibody Modality	1	Secreted protein. Highly accessible to antibody-based therapies. +
Safety	4	Probable safety risks requiring mitigation. More than two of: high off-target gene expression, cancer driver, essential gene, associated deleterious genetic disorder, HPO phenotype associated gene, or black box warning on clinically used drug. −

NIA Funding Initiative: AD Centers for Discovery of New Medicines (RFA-AG-19-010)

-Bringing Open Science to Drug Discovery-

GOAL: Diversify and accelerate therapy development for Alzheimer's through the development of open source tools, reagents and methods for robust validation of candidate targets delivered by AMP-AD and other target discovery programs, and by integrating enabled targets into drug discovery campaigns.

Two Centers, One Mission

U54AG065187

Alan Levey, Emory University
Lara Mangravite, Sage Bionetworks
Aled Edwards, Structural Genomics Consortium

U54AG065181

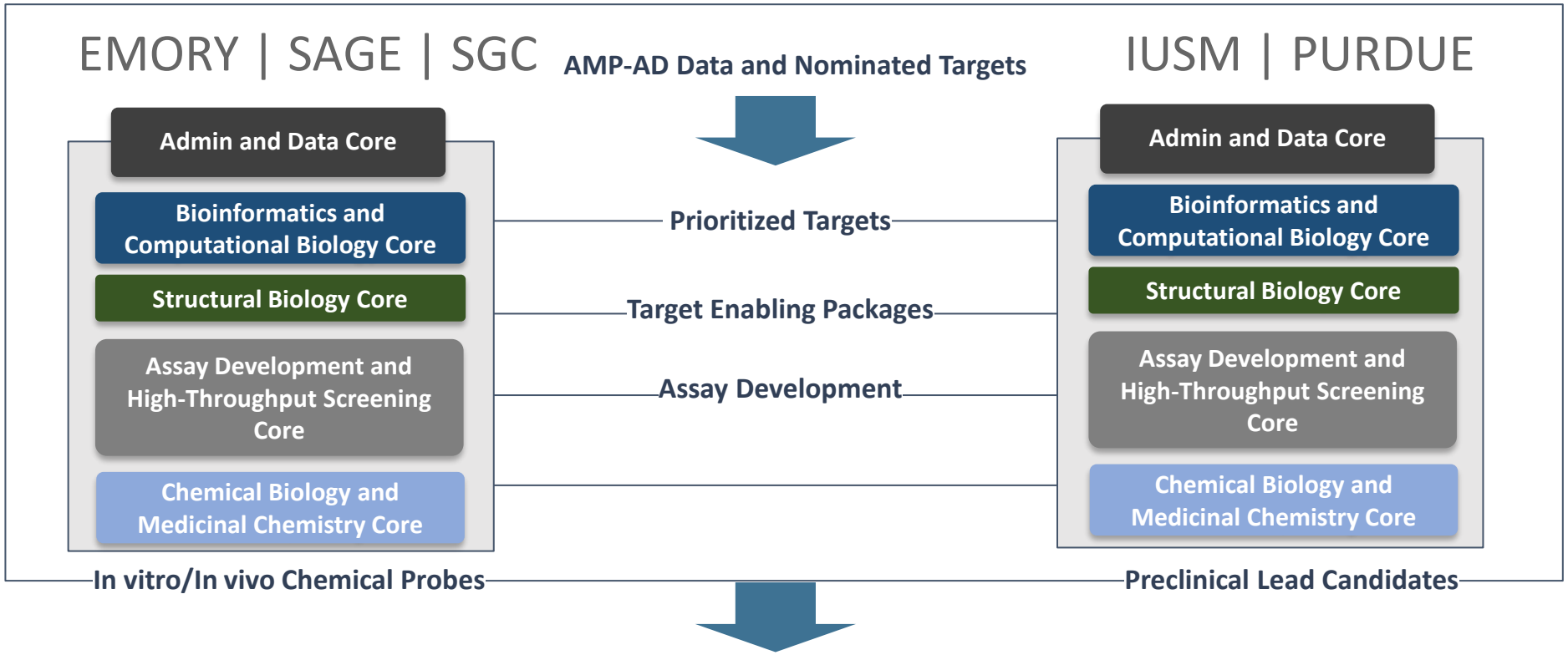
Alan Palkowitz and Bruce Lamb
Indiana University School of Medicine
Purdue University

TREAT-AD

Ta**R**get **E**nablement to **A**ccelerate **T**herapy Development for **AD**

TREAT-AD

TaRget Enablement to Accelerate Therapy Development for AD



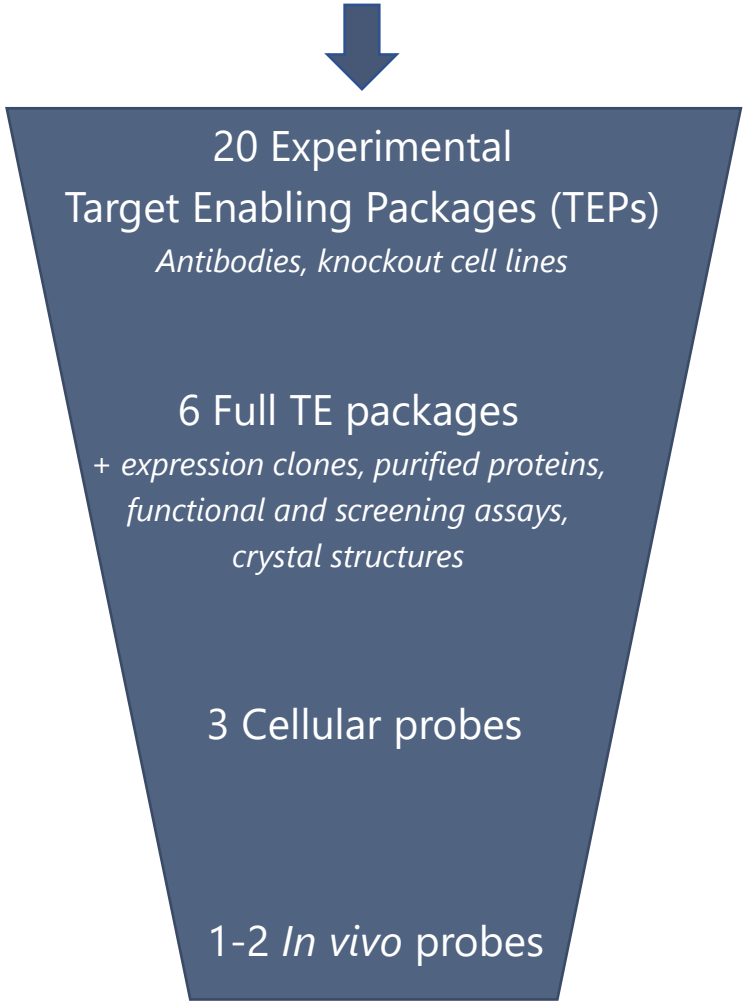
Open distribution of knowledge, data and target enabling tools

https://treatad.org

TREAT-AD
EMORY | SAGE | SGC

Open Source Target Enabling Tools

40 targets per year



Components of a TEP
1. Protein informatics
2. Verified Gene knockout and modifications tools
3. Sequence-characterized knockout cell lines.
4. Well-characterized antibodies for research
5. Expression clones for target proteins
6. Purified proteins and production methods
7. Assay protocols
8. Crystal or cryo-EM structures

Supporting the Study of Emerging Therapeutic Hypotheses

Initial Prioritized Targets for Drug Discovery

TREAT-AD
IUSM | PURDUE

INPP5D (SHIP1)

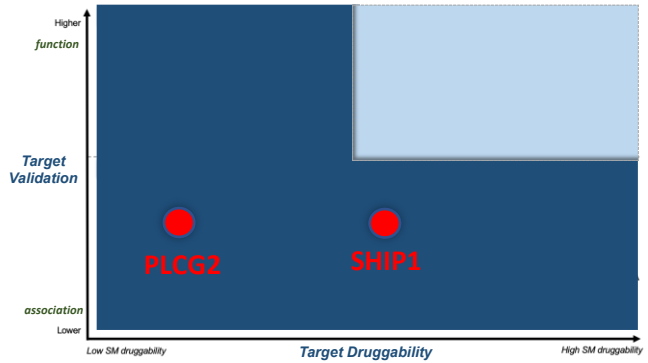
- **AMP-AD nominated target**
- AD risk gene preferentially expressed in lymphoid cells including microglia
- Negative modulator of TREM2 function
- MODEL-AD systems biology approach to evaluate and develop animal models for PK/PD and lead optimization
- Target class (phosphatase) druggability challenge

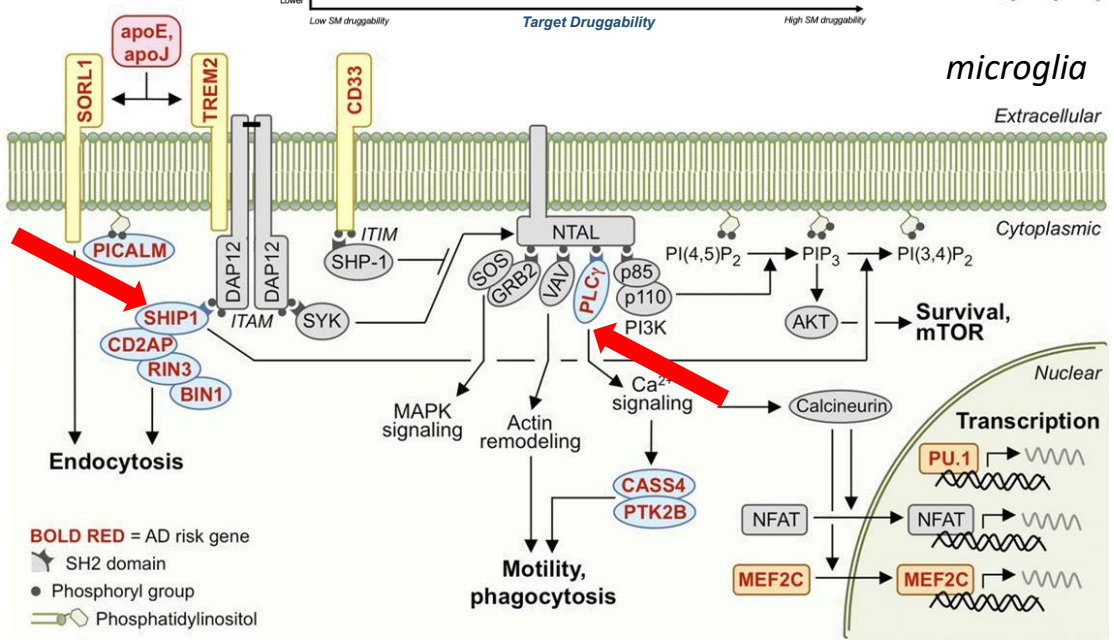
Phospholipase C gamma 2 (PLCG2)

- **AMP-AD nominated target**
- **MODEL-AD Animal Model characterization ongoing**
- Membrane associated signaling enzyme producing second messenger molecules: diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3)
- Implicated in B-cell activation and proliferation
- PLCG2 mRNA upregulated in cortical tissue of LOAD patients
- PLCG2 P522R variant is protective against AD
- No selective small molecule activators known

Guiding Principles for Target Selection/Prioritization

- AMP-AD/MODEL-AD nomination; review of supporting science
- Distribution of portfolio risk
- Opportunity for innovation
- Path to expand functional target validation
- Contributes to systematic study of neuroimmune signaling pathways
- Match to Center capabilities



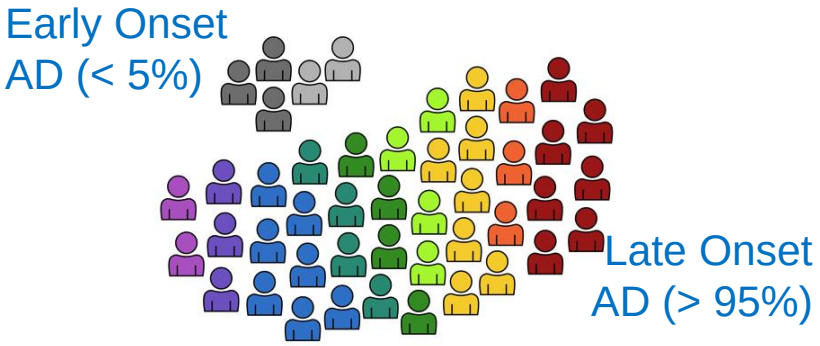


Hansen, D. V. et al. J Cell Biology 2017 DOI: 10.1083/jcb.201709069

https://model-ad.org

MODEL-AD

Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease



- Prioritize LOAD variants for animal modeling
- Create 50 new mouse models with CRISPR (piloting rat models)
- High-capacity screening of all models, deep phenotyping of the most promising models
- Align mouse and human phenotypes (neuropath, omics, imaging)
- Enable rigorous preclinical efficacy testing of promising candidate therapeutics
- **Provide broad, unrestricted distribution of all data and models for use in research and therapy development** (https://www.model-ad.org/strain-table).

RFA-AG16-014

U54 AG054345
Bruce Lamb, IUSM

U54 AG054349
Frank LaFerla, UCI
Andrea Tenner, UCI

Bioinformatics and Data Management Core (BDMC)

Disease Modeling Project (DMP)

Preclinical Testing Core (PTC)

Indiana University

The Jackson Laboratory

Sage BIONETWORKS

U Pitt

UCI University of California, Irvine

Largely focused on Early Onset AD vs Late Onset AD

Are mice an appropriate species?

Models do not develop robust neurodegeneration

Toxic effects of overexpression of transgenes

Legal restrictions for most models

Difficulties in relating behavioral deficits observed in mouse models to human AD

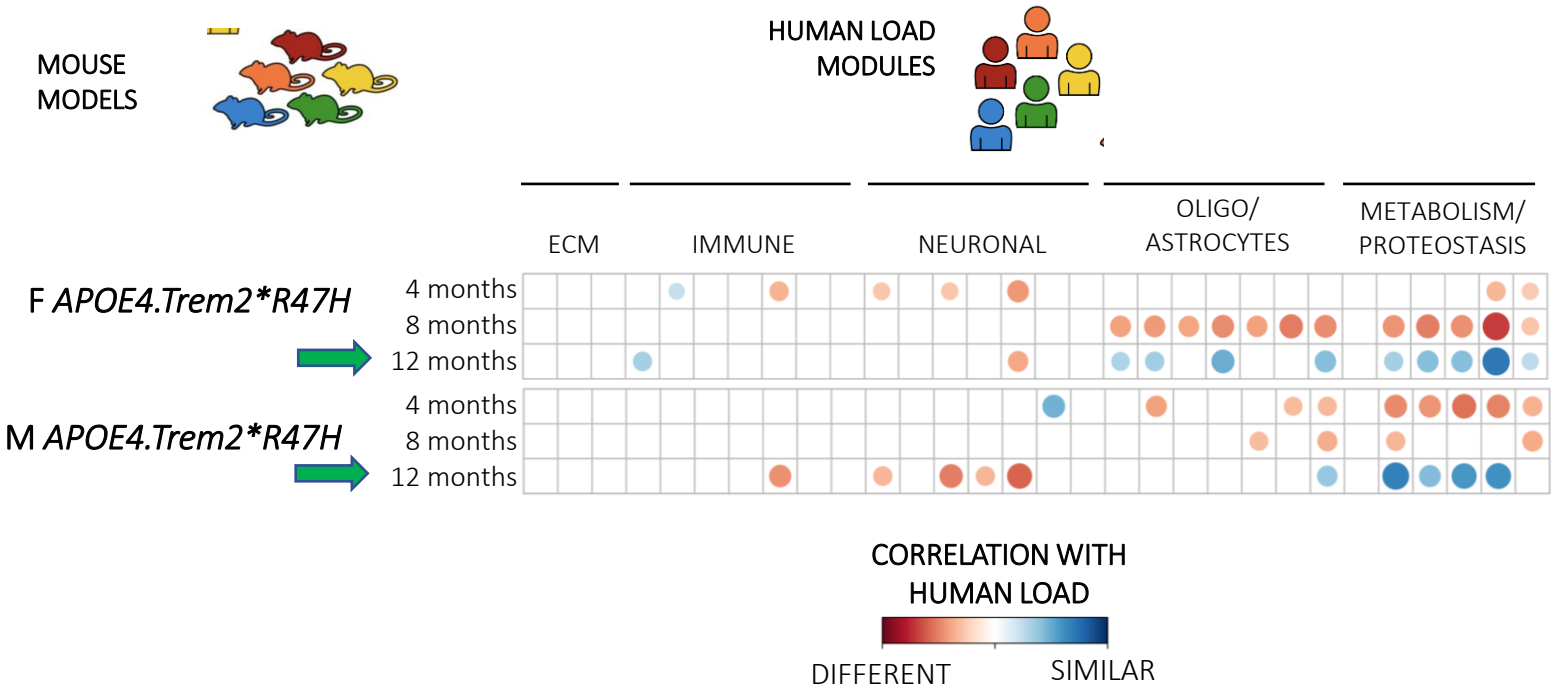
Poor alignment of model pathophysiology with corresponding stages of clinical disease.

Lack of translatable biomarkers.

Poor rigor and reproducibility of efficacy testing in mouse models

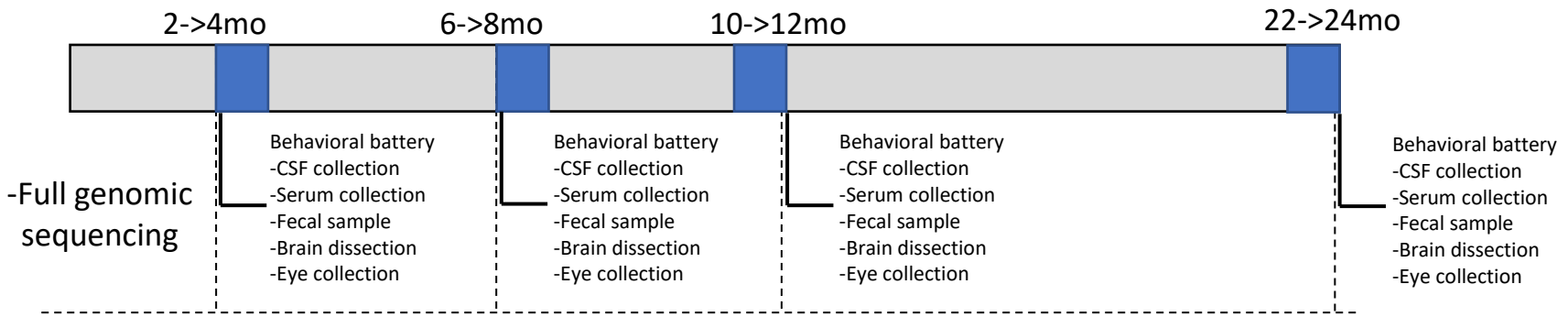
LOAD 2 MICE (*APOE4.Trem2*R47H)*

Transcriptome Alignment with LOAD AMP-AD Modules



Transition of mouse modules from red-to-blue indicates higher correlation with human LOAD transcriptomes

Deep Phenotyping of Prioritized Strains



12M/12F per genotype at each time point

Aspects of deep phenotyping are conducted at IU, JAX and UCI for reproducibility

Metabolic:
Weight
Total Cholesterol, LDL, HDL
Triglycerides and Non-essential Fatty Acids
Glucose

Behavioral Battery:
Aging: Frailty index
Circadian Activity: Homecage wheel running
Exploratory and locomotor behavior: Open field
Cognition: Spontaneous Alternation
Motor Coordination: Rotarod
Neurophysiology: EEG

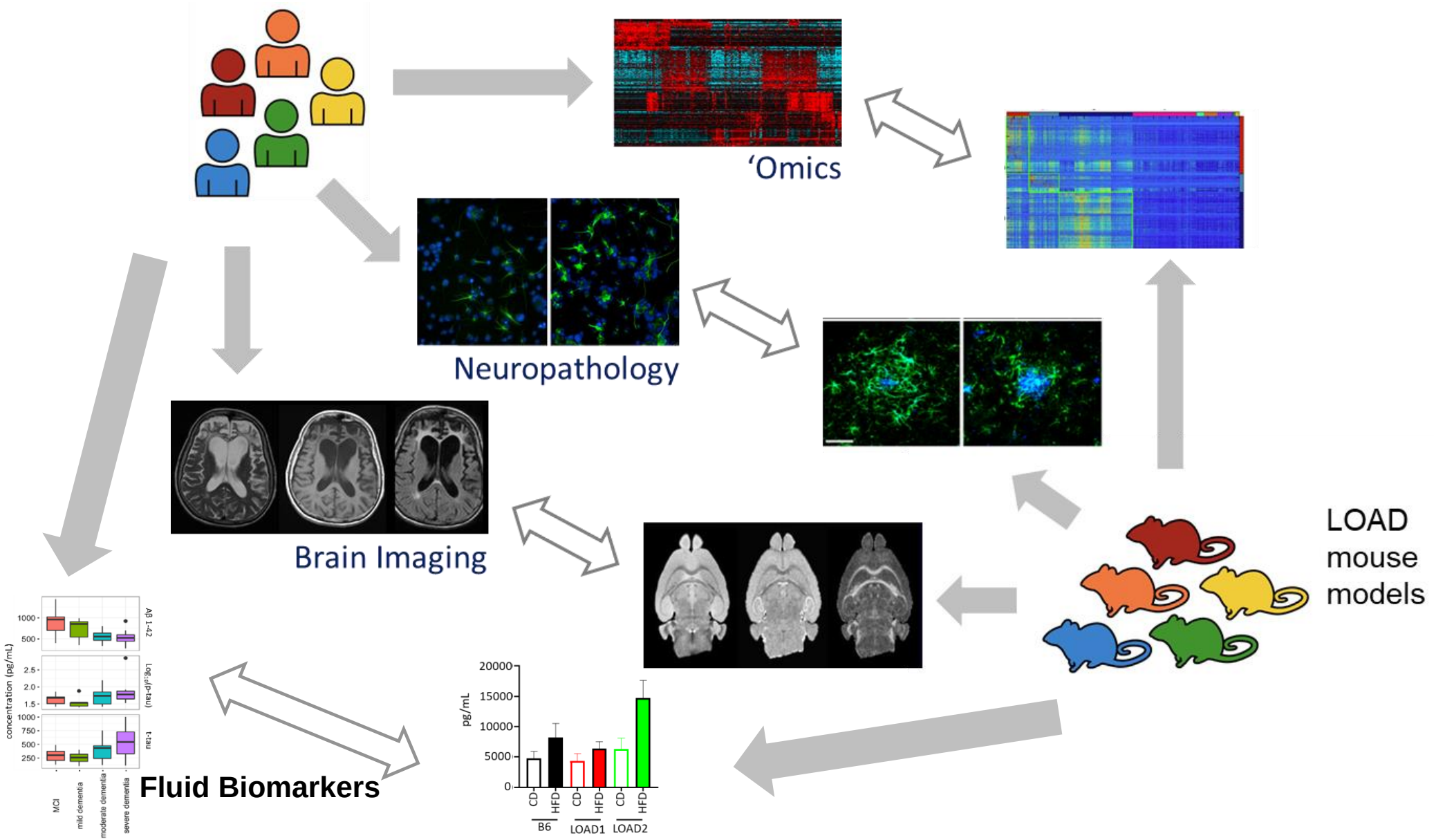
-Omics analyses
RNA-seq
Proteomics
Metabolomics
Microbiome

PET/MR imaging
Amyloid: AV45
Tau: AV1451
Blood flow: PTSM
Glucose metabolism: FDG

Biomarkers in Tissue/CSF/Blood:
Neurogranin
NF-L
Aβ
Tau

Neuropathology
Brain morphology: LFB/CV
Neurons: NeuN/Ctip2
Amyloid/microglia:X34/22C11/IBA1
Tau: AT8/H&E
Astrocyte/microglia: GFAP/IBA1
Vascular/microglia: CD31/Fibrin/IBA1

Aligning human and mouse phenotypes



Currently Available Models

Base models

Allelic Series of APOE

1. *APOE4*
2. *APOE3*
3. *APOE2*

Allelic Series of TREM2

1. *Trem2*R47H*
2. *Trem2*R47H.HSS*
3. *Trem2*Y38C*
4. *Trem2* KO
5. Floxed *Trem2*

APP and MAPT

1. *hAβ*
2. *App* KO
3. *MAPT(H2)*-GR (Koob)

LOAD models

1. *APOE4/Trem2*R47H*
2. *APOE4/Trem2*R47H/hAβ*
3. *APOE4/Trem2*R47H/hAβ/MAPT(H2)*-GF

**APOE4/hAb* and *APOE3/hAb* also available

Coding variants

1. *Abca7*A1527G*
2. *Clasp2*L163P*
3. *Erc2*N542S*
4. *Il34*Y213**
5. *Kif21b*T82T*
6. *Mthfr*C677T*
7. *Mtmr4*V297G*
8. *Picalm*H465R*
9. *Pilra*G85R*
10. *Plcg2*M28L*
11. *Plcg2*P522R*
12. *Ptprb*D57N*
13. *Shc2*V433M*
14. *Slc6a17*P61P*
15. *Snx1*D465N*
16. *Sorl1*A528T*

Knockouts (to model LOF alleles)

1. *Abca7*
2. *Ceacam1*
3. *Il1rap*
4. *Meox2* (as HET)
5. *Plcg2*

Humanized loci

- *hCR1* (KI)

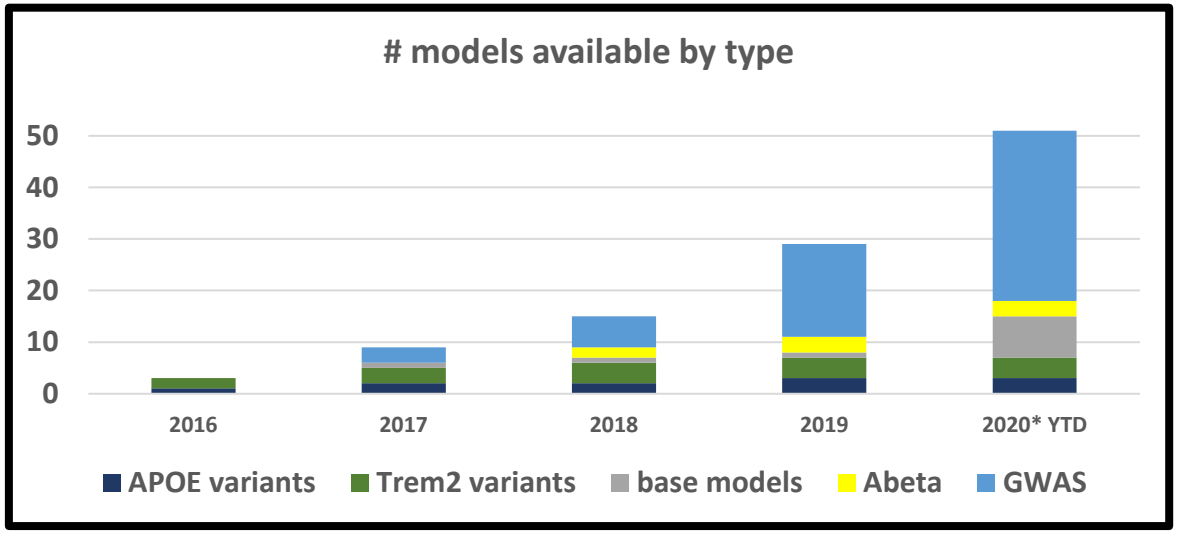
Non-coding variants

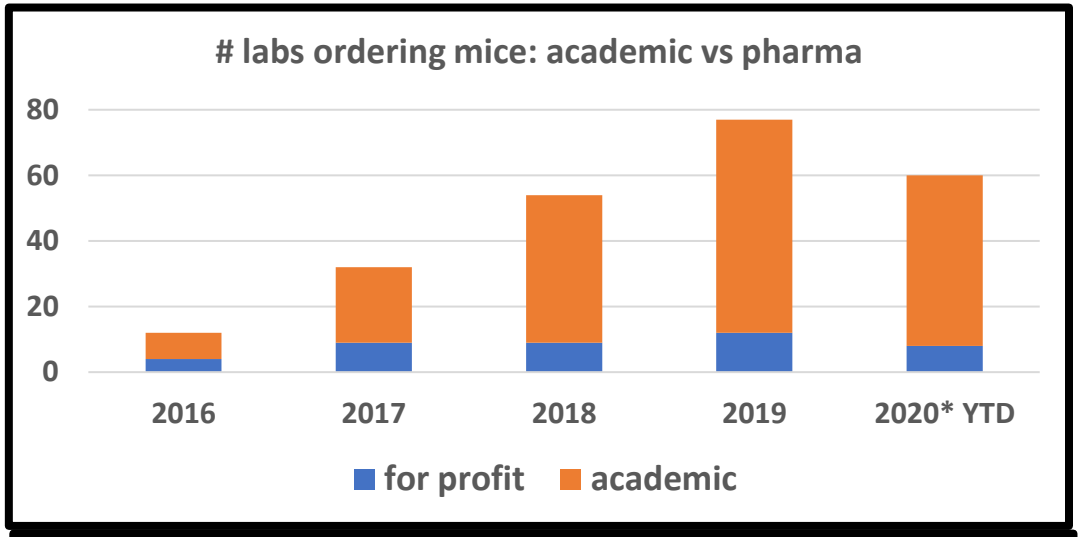
1. Adamts4 enhancer KO
2. Bin1 intron SNP
3. Cd2ap promoter SNP
4. Epha1 exon 1 SNP
5. Ptk2b intron SNP
6. Scimp upstream SNP

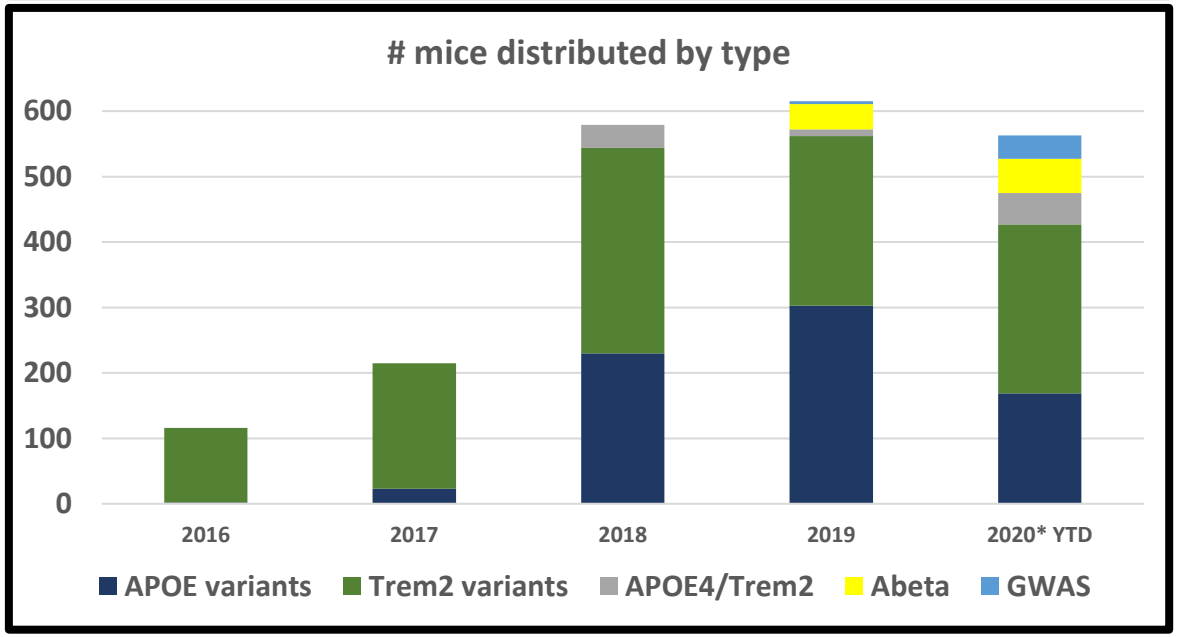
https://www.model-ad.org/strain-table/

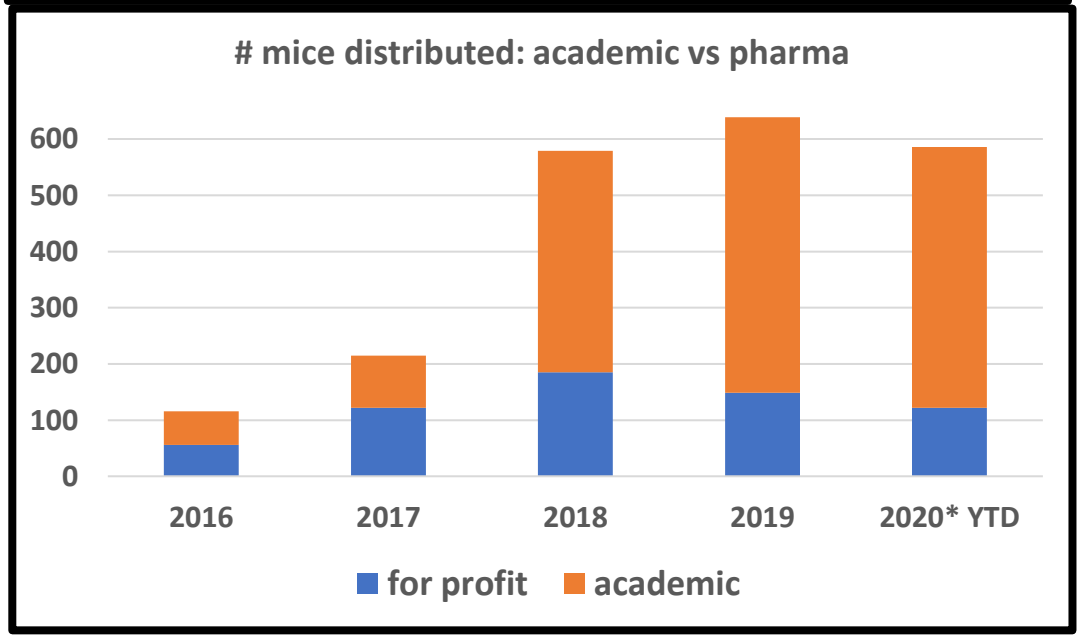
Models Available and Distributed

**2020 metrics as of September 1*





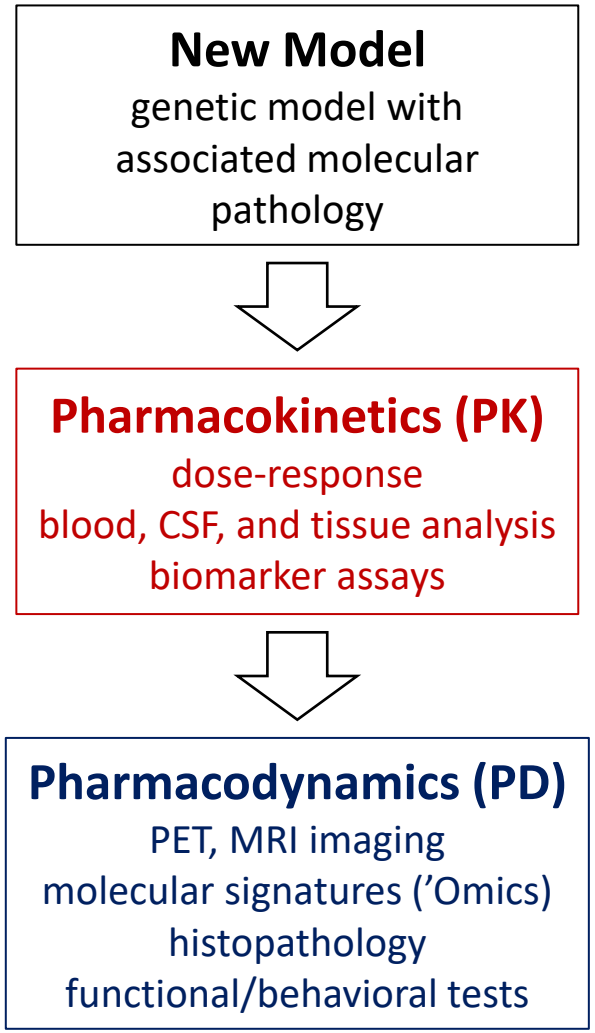




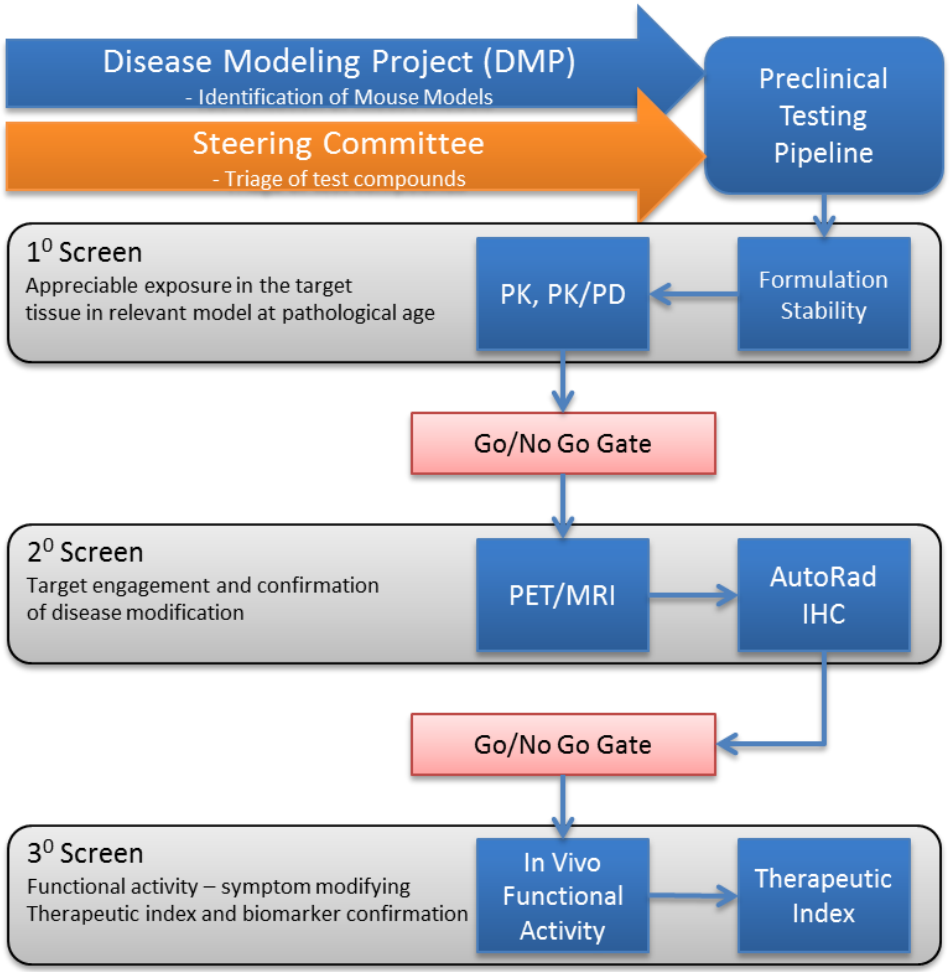
Principle Investigators: Stacey Rizzo, U Pitt and Paul Territo, IU

MODEL-AD Preclinical Testing Core

- ❑ Develop a pipeline for rigorous and standardized preclinical efficacy testing.
- ❑ Pair promising compounds with the most appropriate LOAD models.
- ❑ Make all data, methods and analyses available.



MODEL-AD PTC: Preclinical Testing Pipeline



ARRIVE: Highlights

Model Systems

- Construct validity of models
- Face validity of models

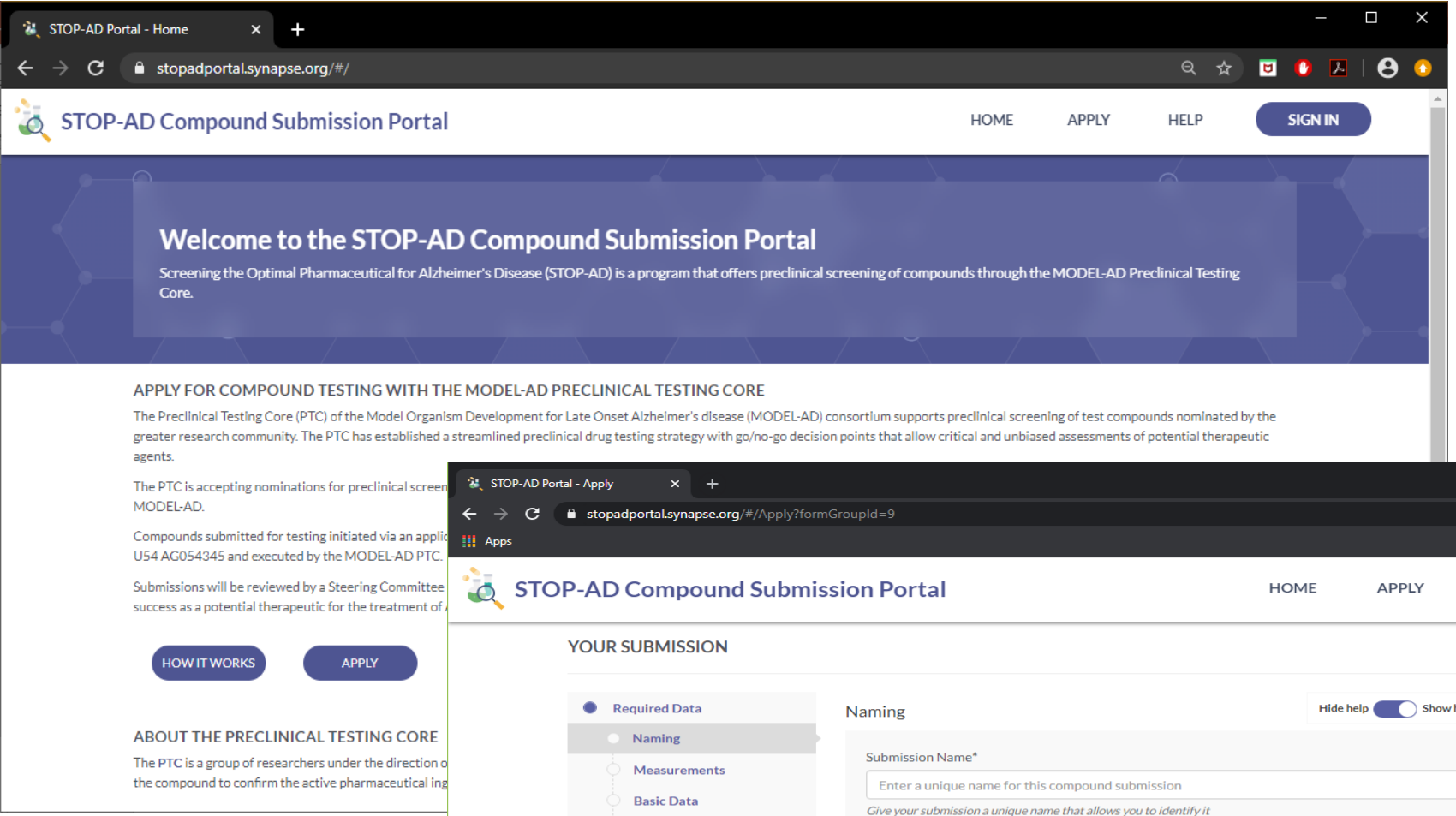
Animal Care

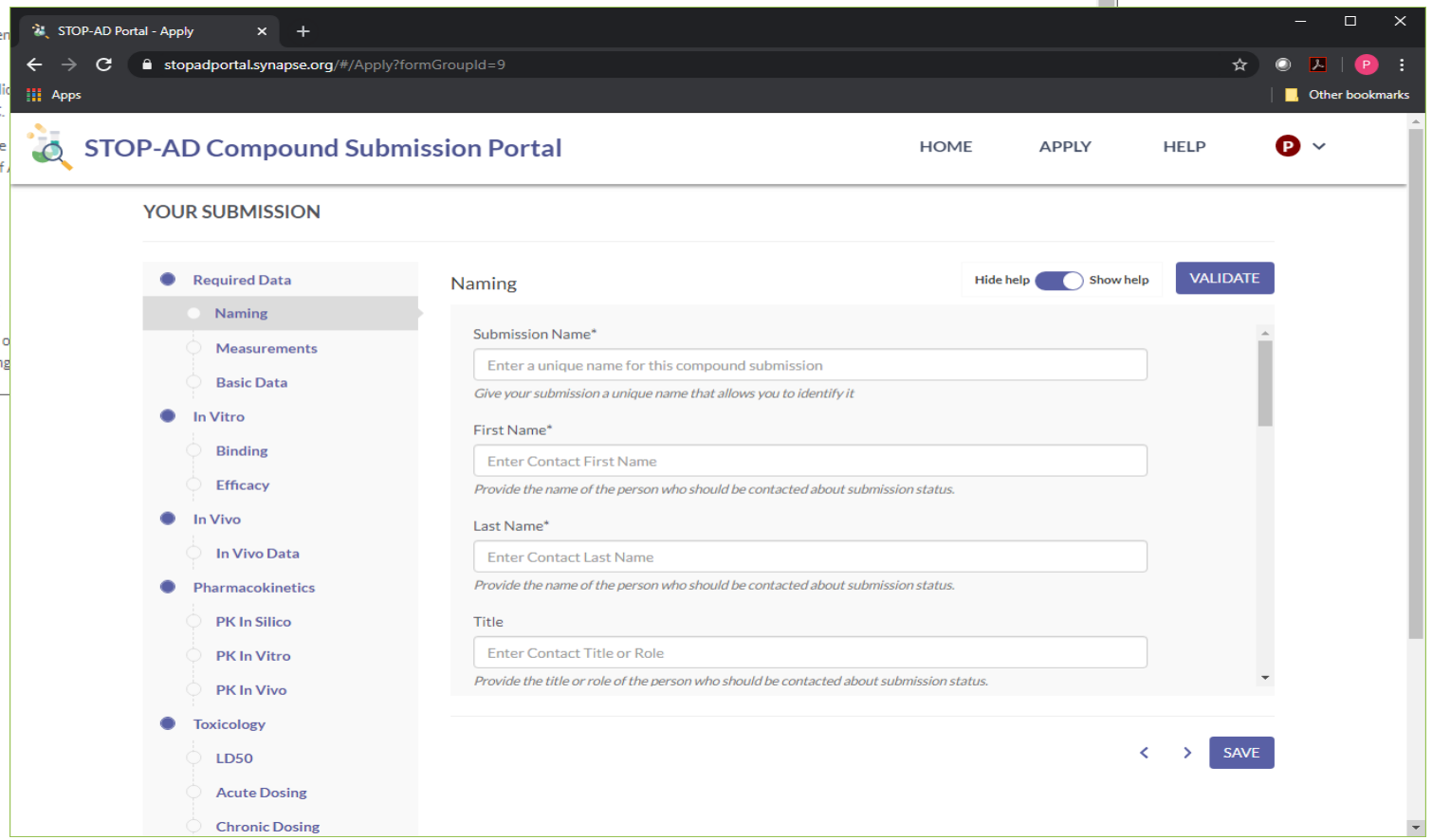
- Housing conditions (single vs. multiple)
- Husbandry (food, water, lighting, bedding)

Study Conduct

- Subject randomization/allocation
- Blinding of study personnel (techs, PI)
- Counter balancing for groups, sex, age
- Sample sizes yielding well powered studies (n=10-12 per sex per dose level per tracer)
- Inclusion/Exclusion criteria

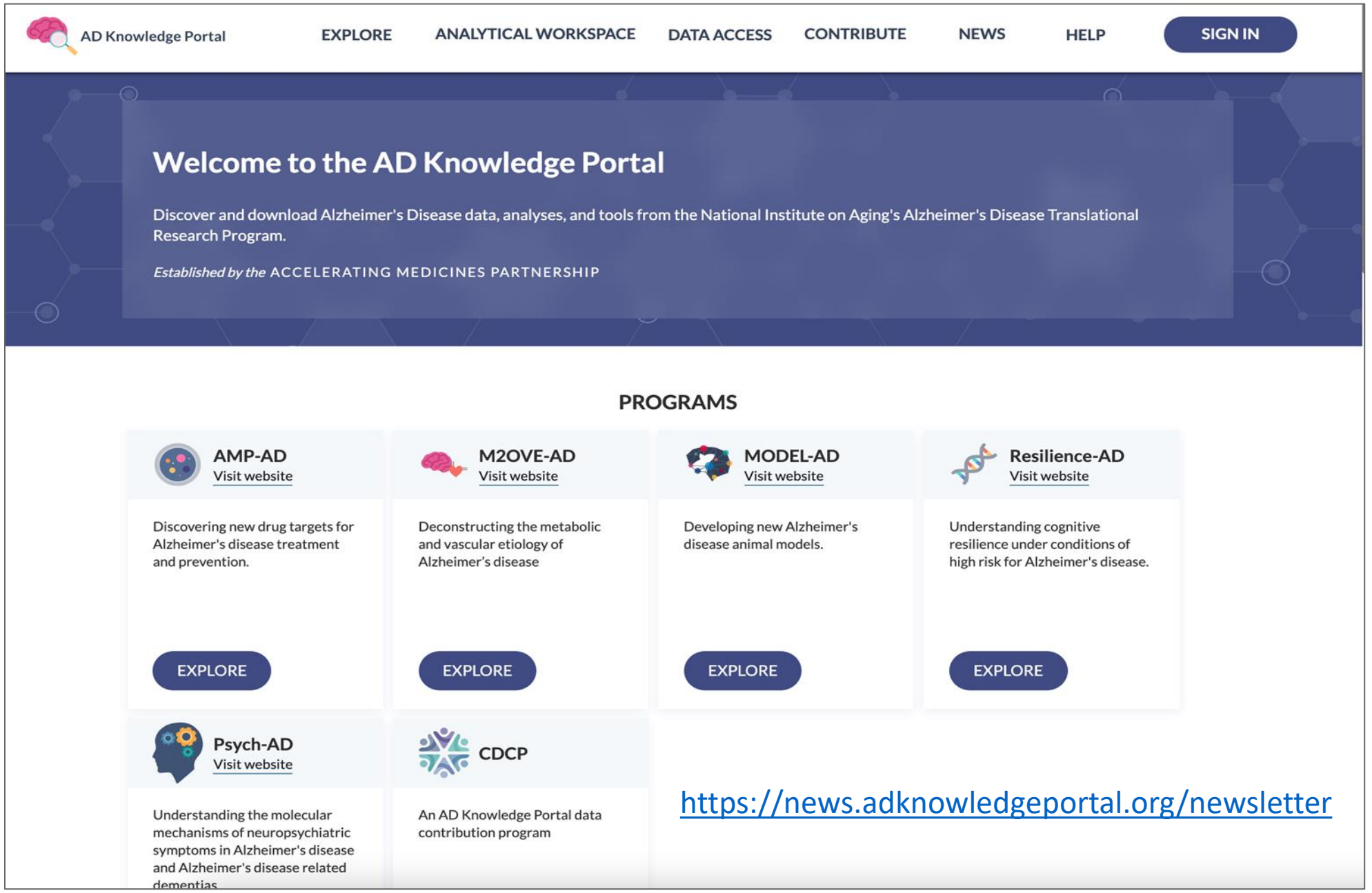
MODEL-AD Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease · INDIANA UNIVERSITY · The Jackson Laboratory Leading the search for tomorrow's cures · UCI University of California, Irvine · University of Pittsburgh · SageBionetworks





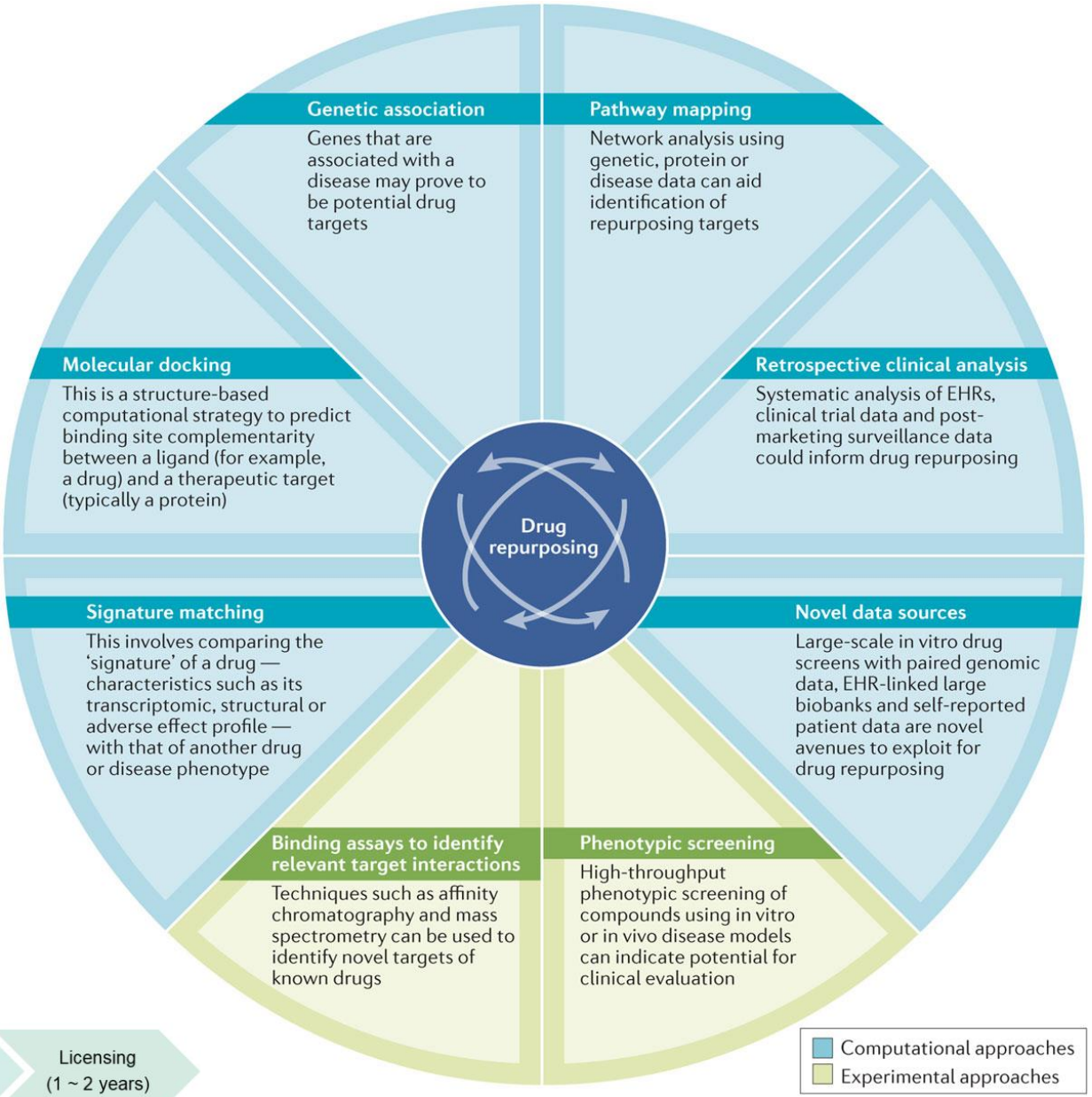
STOP-AD Web Portal

- Required Data
- *In Vitro* Data
- *In Vivo* Data
- Pharmacokinetics
- Pharmacodynamics
- Toxicology
- Clinical Data

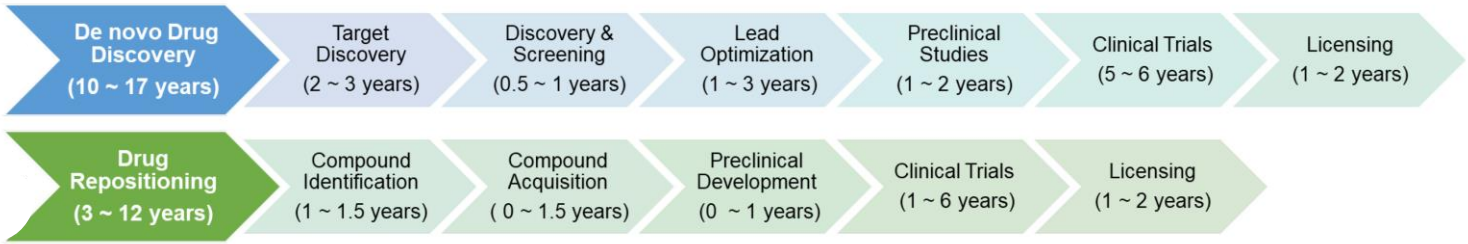


adknowledgeportal.org

Accelerating Therapy Development through Drug Repurposing/Drug Repositioning



Novel uses for existing and failed drugs can save time and cost in bringing new therapeutics to patients.



PAR-20-156 Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease (R01 Clinical Trial Optional)

This funding initiative encourages the use of existing and/or the development of novel computational approaches to identify drugs currently used for other conditions, as well as candidate drugs from failed Phase II/Phase III clinical trials, with potential to be efficacious in AD/ADRD as individual drugs, or as drug combinations.

Launched in 2017 as PAR-17-032; re-issued as PAR-20-156

Active through: May 08, 2023

Program Director: Jean Yuan, MD, PhD
xin.yuan@nih.gov

PAR-20-156 Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease (R01 Clinical Trial Optional)

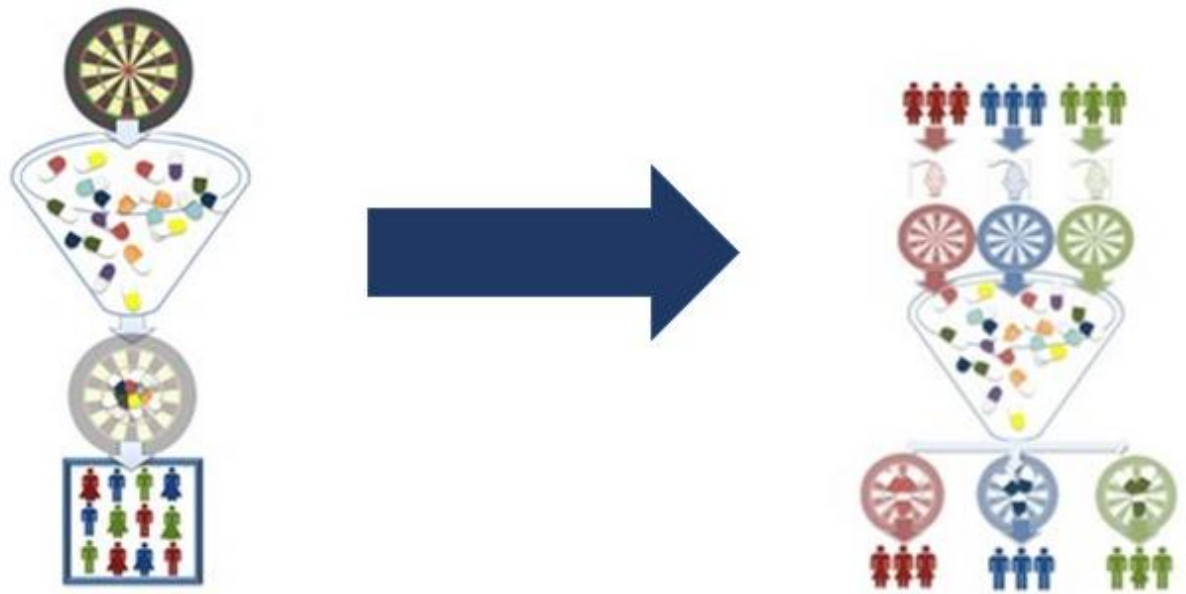
- ❑ Purely computational research aimed at using existing or new methodology to identify drugs or drug combinations with favorable efficacy and toxicity profiles as candidates for repositioning.
- ❑ Research that combines computational and experimental approaches to generate data-driven predictions on the efficacy of repurposed drugs or drug combinations, followed by efficacy testing in proof-of-principle animal studies or in proof-of-principle human trials
- ❑ Development of quantitative, mechanistic methods that can assess the synergy of candidate therapeutics, including synergy between candidate drugs and non-pharmacological perturbations (i.e., diet, sleep, cognitive training).
- ❑ **Integration of clinical and phenotypic data with molecular data generated with biosamples from failed AD/ADRD trials, to identify the molecular determinants of responder phenotypes. (academic-industry collaborations)**

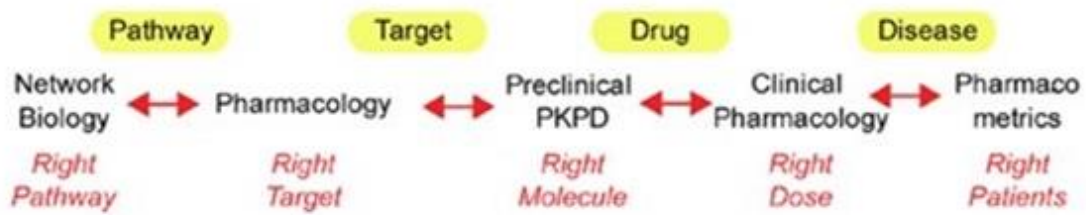
PAR-17-032 Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease (R01)

Funded Projects:

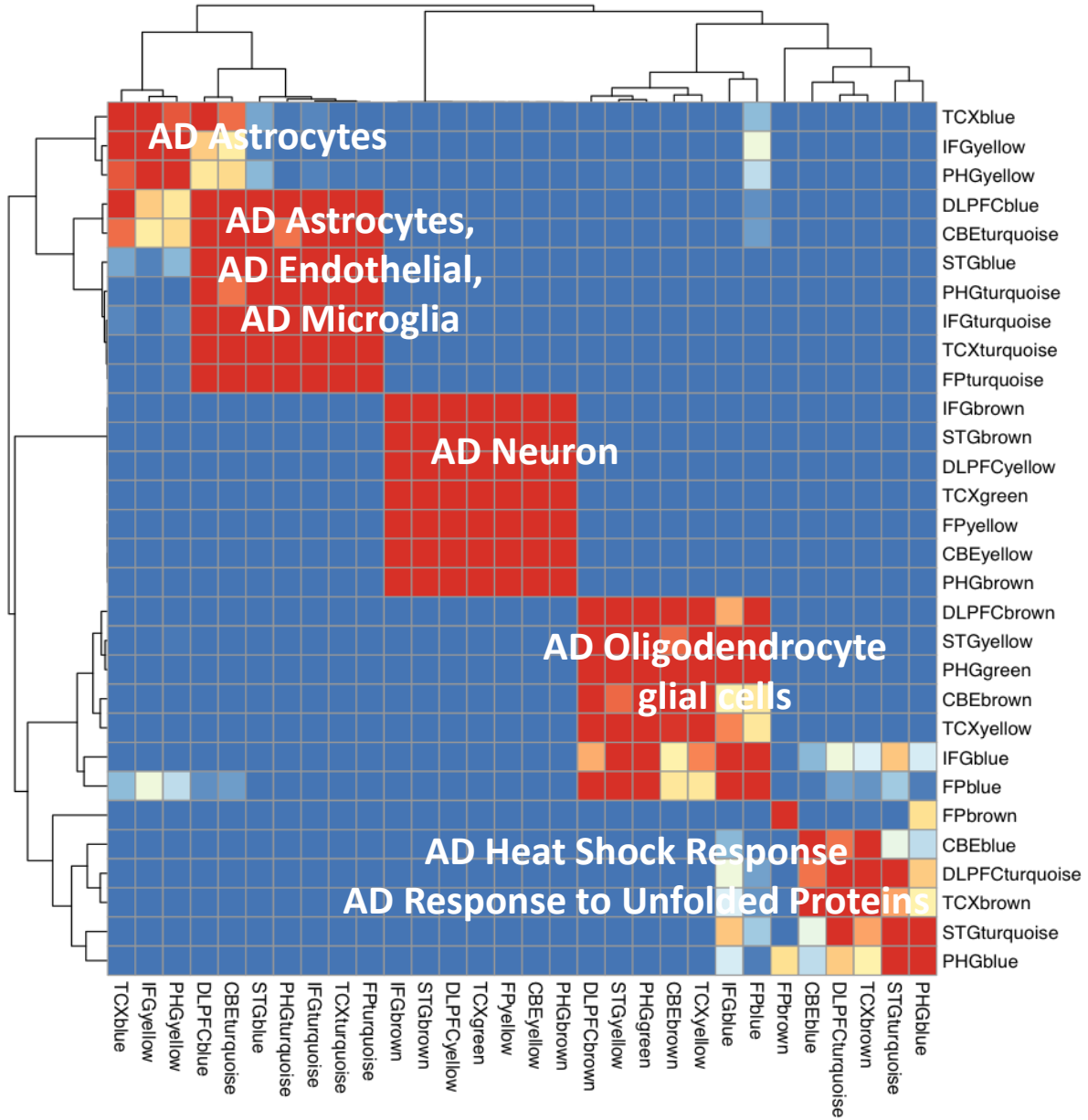
	R01AG066707	CHENG, FEIXIONG	Endophenotype Network-based Approaches to Prediction and Population-based Validation of in Silico Drug Repurposing for Alzheimer's Disease
	R01AG066749	JIANG, XIAOQIAN (contact	Finding combinatorial drug repositioning therapy for Alzheimers disease and related dementias
	R01AG066750	SU, ANDREW I	Compound repositioning for Alzheimer's Disease using knowledge graphs, insurance claims data, and gene expression complementarity
	R01AG068030	ZHANG, BIN (contact)	Novel Network Biology Approaches to Reposition FDA-approved Drugs for Alzheimers Disease
	R56AG061163	CHEN, CHI-HUA	Omic analyses for stratifying Alzheimers subtypes and identifying novel drug targets
	R56AG065352	LI, FUHAI	Combine Genomics and Symptoms Data Driven Models to Discover Synergistic Combinatory Therapies for Alzheimers Disease
	RF1AG059319	GANDY, SAMUEL E (contact);	SYSTEMATIC DRUG REPURPOSING TARGETING IMMUNE ACTIVATION NETWORKS IN ALZHEIMERS DISEASE (AD)
	RF1AG063913	XIA, WEIMING (contact);	Big data and small molecules for Alzheimers disease
	R01AG057555	XIE, LEI	Drug repurposing for Alzheimers disease using structural systems pharmacology.
	R01AG057557	XU, RONG	An Integrated Reverse Engineering Approach Toward Rapid Drug Repositioning for Alzheimer's Disease
	R01AG057635	WONG, STEPHEN TC	Systematic Alzheimers disease drug repositioning (SMART) based on bioinformatics-guided phenotype screening and image-omics
	R01AG057683	HUANG, YADONG (contact); SIROTA, MARINA	ApoE Genotype-Directed Drug Repositioning and Combination Therapy for Alzheimer's Disease
	R01AG058063	ALBERS, MARK W (contact); SORGER, PETER	Harnessing Diverse BioInformatic Approaches to Repurpose Drugs for Alzheimers Disease
	R01AG059854	TEICH, ANDREW FRANKLIN	A Translational Bioinformatics Approach to Rescuing Synaptic and Neurophysiologic Dysfunction in Alzheimers Disease
	R01AG061105	LICHTARGE, OLIVIER	A knowledge map to find Alzheimers disease drugs
	R01AG062547	TANZI, RUDOLPH EMILE (contact)	The Alzheimers Disease Resiliome: Pathway Analysis and Drug Discovery.
	R01AG061911	WAHLESTEDT, CLAES ROBERT (contact)	Leveraging the Human Non-Coding Transcriptome to Identify Therapeutics for Healthy Aging and Alzheimers Disease
	R01AG062620	CHANG, RUI (contact)	Predictive Networks-based in-silico approach for Precision Medicine-repurposing for Alzheimer's Disease

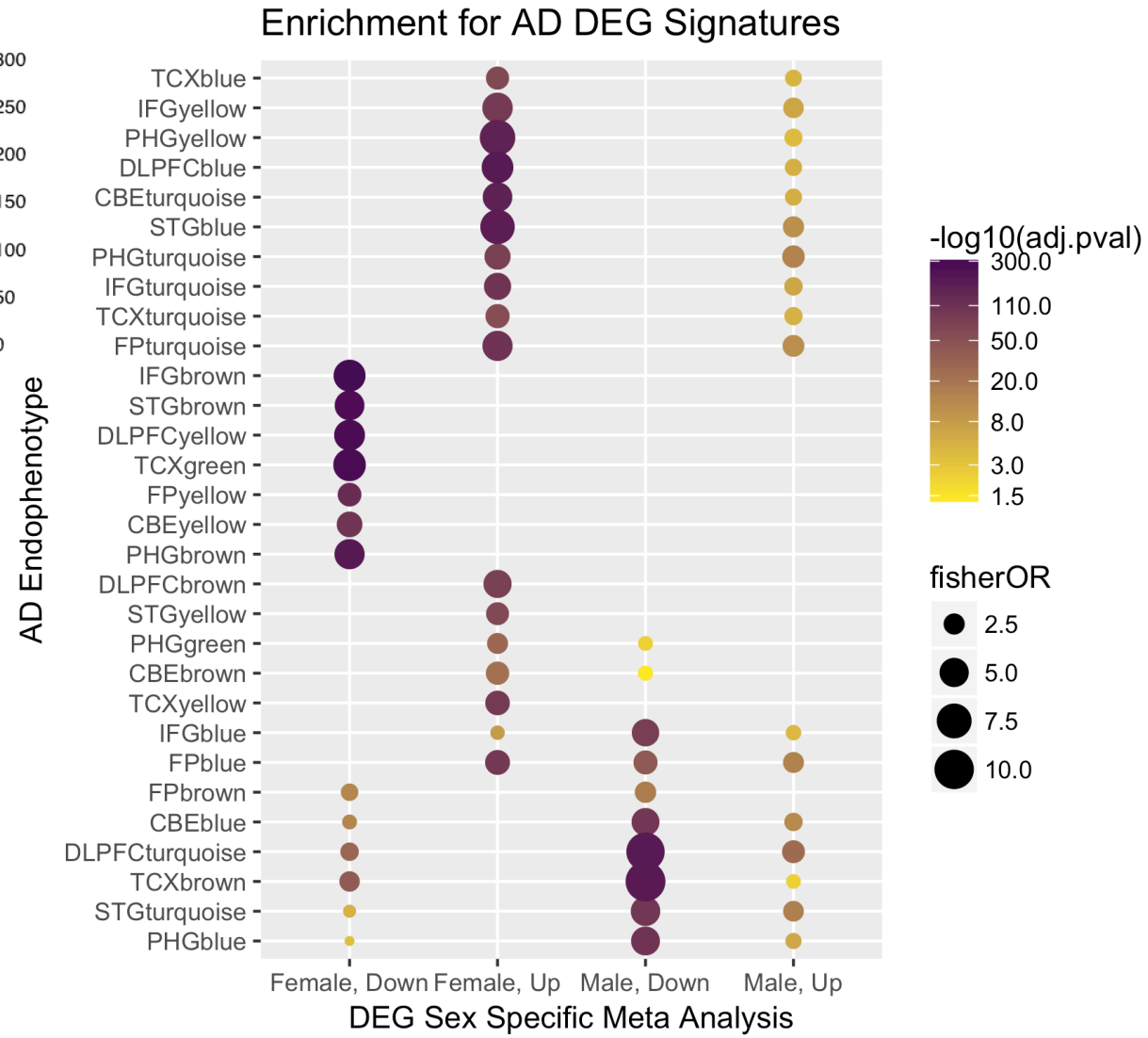
A Precision Medicine Approach to AD Treatment and Prevention





AD Molecular Endophenotypes Show Strong Sex Specificity





AMP-AD Consortium - Logsdon et al. – https://doi.org/10.1101/510420

PAR-17-033* Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (R01)*

Funded Projects:

	R01AG065209	NALVARTE, IVAN	Understanding the Role of Menopause and Estrogen Receptor Activation for Alzheimer's Disease Risk
	RF1AG057884	DONG, HONGXIN	Sex Differences in Central Stress Response and Alzheimer's Disease Neuropathology
	RF1AG057895	COLTON, CAROL ANNE (contact); BADEA, ALEXANDRA ; GOTTSCHALK, WILLIAM KIRBY; LUTZ, MICHAEL WILLIAM; THOMPSON, JOSEPH WILBUR; WILLIAMS, CHRISTINA L	Sex and APOE Genotype Interact to Alter Immune Regulated Metabolism in AD
	RF1AG058068	PIKE, CHRISTIAN J (contact); GATZ, MARGARET ; LADU, MARY JO	Sex Differences in the Relationship Between APOE and AD: Role of Sexual Differentiation
	RF1AG059093	KADDURAH-DAOUK, RIMA F (contact); BRINTON, ROBERTA EILEEN; CHANG, RUI ; KASTENMULLER, GABI	Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment
	RF1AG068325	DUBAL, DENA BOU	Mechanisms of X-Chromosome-dependent Sex Difference in Alzheimers Disease
	RF1AG057931	BRINTON, ROBERTA EILEEN (contact); CHANG, RUI ; MOSCONI, LISA	Sex Differences in the Molecular Determinants of Alzheimer's Disease Risk: Prodromal Endophenotype
	R01AG060393	SIROTA, MARINA	An Integrative Multi-Omics Approach to Elucidate Sex-Specific Differences in Alzheimers Disease
	R01AG057307	SCHREURS, BERNARD G (contact); GHRIBI, OTHMAN	Modeling Sex Differences in Alzheimer's Disease Cognition and Pathology

*re-issued as RFA-AG-21-029

RFA-AG-21-029 Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (R01 Clinical Trial Optional)

- ❑ Develop robust research programs that will explore how genes, environment, and hormonal status (gonadal and brain-derived) interact at various levels of biologic complexity (cell, tissue, organs/organ systems, and populations) to produce heterogeneous phenotypes of disease risk and responsiveness to therapy in AD/ADRD.
- ❑ A cross-disciplinary team-science approach that brings together experts in neuroscience, physiology, computational biology and data science, and translational and clinical research is strongly encouraged, as is the integrative use of human data and biosamples with cell-based and animal models.
- ❑ This FOA encourages studies that integrate and analyze multimodal data, such as -omics, imaging, and clinical data, as well as electronic health records and digital health data from biosensors or smart devices.
- ❑ **Of particular interest are projects that use biosamples and/or data collected from prior or ongoing AD/ADRD clinical trials to assess sex differences in response to interventions and to examine the molecular basis of this effect.**

Submission Deadline: November 10, 2020

Program Director: Jean Yuan, MD, PhD xin.yuan@nih.gov

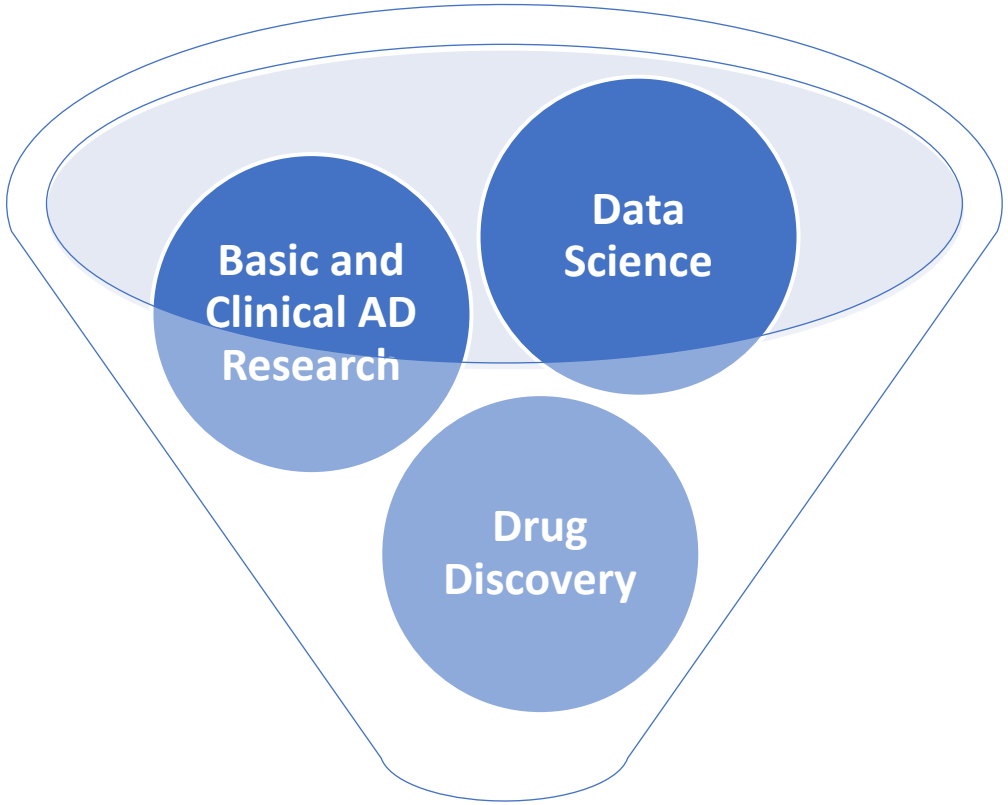
PAR-20-156 Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease (R01 Clinical Trial Optional)

RFA-AG-21-029 Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (R01 Clinical Trial Optional)

Emphasis on Data Sharing, Scientific Rigor and Reproducibility:

- Applicants are expected to follow **open-science, open-source principles** for sharing data and research tools.
- The preclinical efficacy studies are expected to follow the general ARRIVE guidelines for animal research and the best practice guidelines for AD preclinical efficacy studies.

Training the New Translational Workforce



Institutional Training Programs to Advance Translational Research on Alzheimer's Disease and AD Related Dementias (T32) PAR-21-112*

Program Director: Yuan Luo, PhD
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* re-issue of PAR-18-524

Upcoming Funding Initiatives for Training

https://www.nia.nih.gov/approved-concepts

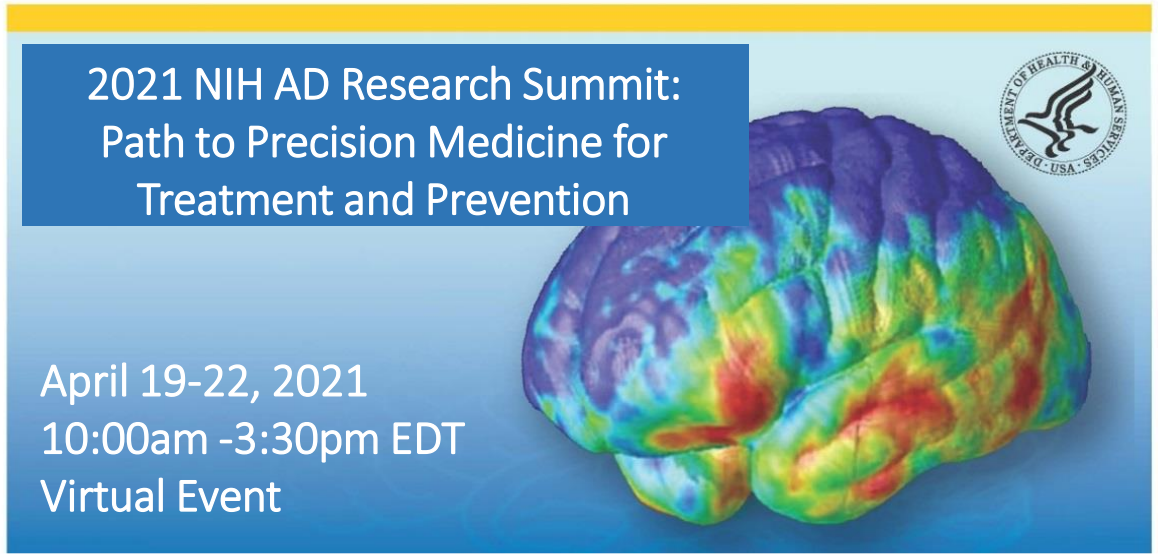
Fellowship and Career Development Awards to Promote Diversity in Translational Research for AD/ADRD

- ❑ Establish a **training pipeline for predoc, postdoc and junior faculty from under-represented groups.**
- ❑ This training initiative will emphasize the development and application of **skills in data science and drug discovery disciplines.**
- ❑ The goal is to **develop a diverse translational workforce** that can effectively participate in and/or lead a **team-science, precision medicine approach** to AD/ADRD treatment, prevention, early detection, disease management and care.

Formulate a blueprint for an integrated, translational research agenda that will enable the development of effective therapies (disease modifying and palliative) across the disease continuum for the cognitive as well as neuropsychiatric symptoms of Alzheimer's disease.

NIH AD Research Summits: Key Recommendations

- ❑ Recognize the heterogeneity and the multifactorial nature of the disease.
- ❑ Understand all aspects of healthy aging and resilience to AD to inform new prevention strategies.
- ❑ Support extensive molecular of existing and establish new cohorts to fill the gaps in large-scale human data needed to build predictive models of disease and wellness.
- ❑ Employ data-driven research paradigms such as systems biology and systems pharmacology.
- ❑ Build new multidisciplinary translational teams and create virtual and real spaces where these teams can operate.
- ❑ Engage patients, caregivers and citizens as direct partners in research.
- ❑ Enable rapid and extensive sharing of data, disease models, and biological specimens.
- ❑ Develop computational tools and infrastructure for storage, integration, and analysis of large-scale biological and other patient-relevant data.
- ❑ Support and enable open science.
- ❑ Change academic, publishing, and funding incentives to promote collaborative, transparent, and reproducible research.



Program Sessions:

- ❑ Deconstructing Disease Complexity:
  from Populations to Single Cells, from Genes to Multiscale Models
- ❑ Enabling Infrastructure and Incentives to Improve Research Rigor, Reproducibility and Translatability
- ❑ Accelerating Therapy Development: Open Science from Targets to Trials
- ❑ Diversifying the Therapeutic Pipeline to Develop Precision Medicines
- ❑ Emerging Biomarkers Landscape
- ❑ Advancing Drug Repurposing and Combination Therapy Development
- ❑ Understanding the Impact of the Exposome on Brain Health to Advance Disease Prevention

https://www.nia.nih.gov/2021-alzheimers-summit

FORTUNE MAGAZINE COMMENTARY DRUG DEVELOPMENT

The coronavirus pandemic has shattered the status quo on drug development. We should build on that

BY **E. RICHARD GOLD**

March 26, 2020 7:30 AM EDT

New drugs produce on average either flat or declining additional benefit over their predecessors, according to a 2018 study on cancer drugs. In fact, a recent working paper by Stanford and MIT researchers found that the U.S. must double its investments every 13 years just to stay at the same level or, in some cases, fall behind.

The COVID-19 pandemic shattered this status quo. In the face of this, scientists and governments turned to a new model of drug discovery: open science partnerships. Scientists and governments quickly abandoned proprietary science when faced with the COVID-19 pandemic. They shared data, molecules, and genetic sequences as they were identified and worked together to develop diagnostic kits and repurpose existing drugs.

Open science partnerships play a critical role in drug development by de-risking innovation through cost sharing, leveraging financing, and bringing together actors with diverse skills, tools, materials, and knowledge. All stakeholders have a role in promoting these partnerships.

This requires new forms of research grants targeting open science, increased corporate funding and participation, and changing university promotion and tenure rules to reward data and materials sharing. Researchers should also more actively share data, tools, and materials before publication, such as through e-lab books and regular data uploads.

ACKNOWLEDGMENTS

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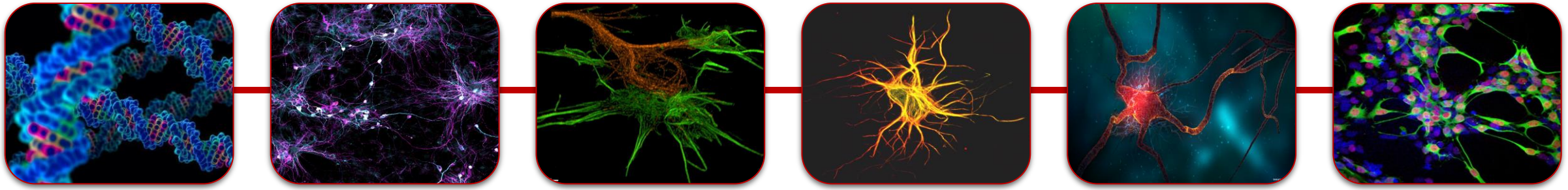


Drug Development for Alzheimer's Disease and Related Disorders (ADRD): Cross-Disease Opportunities

Jeffrey Cummings, MD, ScD

Joy Chambers-Grundy Professor of Brain Science

Director, Chambers-Grundy Center for Transformative Neuroscience

Department of Brain Health

University of Nevada Las Vegas (UNLV)

Disclosures

Dr. Cummings has provided consultation to Acadia, Actinogen, Acumen, Alector, Alkahest, Alzheon, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Cassava, Cerecin, Cerevel, Cortexyme, Cytox, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Janssen, Jazz, Karuna, Merck, Novo Nordisk, Otsuka, ReMYND, Resverlogix, Roche, Samumed, Samus, Signant Health, Sunovion, Suven, United Neuroscience, and Unlearn AI pharmaceutical and assessment companies. Dr. Cummings has stock options in ADAMAS, AnnovisBio, MedAvante, BiOasis and United Neuroscience. Dr. Cummings owns the copyright of the Neuropsychiatric Inventory. Dr Cummings is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; and NIA grant P20AG068053.

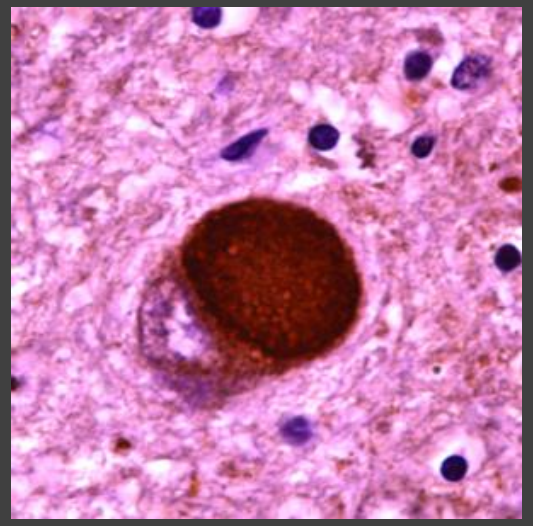
Drug Development for Alzheimer's Disease and Related Disorders (ADRD): Cross-Disease Opportunities

Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) Coalition

- ADRD shared biology
- ADRD cross-disease treatments
- ADRD informative trials
- Neurofilament light (NfL) for ADRD trials
- Discussion points

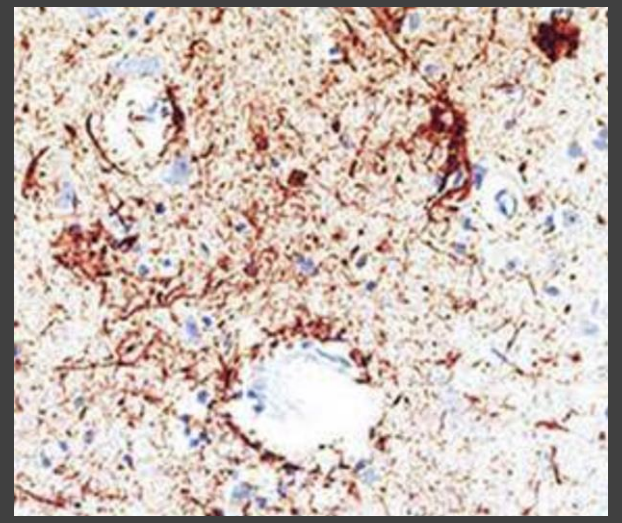
Key Points

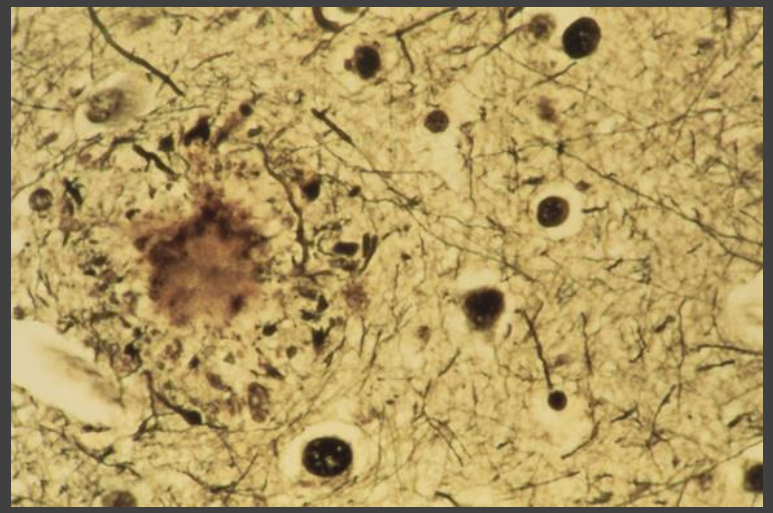
- ADRD are characterized by protein aggregation
  - Proteinopathy is common across ADRD
  - The type of protein differs among ADRD
  - The location of protein aggregation and neuronal loss differs among ADRD
- Protein aggregation initiates processes leading to cell death that have shared features across ADRD
- Shared features suggest that there may be opportunities for
  - Cross ADRD learnings
  - Cross ADRD therapies



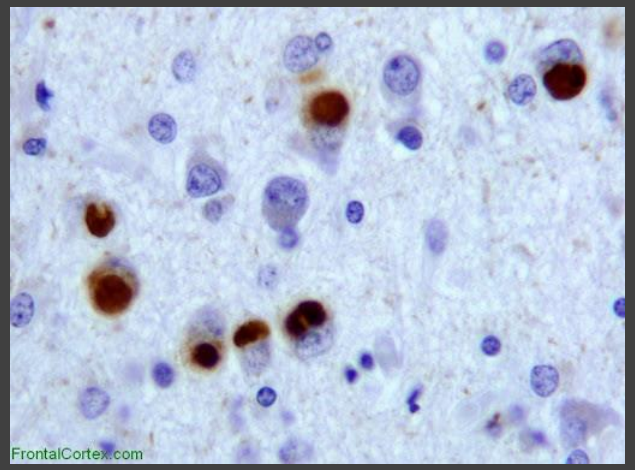
PD/DLB/MSA
Lewy body

CTE/PART
Tau

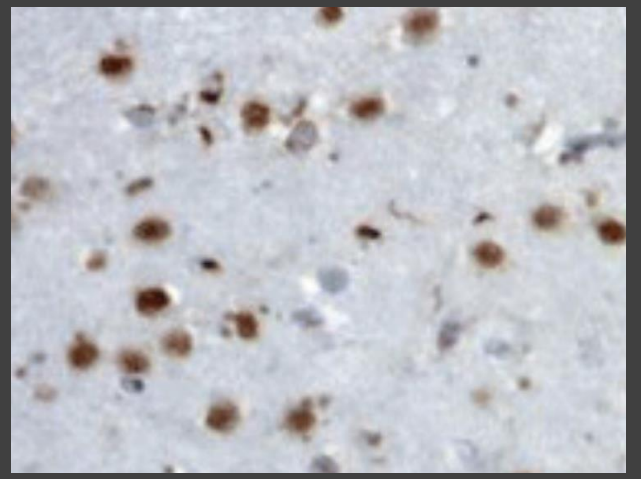




Alzheimer
Amyloid

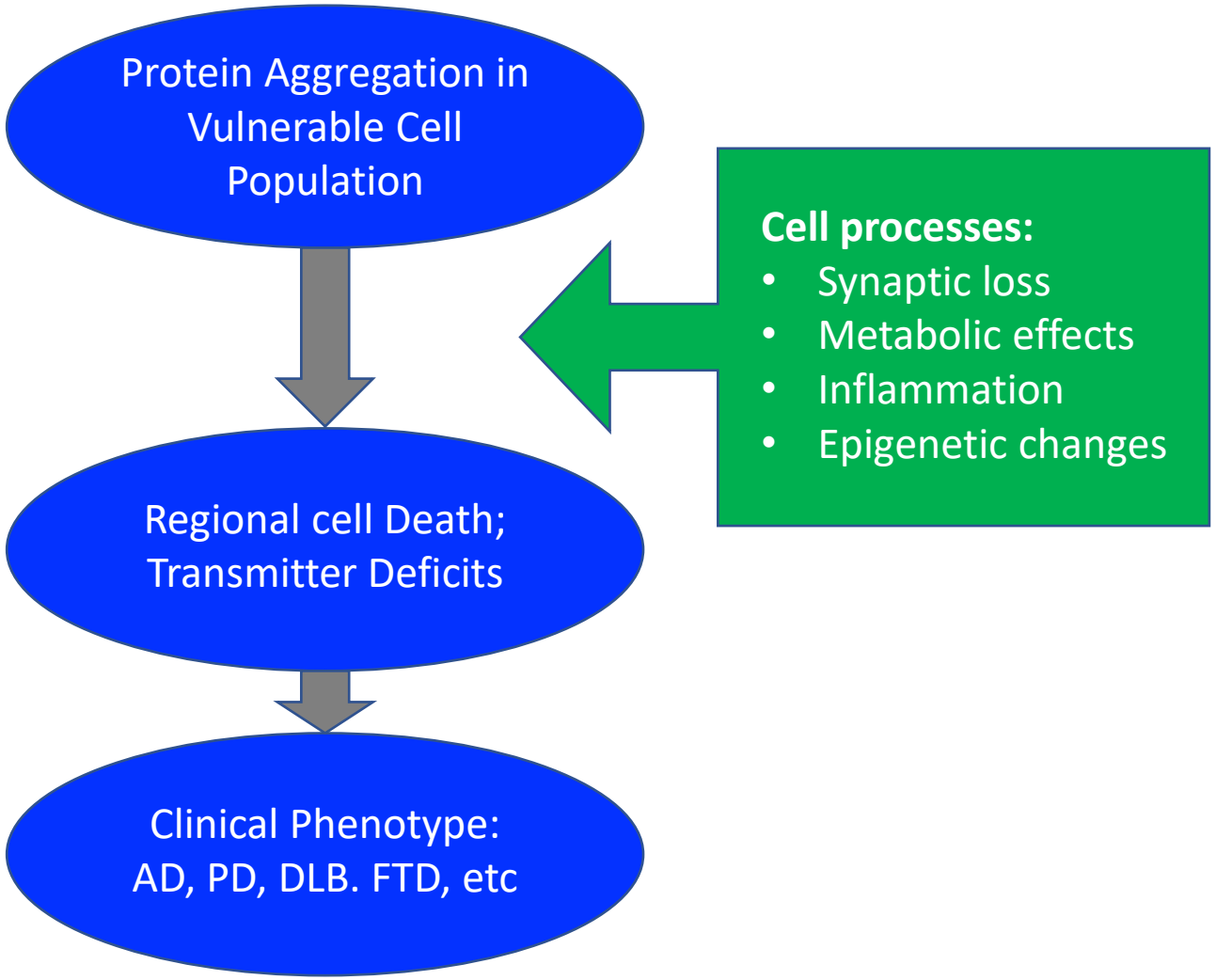


FTD
Pick

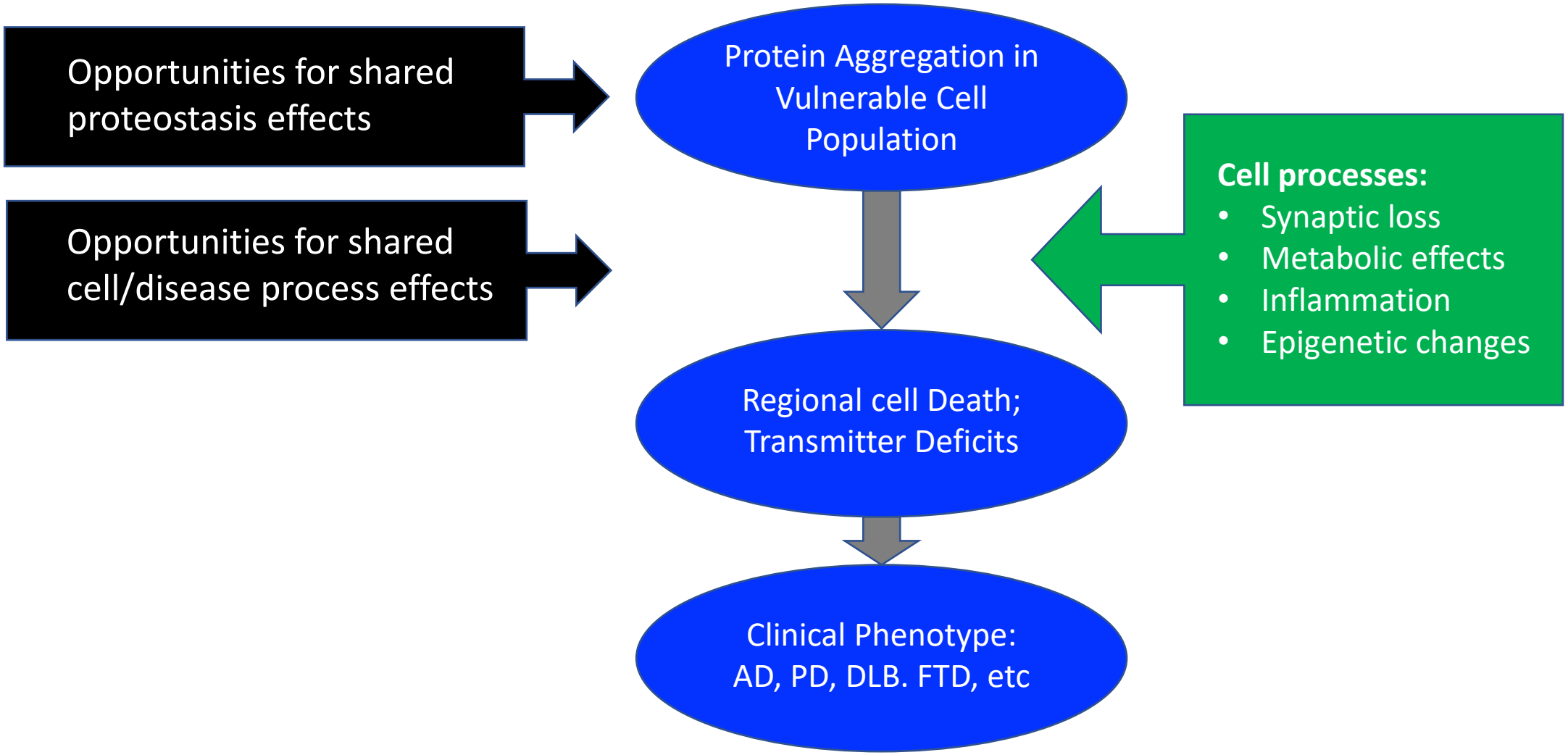


ALS/FTD/LATE
TDP-43

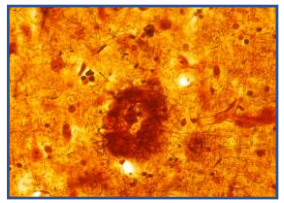
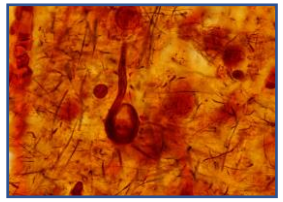
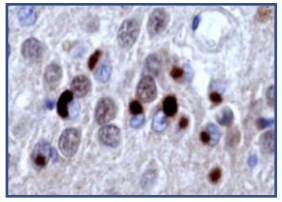
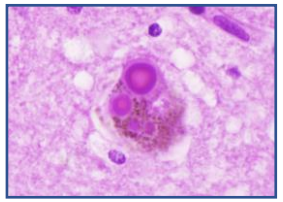
Generalizable Model of ADRD



Generalizable Model of ADRD



Disease-Specific and Non-specific Targets

Amyloid	Tau	TDP-43	a-Synuclein
			
AD; DLB	AD; FTLD; PART	FTLD; ALS; LATE	PD; DLB; MSA

ApoE/lipids	Vasculature
Neurotransmitter receptors	Growth factors/hormones
Inflammation	Synaptic plasticity
Oxidative stress	Epigenetic regulators
Cell death	Neurogenesis
Metabolism/bioenergetics	Gut-brain axis

https://iadrp.nia.nih.gov/about/cadro

Protein-specific
- Monoclonal antibodies
- Protein-specific treatment

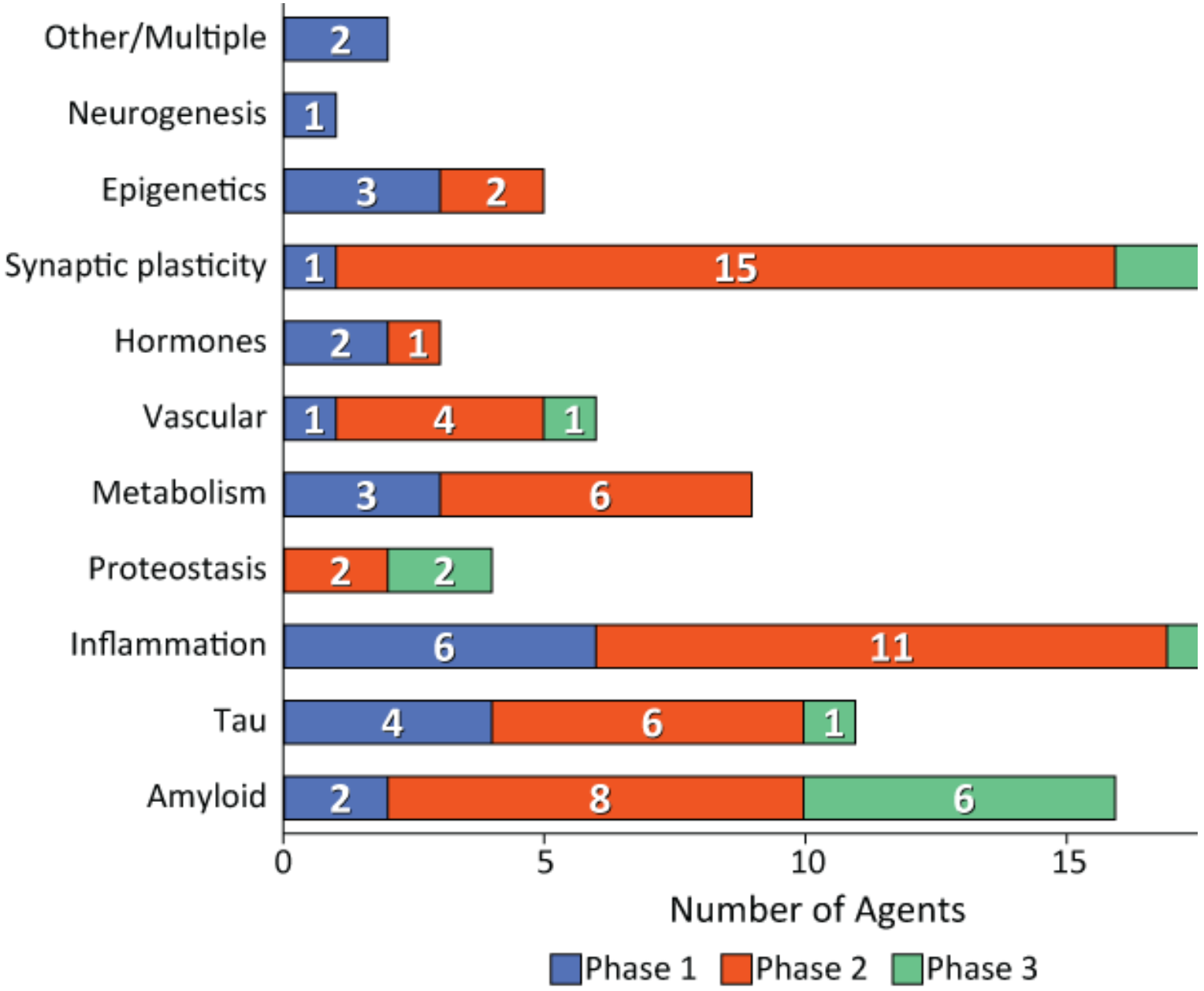
Protein-nonspecific
- Aggregation inhibitors
- Could apply cross-disease

Disease-preferential
- ApoE/Alzheimer
- Vascular/VaD
- Epigenetic
- Neurogenesis
- Growth factors
- Gut-brain axis

Disease-nonpreferential
- Inflammation
- Synaptic plasticity
- Oxidative stress
- Cell death

Current Alzheimer Trials by CADRO Mechanism of Action/Target

CADRO – Common Alzheimer's Disease Research Ontology (iadrp.nia.nih.gov)



Cross-Disease Trials in Progress

(from clinicaltrials.gov accessed 12/27/2020)

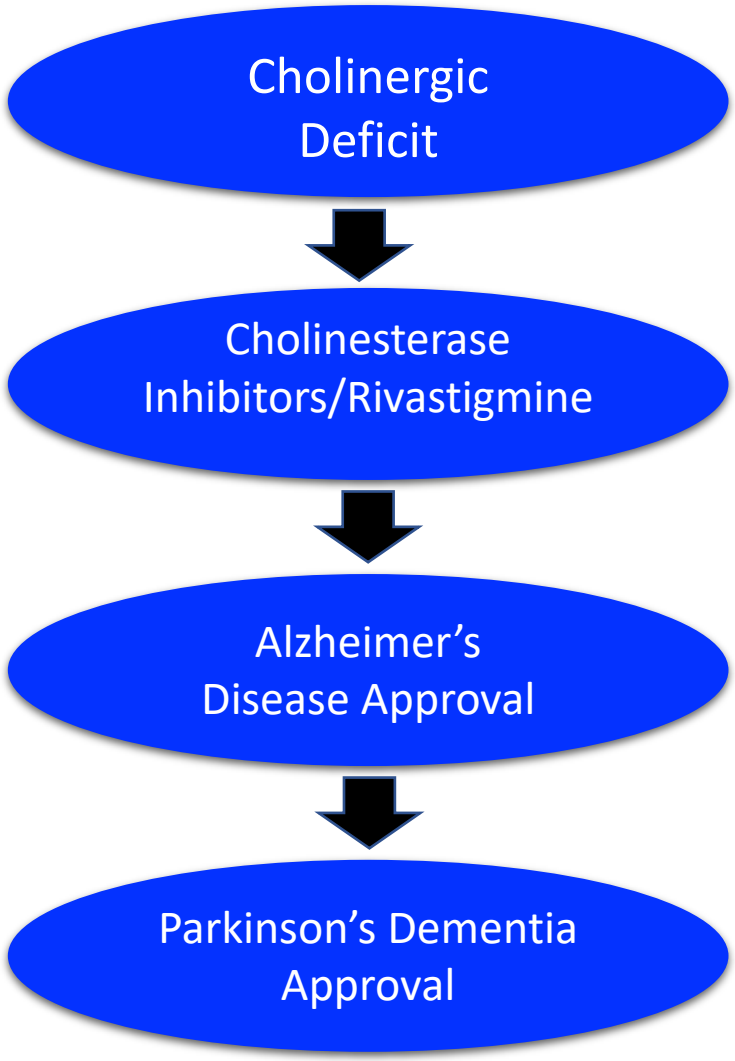
Agent	Mechanism of Action	AD	PD/PDD	DLB	FTD	ALS
Ambroxol	$\mathcal{B}$-glucocerebrosidase chaperone					
Nalfamapimod	P38∂ inhbitor					
Nilotinib	Tyrosine kinase inhibitor					
Intranasal insulin	Glucose metabolism					
Metformin	Insulin sensitizer					
PU-AD	Epichaperome inhibitor					
ALZ-OP1a	Anti-aggregation + anti-inflammatory					
Masitinib	Kinase inhibitor; microglial modulator					
L-serine	Amino acid supplement					
Posiphen	Protein production inhibitor					

Rivastigmine is an Example of a Successful/ Approved Cross-ADRD Therapeutic

Shared biology across several ADRD

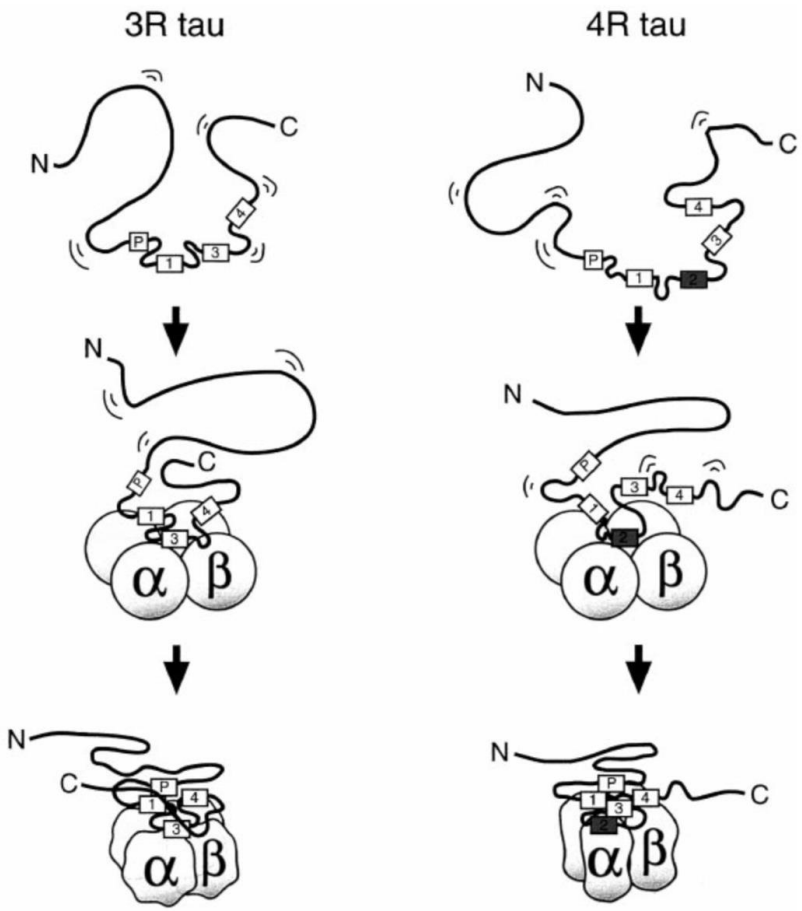
- Cholinergic deficit
- PDD – (-)20%
- DLB – (-)20.3%
- PD w/o dementia – (-)19.9%
- AD – (-) 15% (temporal)

Bohnen N et al. Arch Neurol 2003; 60: 1745-1748; Nejad-Davarani S et al. Mol Psych 2019; 24: 322-327; Emre M et al. NEJM 2004; 351: 2509-2518



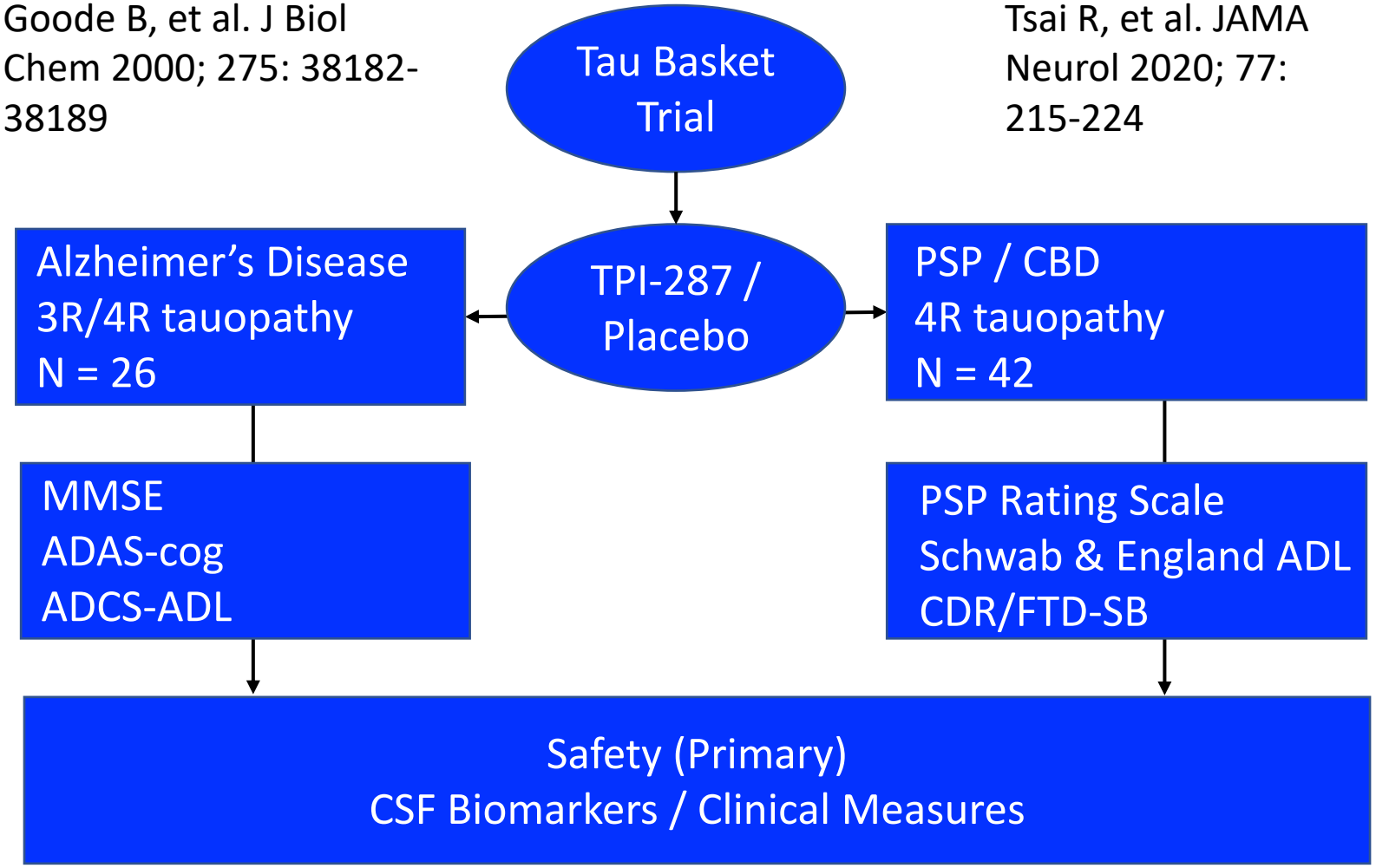
AD – Alzheimer's disease; DLB – dementia with Lewy bodies; PD – Parkinson's disease; PDD – Parkinson's disease dementia

Tau Basket Trial: Alzheimer, Progressive Supranuclear Palsy, Corticobasal Degeneration



Goode B, et al. J Biol Chem 2000; 275: 38182-38189

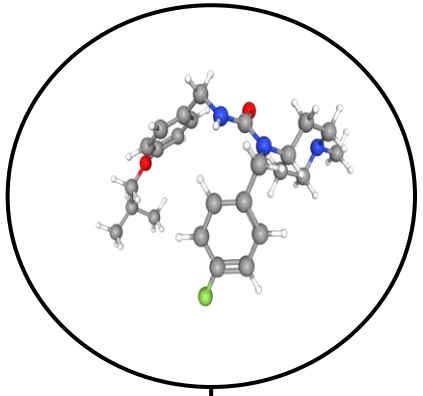
Tsai R, et al. JAMA Neurol 2020; 77: 215-224



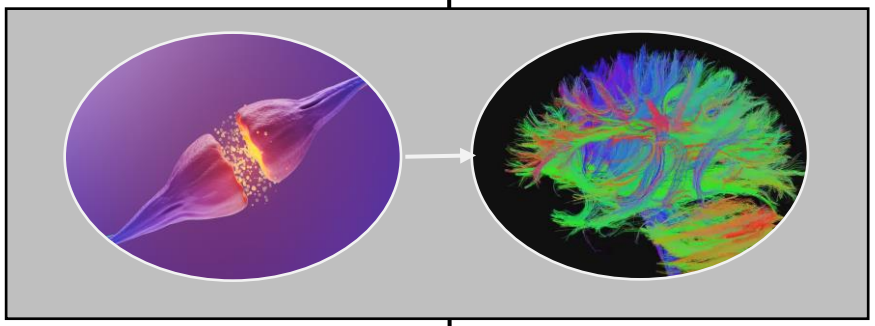
Pimavanserin for Dementia-Related Psychosis (DRP)

Harmony Trial

- Randomized withdrawal
- Open label initial phase
- DB withdrawal period
- 5 types of dementia
- No biomarker confirmation
- Significant d-p difference in relapse of psychosis
- Currently undergoing FDA review



Pimavanserin (Nuplazid™)
5-HT_{2A} inverse agonist

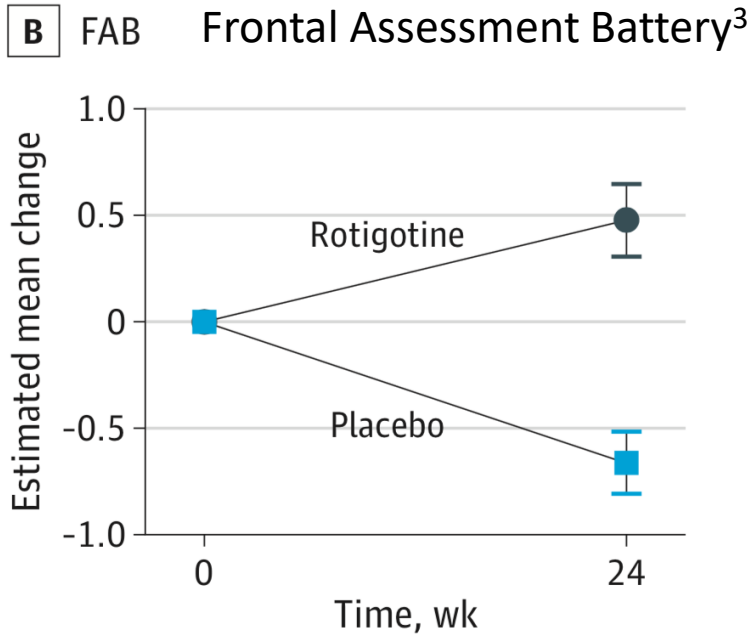


Final common circuit hypothesis

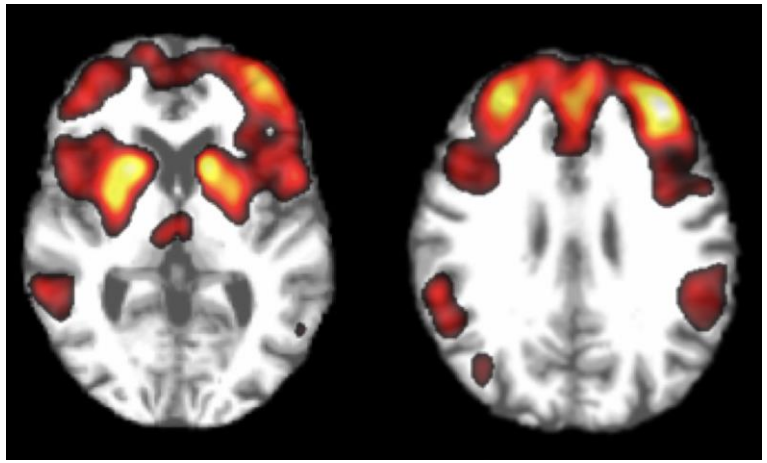
- Alzheimer's Disease
- Dementia w Lewy Bodies
- Parkinson's Dis Dementia
- FTLD w Dementia
- Vascular Dementia

Dopaminergic Agents May Produce Cognitive Enhancement in Alzheimer's Disease and Parkinson's Disease

- Rasagiline produced cognitive enhancement in PD[1]
- Rasagiline produced cognitive and brain metabolism benefit compared to placebo in AD[2]
- Rotigotine improved executive function and decreased decline in ADLs in AD[3]
- DA1 receptor agonists are being considered for apathy in ADRD[4]

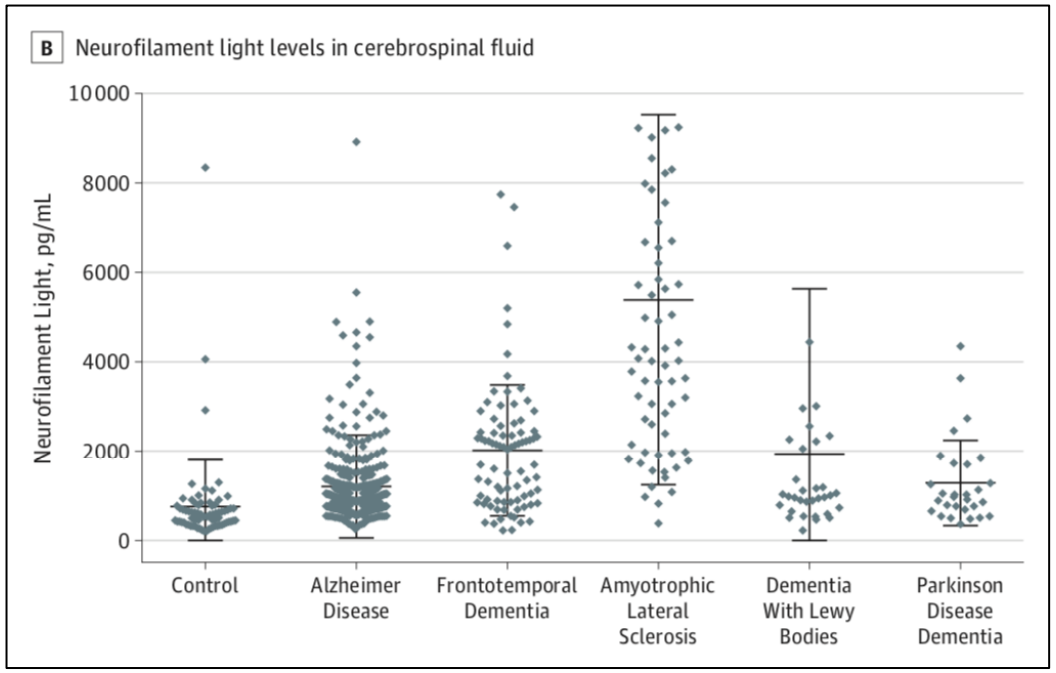


FDG PET areas with less decline with rasagiline treatment[2]



[1]Rascol O et al. Lancet Neurol 2011; 10: 425-423;
[2]Matthews D ewt al. Alz Dem: TRCI 2021 in press;
[3]Koch G et al, JAMA Neurol Network Open 2020;
[4]Chong T, Husain M. Prog Brain Res 2016; 229-389

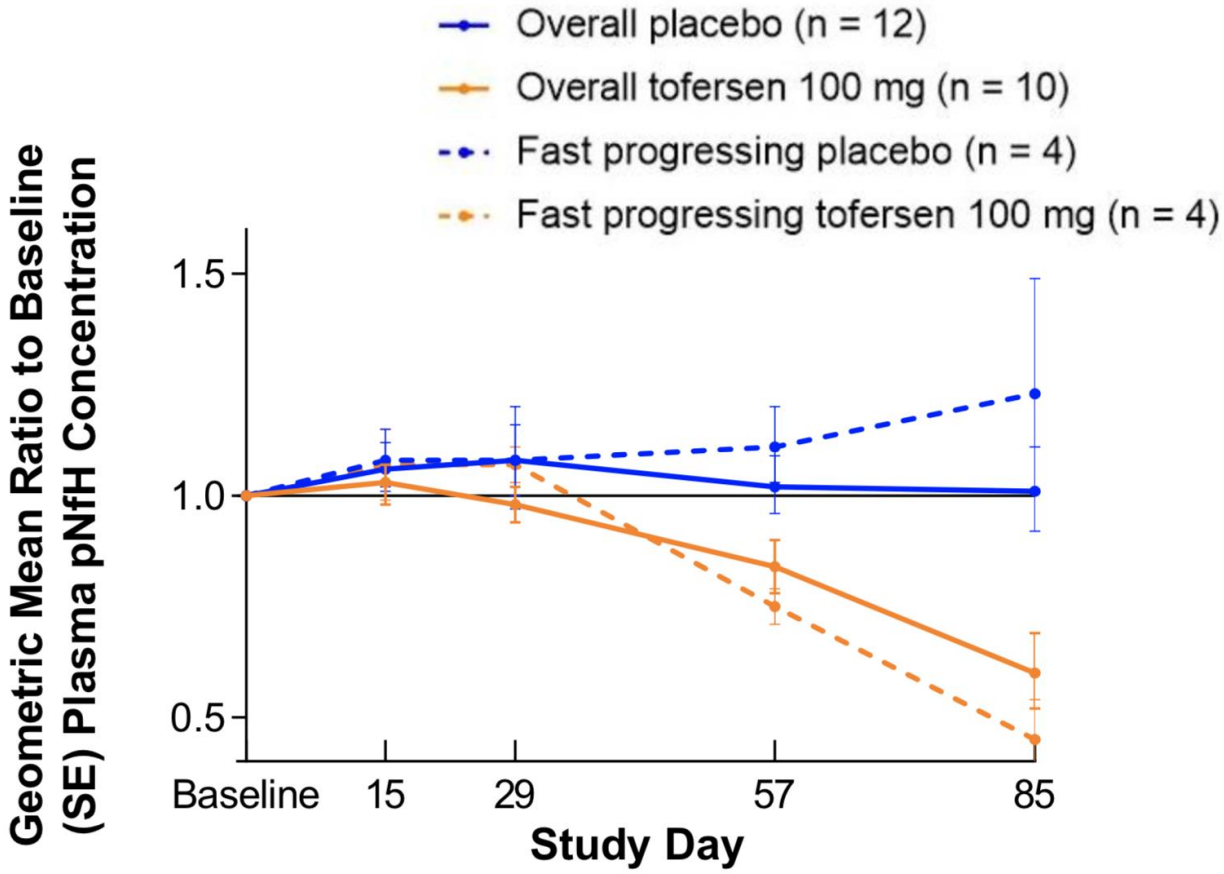
Neurofilament Light (NfL) is Positioned to Assist ADRD Drug Development



NfL is elevated across ADRD.
(Olsson B et al. JAMA Neurol 2019; 76: 318-325)

Biomarkers

- Disease-specific A$\mathcal{B}$42/40
- ADRD - NfL



Toferson reduced plasma and CSF NfL in an ALS clinical trial (BIIB Earnings Call 22OCT2019.pdf)

Summary

- Exciting time in treatment development for ADRD
- ADRD share many biological features
- AD drug development includes target relevant to ADRD
- Cross disease therapy has occurred (rivastigmine); trials include > 1 ADRD focusing shared mechanisms
- Novel trial designs for ADRD are promising
- Biomarkers relevant to ADRD trials are emerging

Discussion Points with the FDA

- Would orphan disease strategies (e.g, historical controls) be acceptable in support of an indication for a rare neurodegenerative disorder such as progranulin mutation carriers with FTD?
- Could a positive outcome of a prespecified group in a basket trial constitute 1 of 2 trials for a regulatory package?
- Could a smaller trial with a positive outcome on a biomarker reasonably likely to predict clinical benefit with a larger trial demonstrating a positive clinical outcome constitute the 2 trials of a regulatory package?

Discussion Points with the FDA

- Many non-Alzheimer neurodegenerative disorders do not have diagnostic biomarkers. Is the FDA comfortable with an “indication” based on the clinical phenotype?
- Given the shared biological features, would the FDA view PD dementia and DLB as the same disorder? Could trials of an approvable package include both disorders in the same trials?
- When drugs are being developed to treat neuropsychiatric symptoms in Alzheimer’s disease, will the FDA require biomarker confirmation of the diagnosis of Alzheimer’s disease?
- If a drug were being developed for a process such as inflammation that is present across many ADRD, would the FDA allow an indication such as “for the treatment of Alzheimer’s disease and related disorders”?

Thank you; stay safe; get vaccinated

Research into Molecular Underpinning of Dementia

David A. Bennett, M.D.
Director, Rush Alzheimer's Disease Center
Robert C. Borwell Professor of Neurological Sciences
Rush University Medical Center
Chicago, IL

13th Annual FDA/ACT-AD Allies Meeting

Common Threads: Learning from the Related Dementias
February 3, 2021

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Melissa Lamar, PhD
Brittney Lange-Maia
Sue Leurgans, PhD
Rupal Mehta, MD
Sukriti Nag, MD, PhD
Bernard Ng, PhD
Shahram Oveisgharan, MD
Victoria Poole, PhD
Julie Schneider, MD
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Jingyun Yang, PhD
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Vilas Menon, PhD
Emory School of Medicine
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Staff of the Rush Alzheimer's Disease Center

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Alzheimer's Association
Rush University Medical Center

Study Participants:
Religious Orders Study
Rush Memory and Aging Project

Disclosures

I have no relevant disclosures.

Objectives

- Motivating questions
- Risk factors, pathology, cognitive decline and Alzheimer’s dementia
- Identifying the molecular basis of dementia

Motivating Questions

- Why do older people lose cognition as they age?

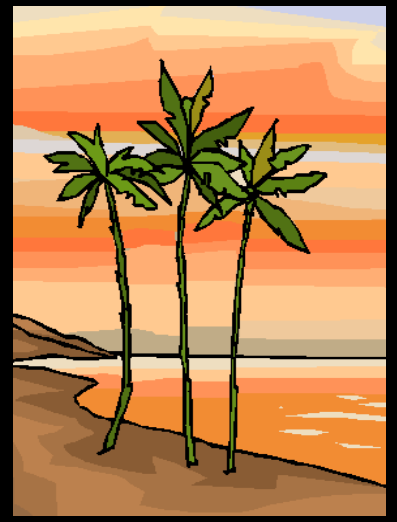
Motivating Questions

- Why do older people lose cognition as they age?

We need to study older persons without dementia who agree to:

- Tell us all kinds of things about their lifestyles that possibly could be related to the development of ADRD
- Detailed clinical evaluations every year for ADRD
- Donate blood every year
- Brain donation
- Wait….. for the omic revolution!
- It’s here!

The Religious Orders Study



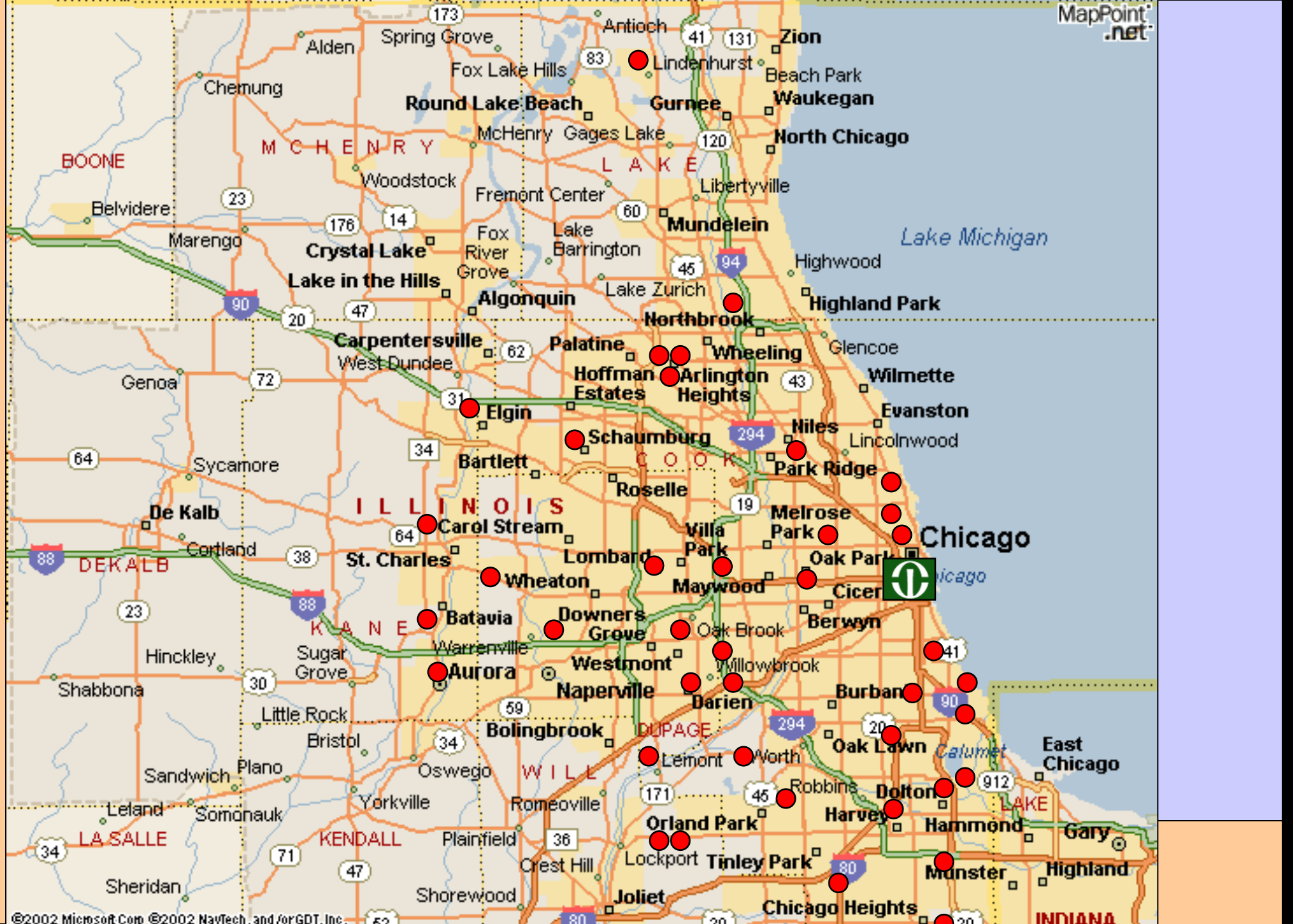
- Began in 1993
- > 1,500 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual clinical evaluation
- All agreed to brain donation
- > 375 have developed dementia
- > 600 have developed MCI
- > 750 brain autopsies

Religious Orders Study: Participating Sites

The Memory and Aging Project

… because memories should last a lifetime

- Began in 1997
- > 2,100 residents from across the Chicago area
- All agreed to annual clinical evaluation
- All agreed to donate brain, spinal cord, muscle, and nerve at the time of death
- > 375 have developed dementia
- > 625 have developed MCI
- > 800 autopsies


MapPoint.net
Antioch
Zion
Lindenhurst
Beach Park
Waukegan
Spring Grove
Alden
Fox Lake Hills
Chemung
Round Lake Beach
Gurnee
North Chicago
McHenry
Gages Lake
M C H E N R Y
L A K E
BOONE
Woodstock
Libertyville
Fremont Center
Belvidere
Mundelein
Lake Michigan
Marengo
Crystal Lake
Fox River Grove
Lake Barrington
Highwood
Lake in the Hills
Algonquin
Lake Zurich
Highland Park
Northbrook
Carpentersville
West Dundee
Palatine
Wheeling
Glencoe
Genoa
Hoffman Estates
Arlington Heights
Wilmette
Elgin
Evanston
Schaumburg
Niles
Lincolnwood
Sycamore
Bartlett
C O O K
Park Ridge
Roselle
I L L I N O I S
De Kalb
Melrose Park
Carol Stream
Villa Park
Chicago
Cortland
St. Charles
Lombard
Oak Park
D E K A L B
Wheaton
Maywood
Cicero
Batavia
Downers Grove
Oak Brook
Berwyn
K A N E
Hinckley
Sugar Grove
Warrenville
Westmont
Willowbrook
Aurora
Naperville
Darien
Burbank
Shabbona
Little Rock
Bolingbrook
D U P A G E
Oak Lawn
Calumet
East Chicago
Bristol
Lemont
Worth
Sandwich
Plano
Oswego
W I L L
Robbins
Dolton
Yorkville
Romeoville
Harvey
Hammond
Gary
Leland
Somonauk
Orland Park
LA SALLE
KENDALL
Plainfield
Crest Hill
Lockport
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Munster
Highland
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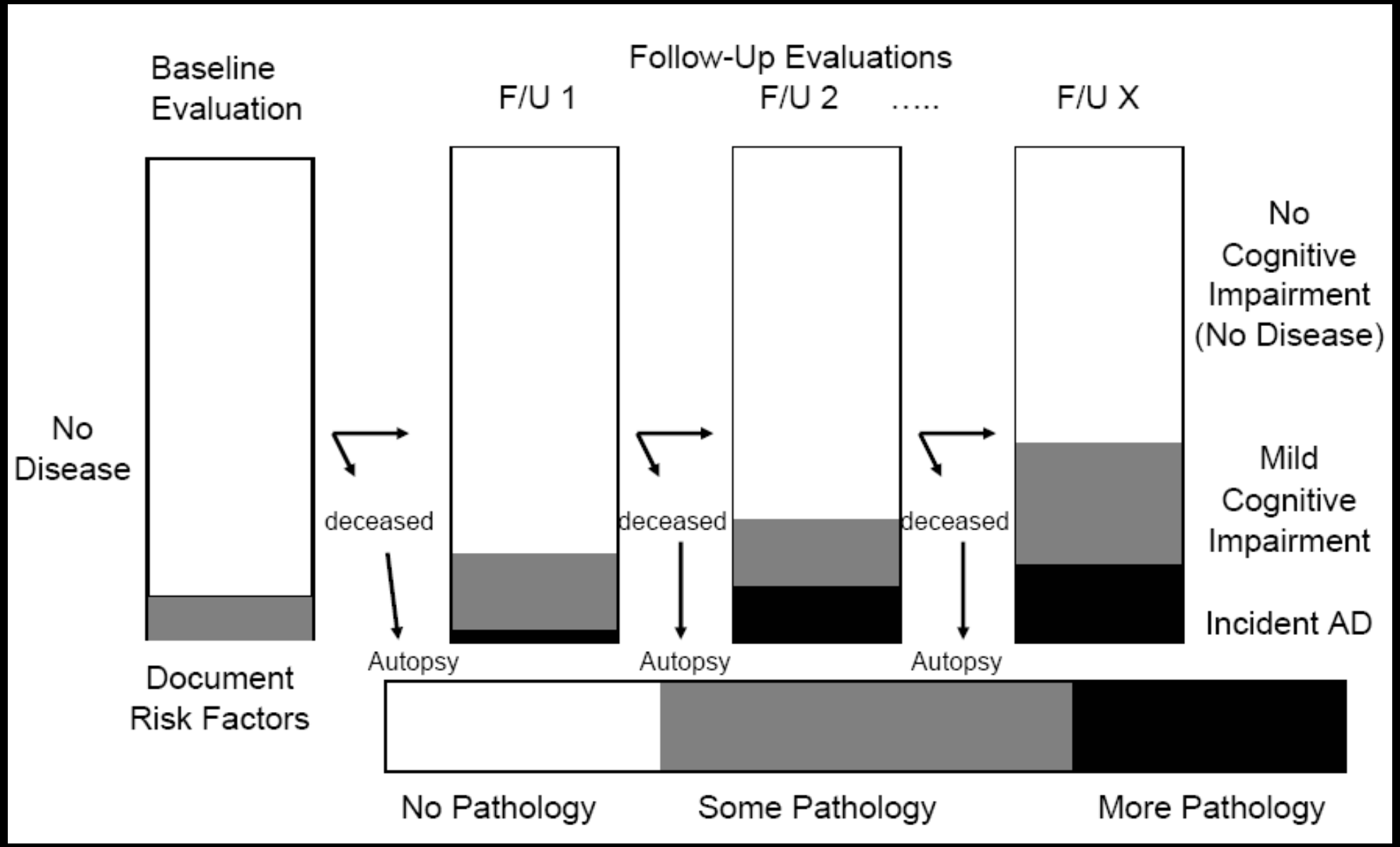
The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort



Bennett DA, et al. *Neuroepidemiology.* 2005;25:163–175.

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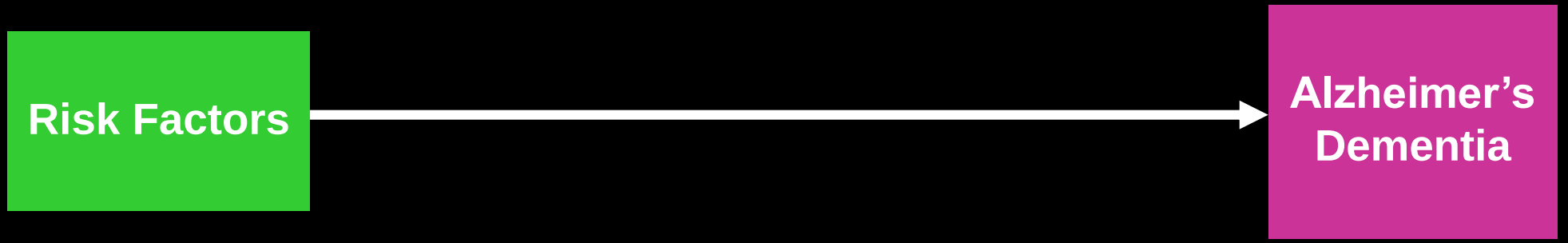
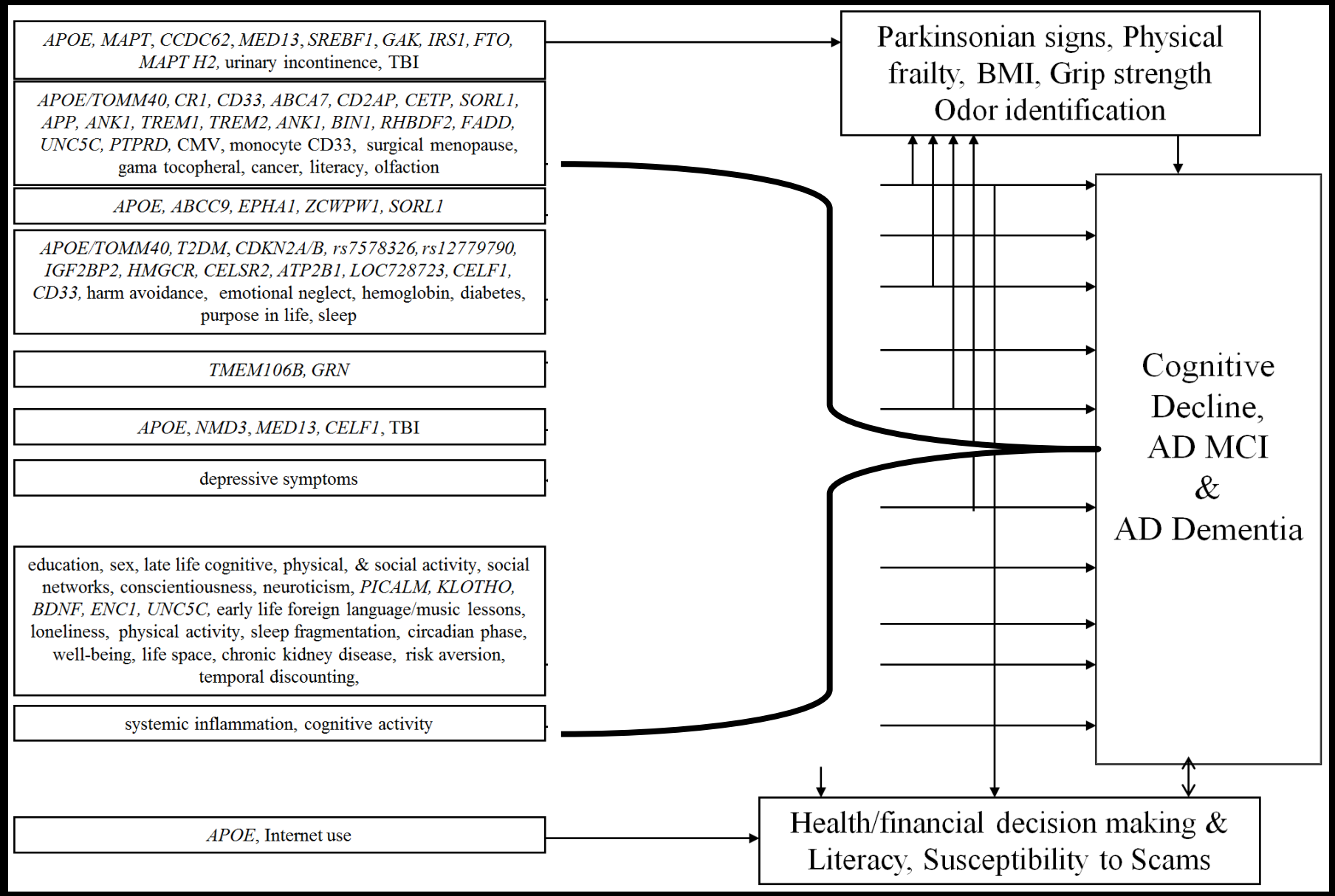

Risk Factors
Alzheimer's Dementia

Religious Orders Study and Rush Memory and Aging Project



Bennett DA, et al. *J Alz Disease.* 2018;64:S161-S189.

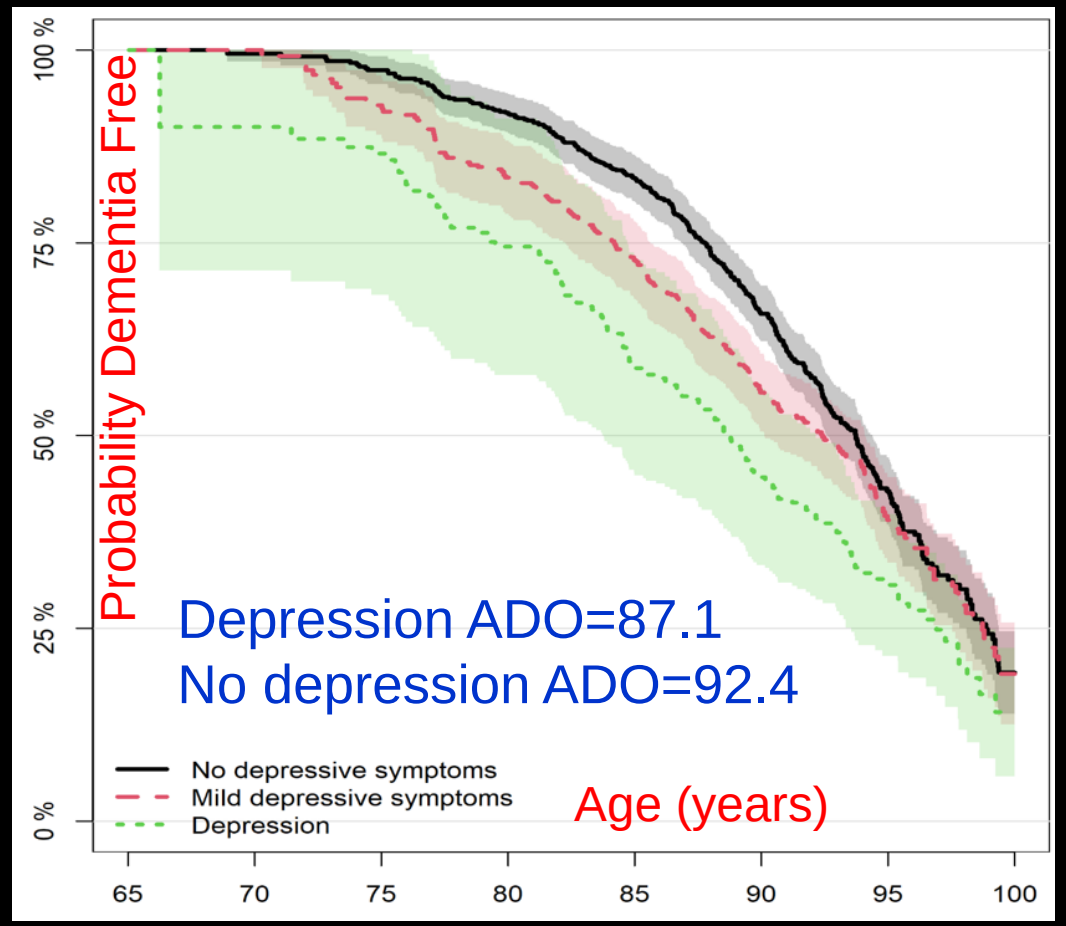
Risk Factors for Cog Decline and AD dementia

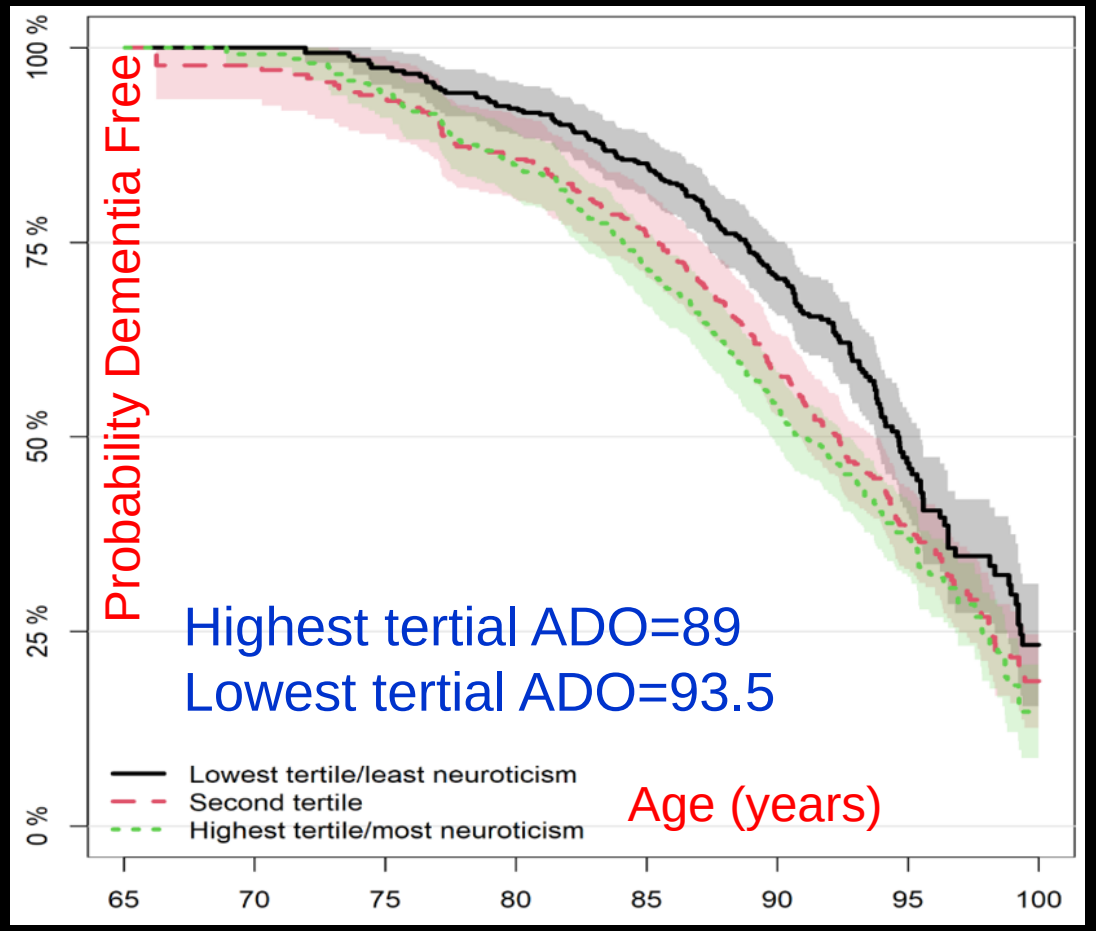
Genes/Proteins	Experiential	Psychological	Medical
APOE, CR1, CD33, ABCA7, CD2AP, CETP, SORL1, APP, ANK1, TREM1, TREM2, ANK1, BIN1, RHBDF2, FADD, PTPRD, SRCAP, UNC5C, ABCC9, EPHA1, TOMM40, T2DM, CDKN2A/B, rs7578326, rs12779790, IGF2BP2, HMGCR, CELSR2, ATP2B1, LOC728723, CELF1, NMD3, MED13, CELF1, PICALM, KLOTHO, BDNF, FOXF2, MS4A, PINX1, CD2AP, CLDN IGFBP5, AK4, ITPK1, HSBP2,	Education, Late life Cognitive, Physical, & Social Activity, Social Networks, Early life foreign language or music lessons, Physical activity, Life space	Harm avoidance, Emotional neglect, Purpose in life, Depressive symptoms, Conscientiousness, Neuroticism, Loneliness, Risk aversion, Temporal discounting	Sex, CMV, Monocyte CD33, Anemia, Surgical menopause, Gama tocopheral, Cancer, Seafood, Sleep, Circadian phase, Fractal regulation. Head trauma, Chronic kidney disease, MEDI diet, DASH diet, MIND diet

Health/financial decision making & Literacy, Susceptibility to Scams

Parkinsonian signs, Physical frailty, BMI, Grip strength Odor identification

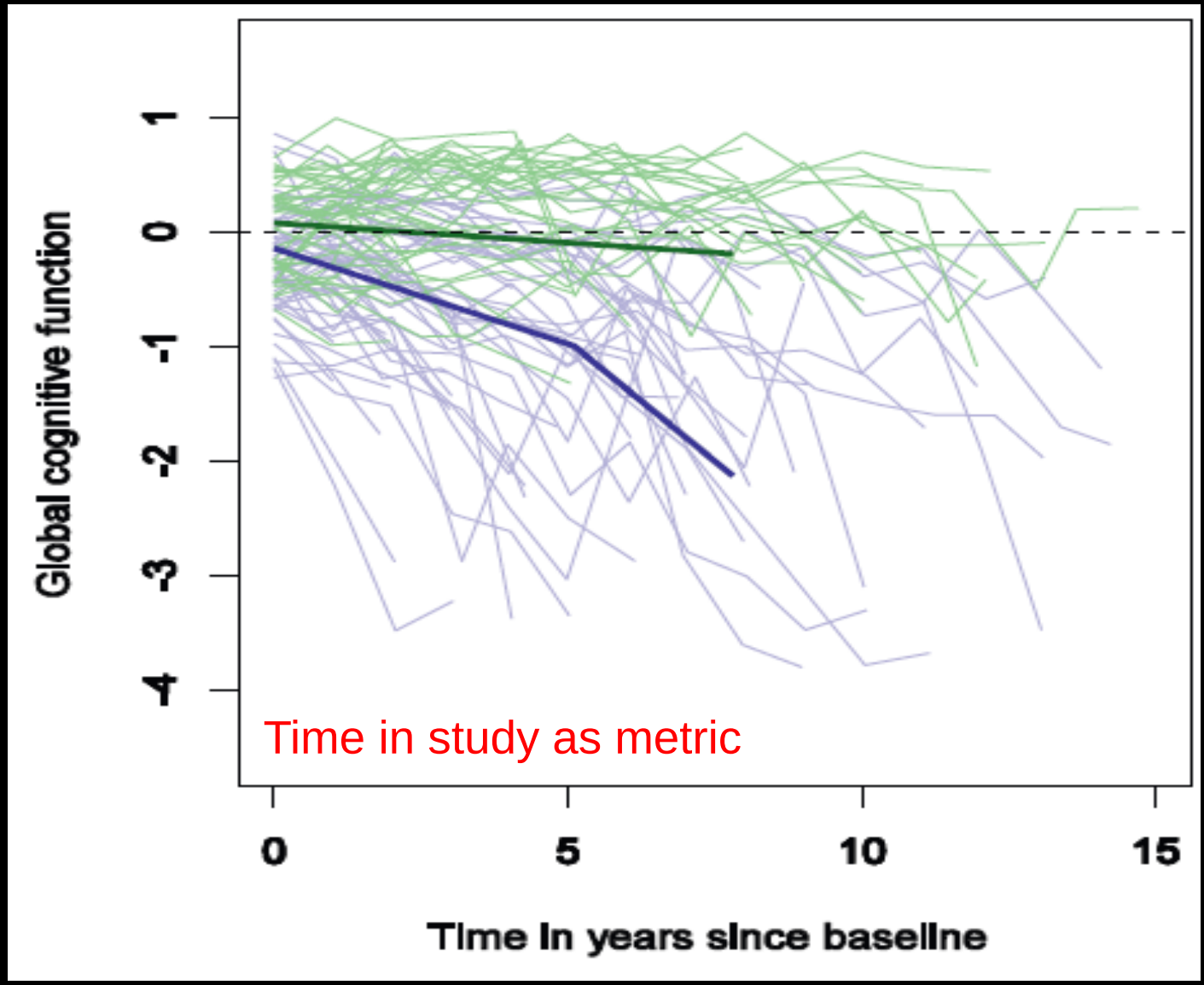
PSYCHOSOCIAL FACTORS IN RELATION TO AGE AT ONSET OF DEMENTIA IN OLDER PERSONS



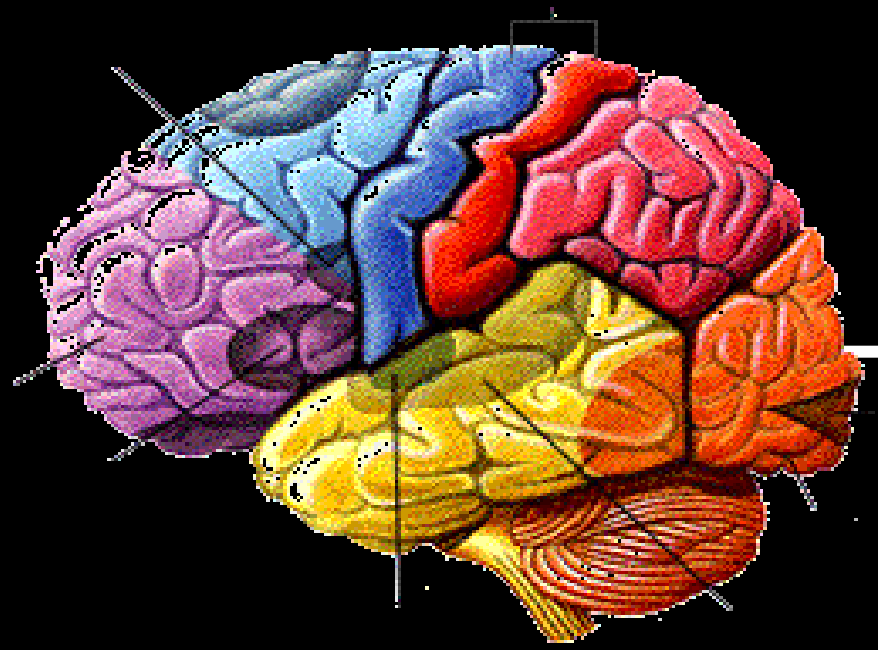


Grodstein F, et al. *Pending revisions.*

Building a pipeline to discover and validate novel therapeutic targets and lead compounds for Alzheimer's disease

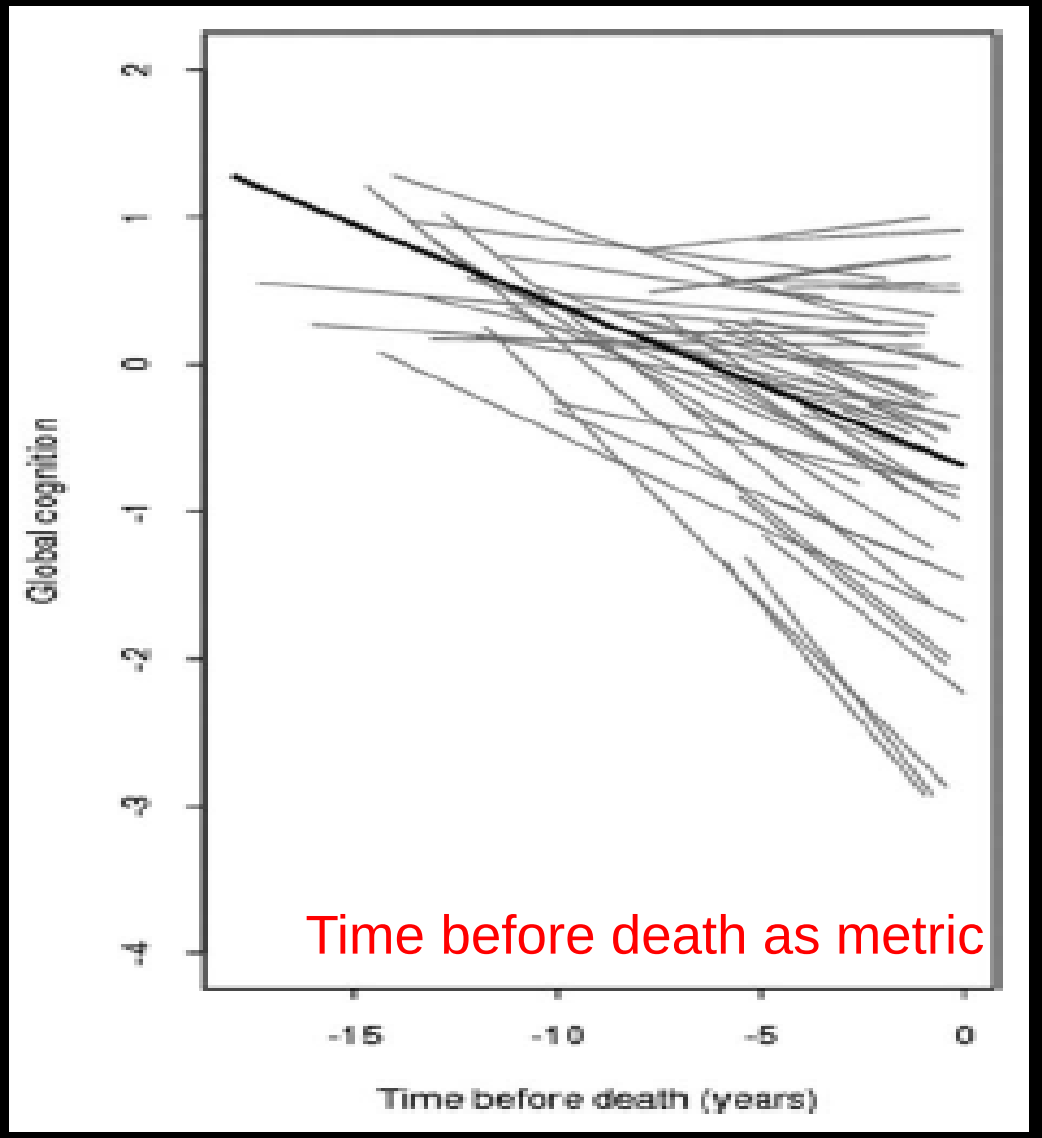


Bennett DA, et al. *Biochemical Pharmacology*. 2014;88:617-630.



Alzheimer's Dementia

Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies



Boyle PA, et al. *Annals Neurology.* 2013;74:478-89

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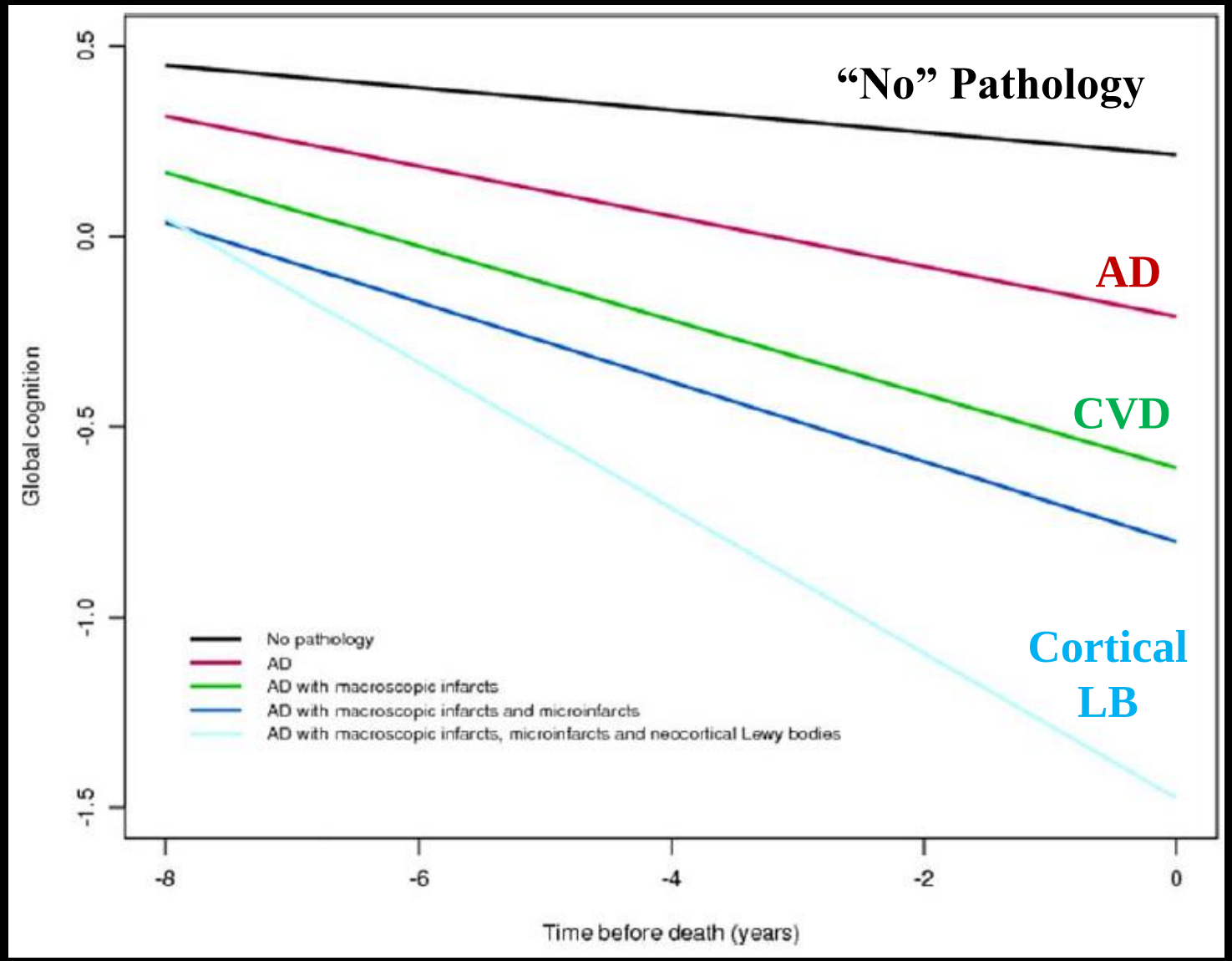

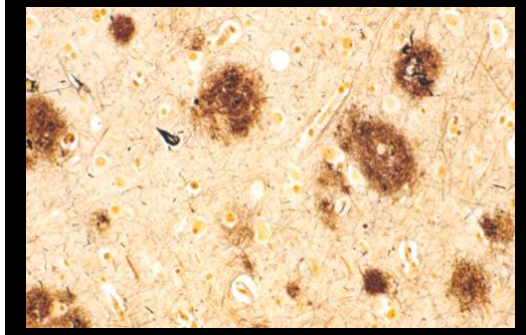

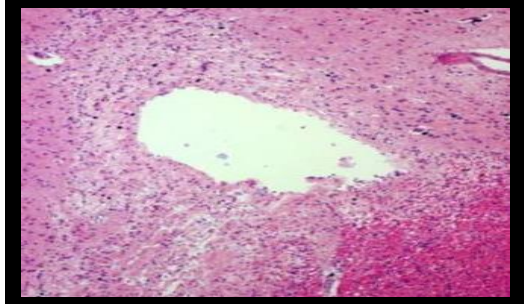

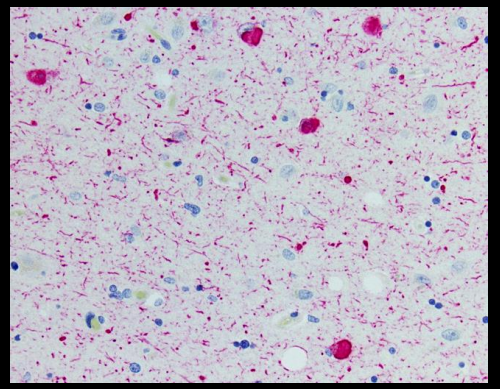

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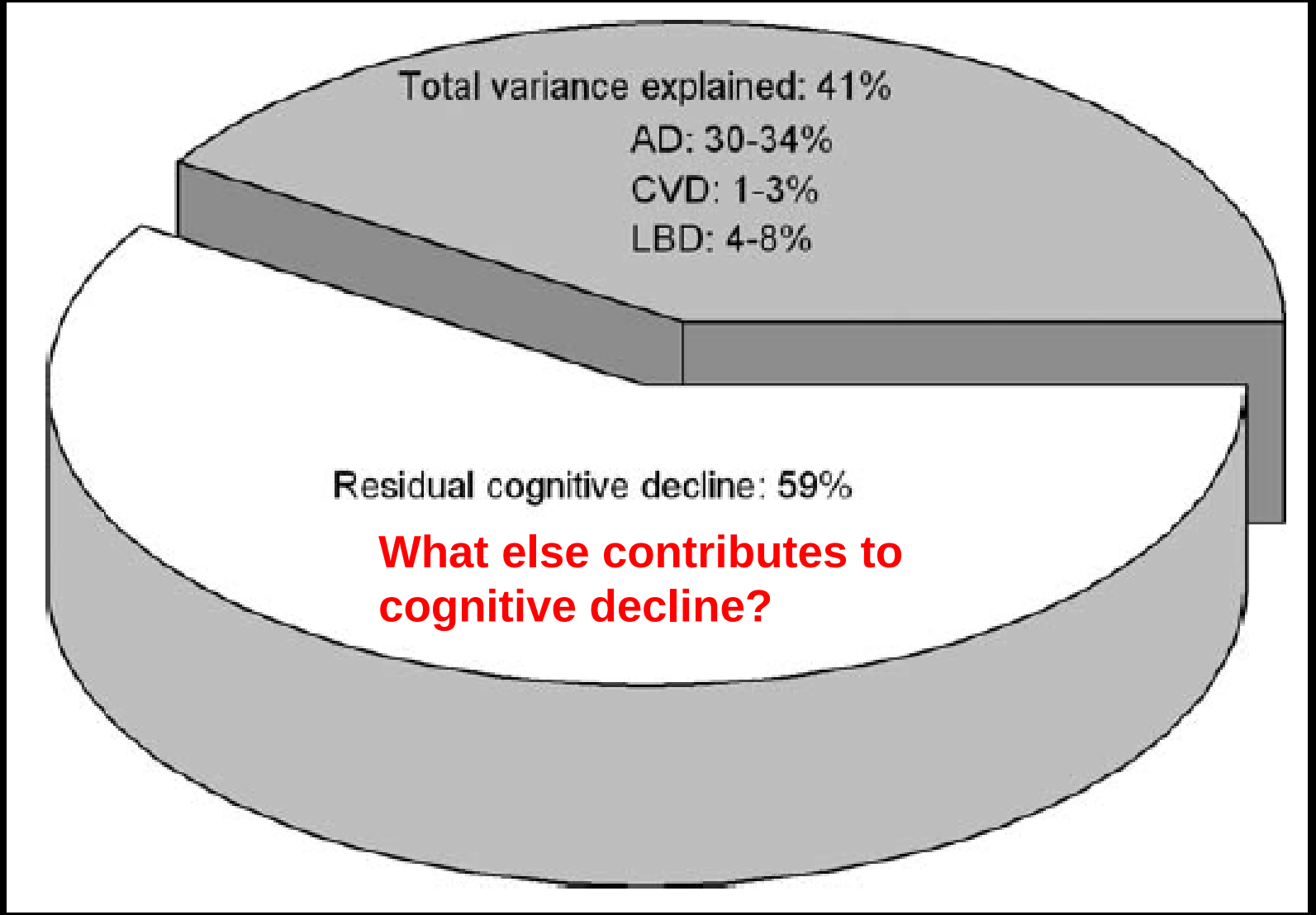
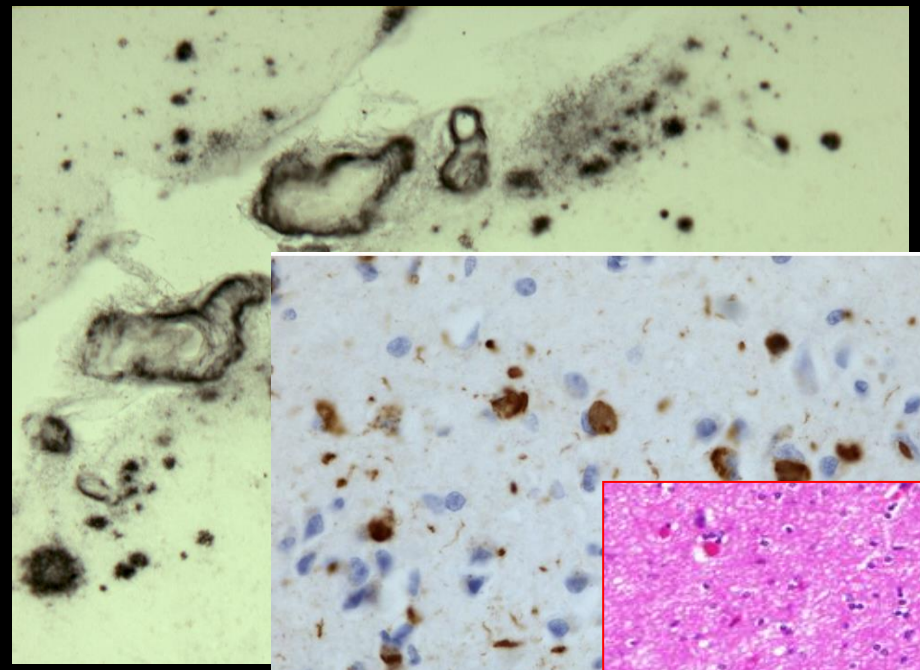


Boyle PA, et al. *Annals Neurology.* 2013;74:478-89



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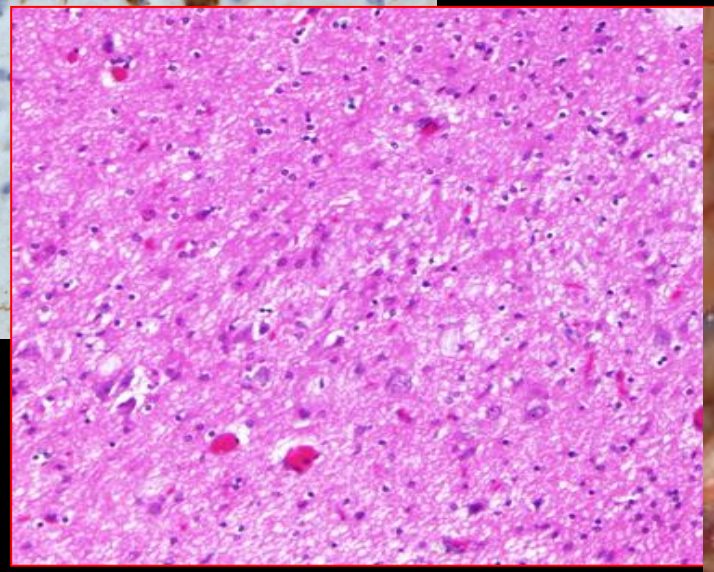
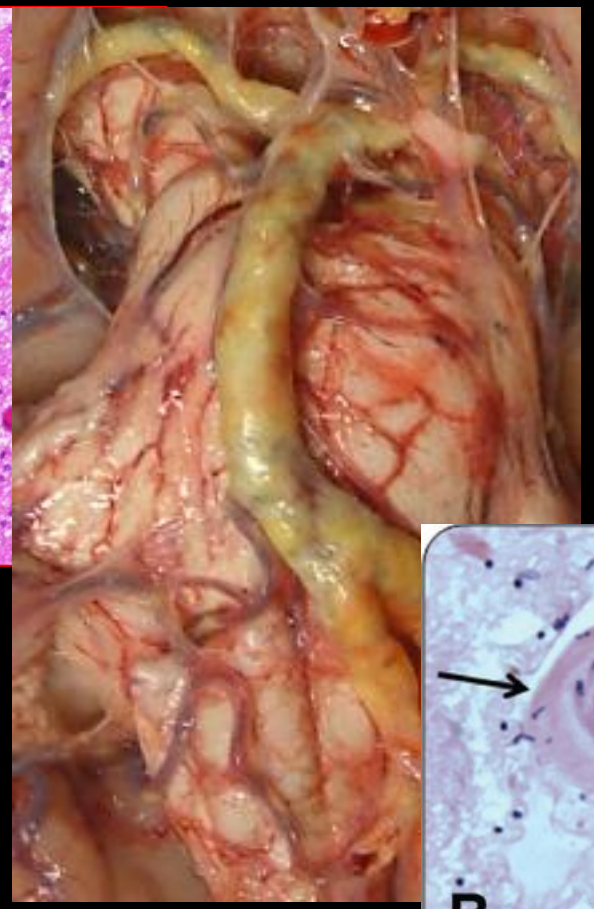
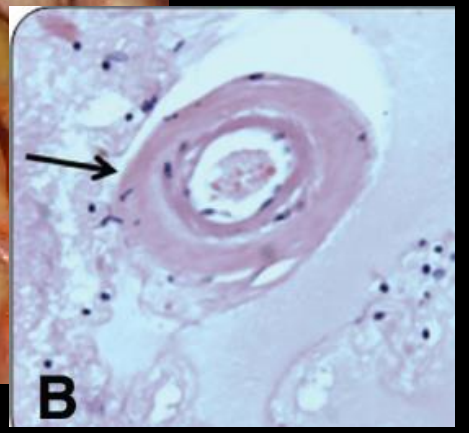
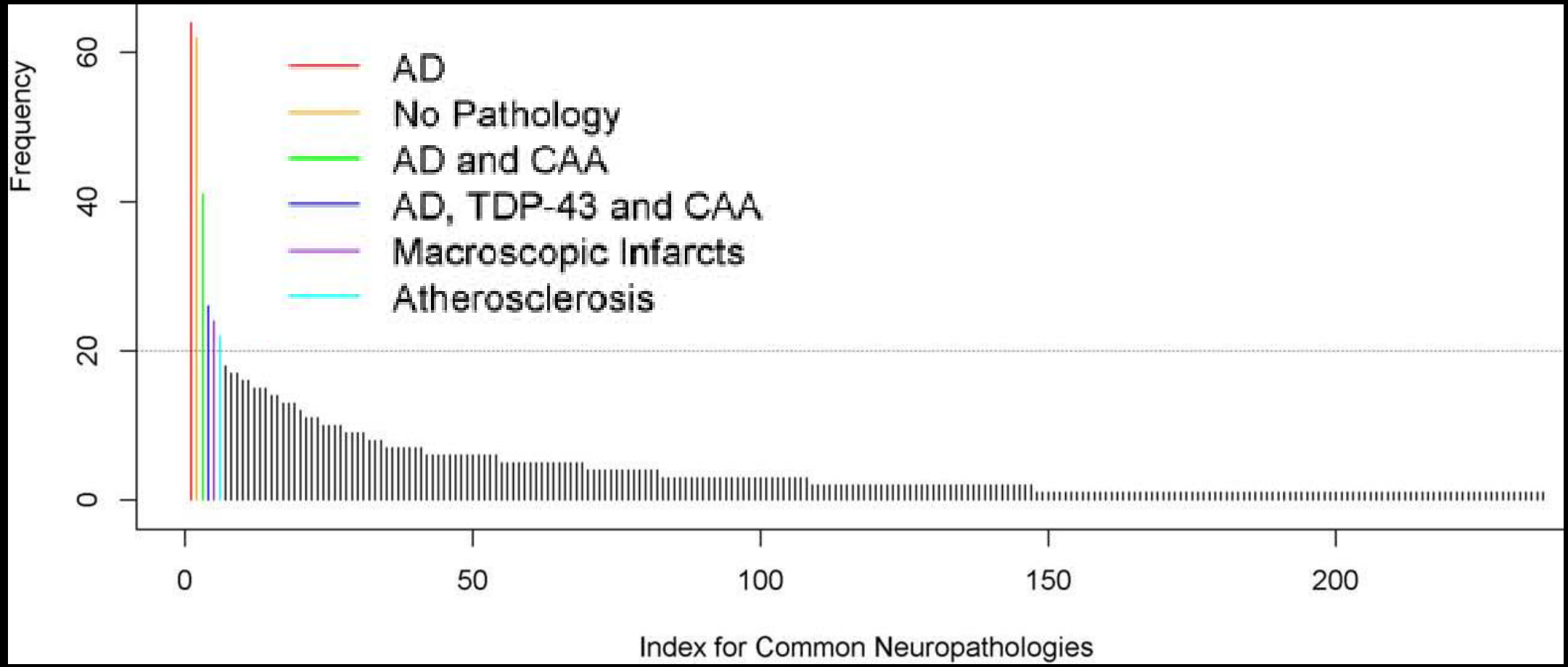





B

Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age



Boyle PA, et al. *Ann Neurol*. 2018;83:74-93.

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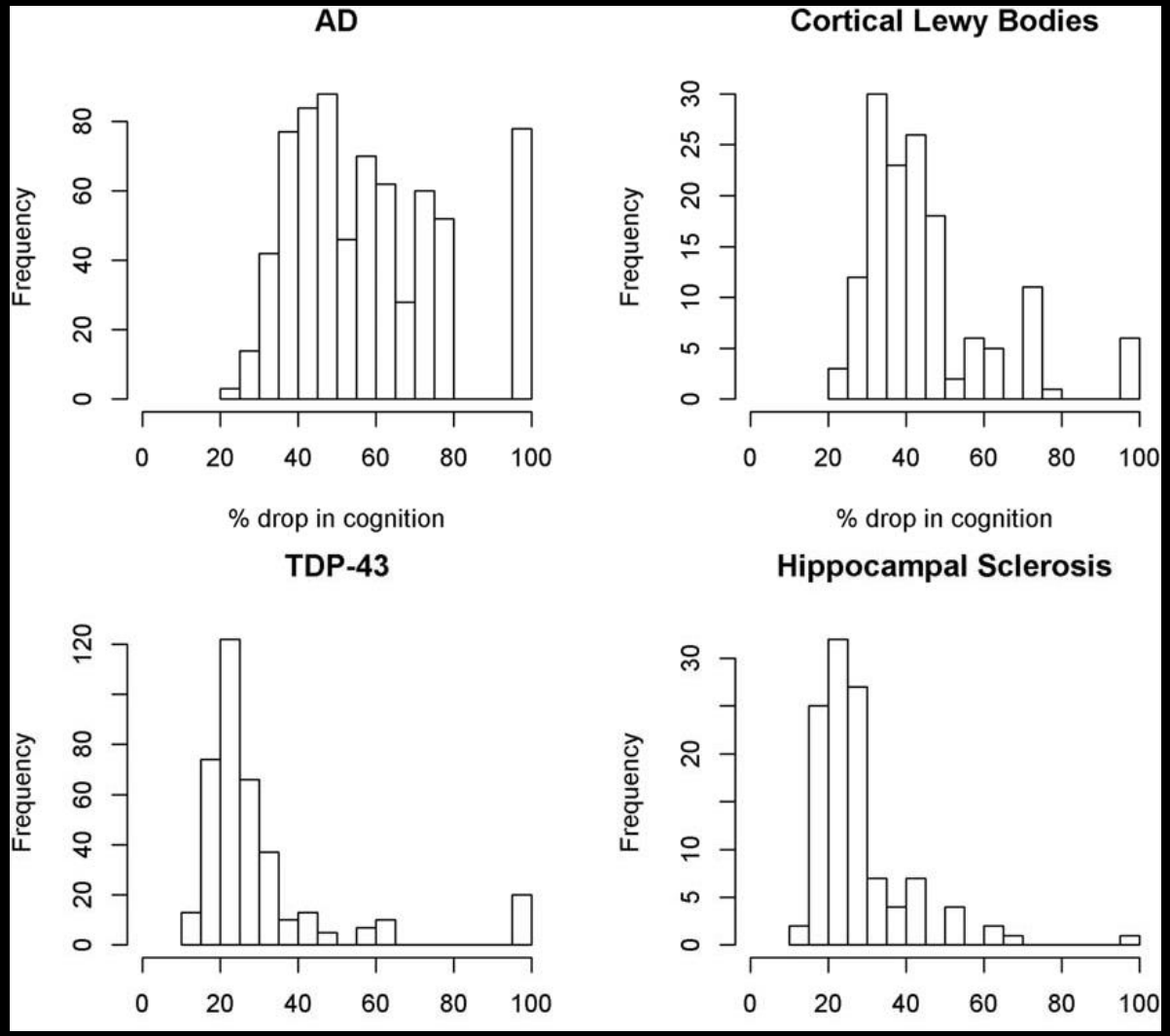
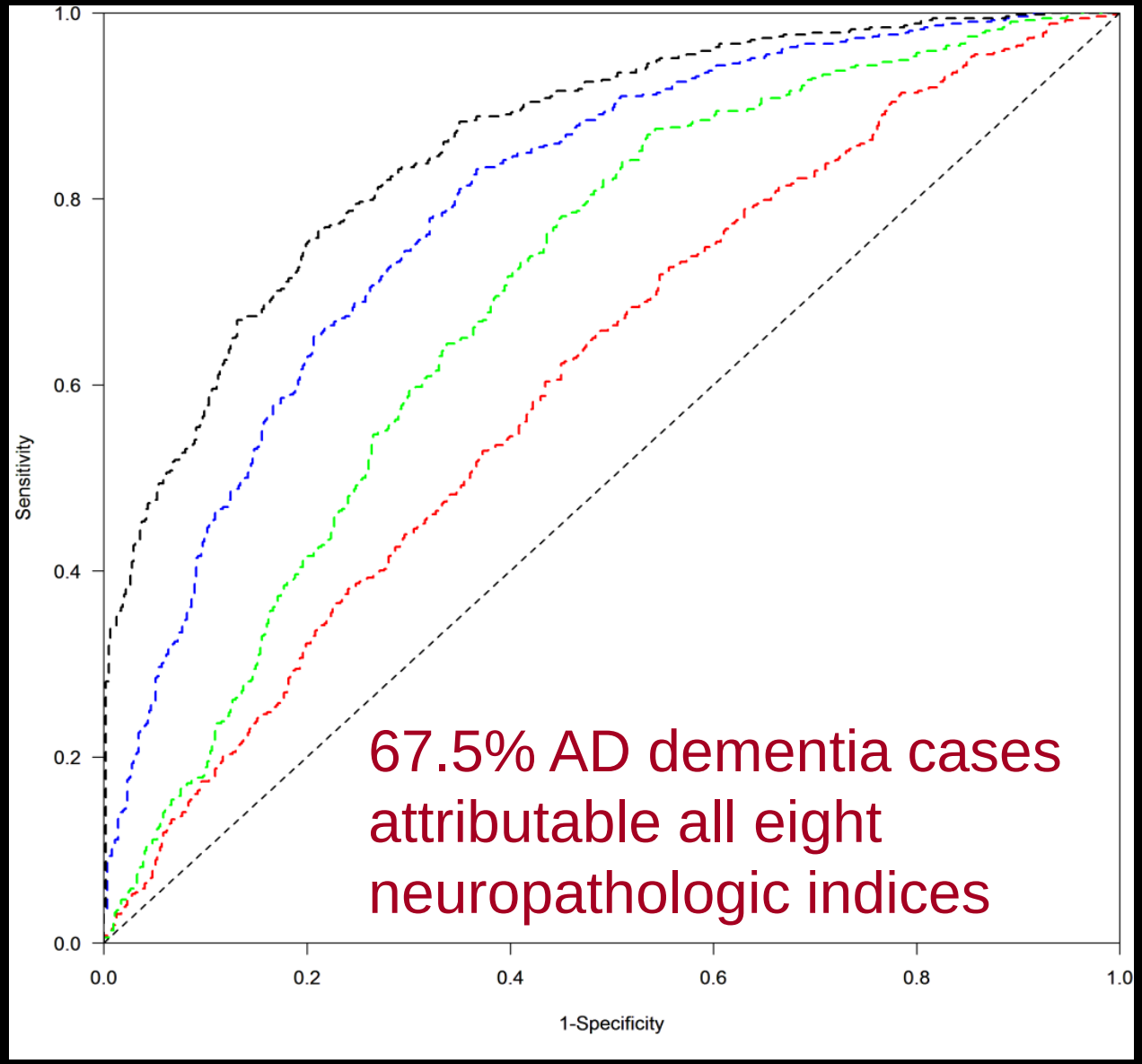


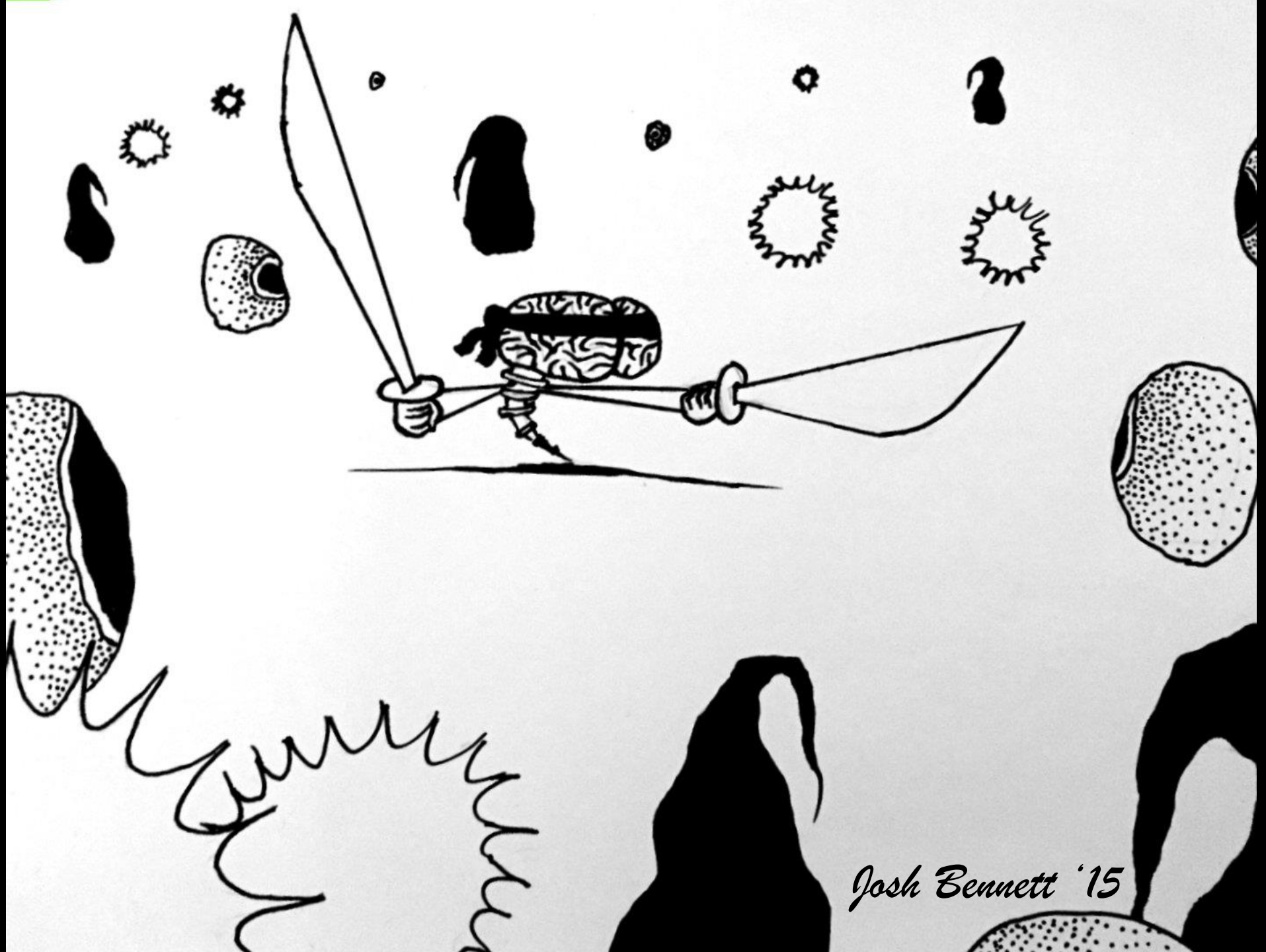
Boyle PA, et al. *Ann Neurol*. 2018;83:74-93.

Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies

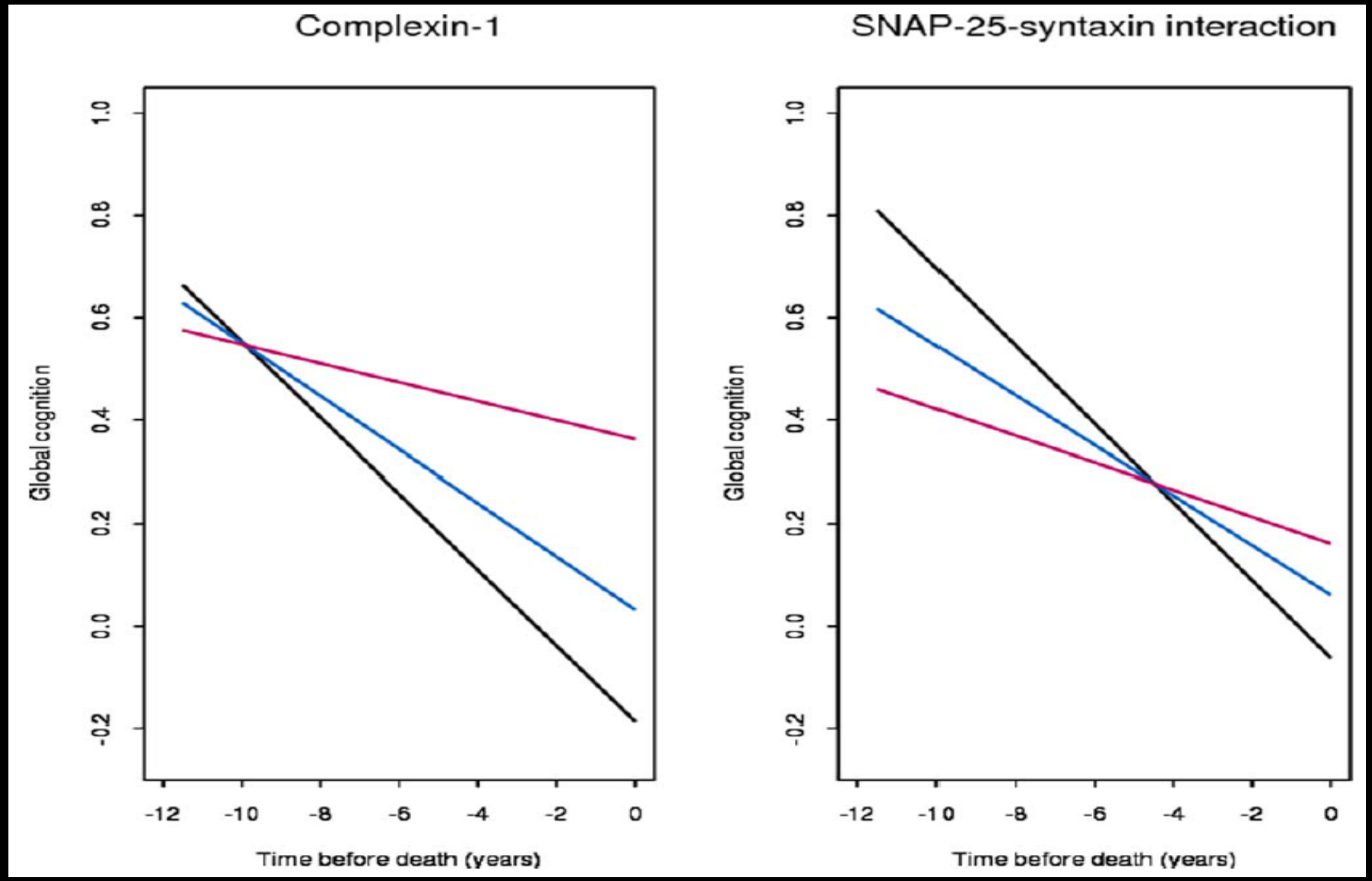
Demographics
And Pathologic AD
And 7 other pathologies
And an indicator for unaccounted AD dementia cases



Boyle PA et al. *Ann Neurol*. 2019;85;114-124.

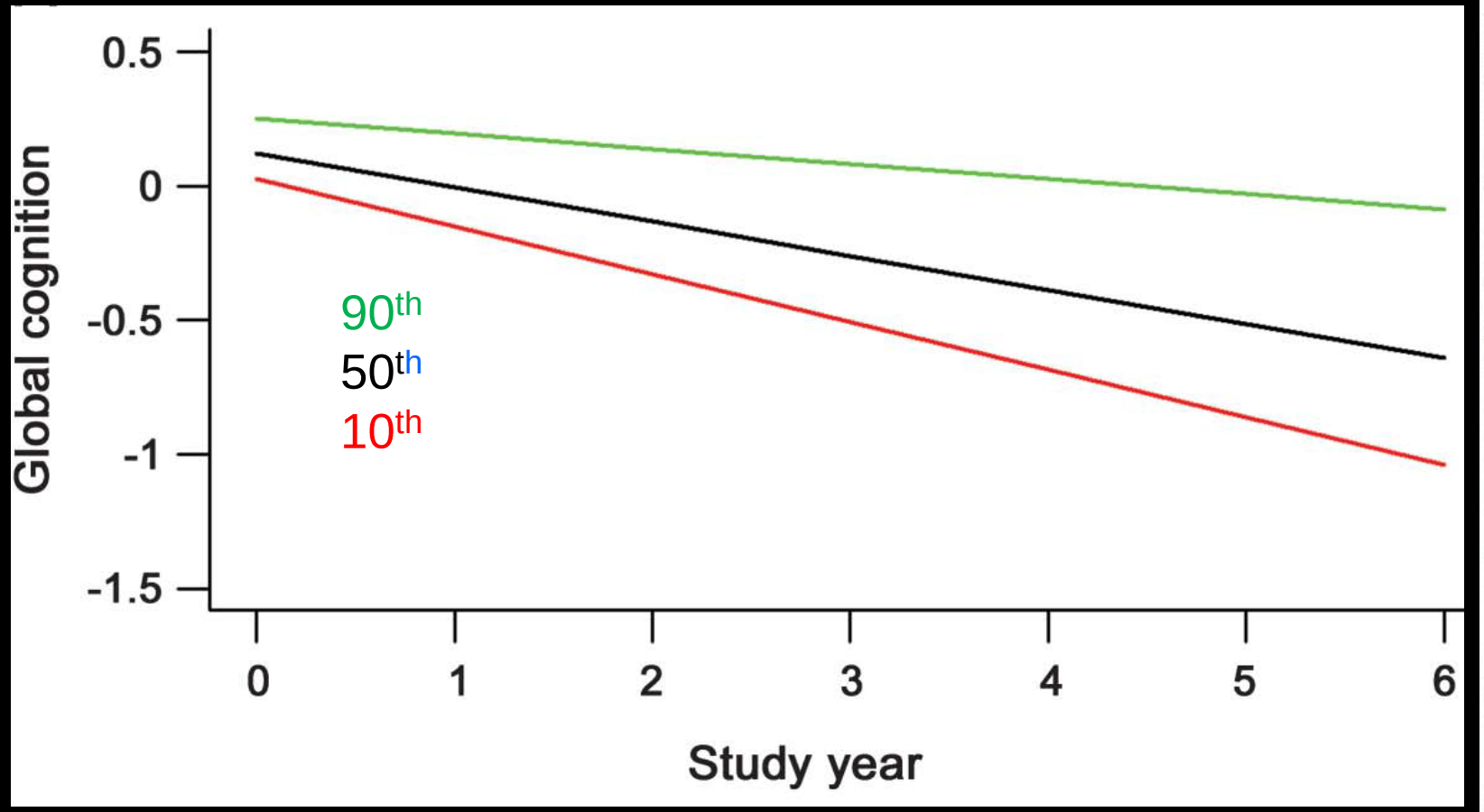

Josh Bennett '15

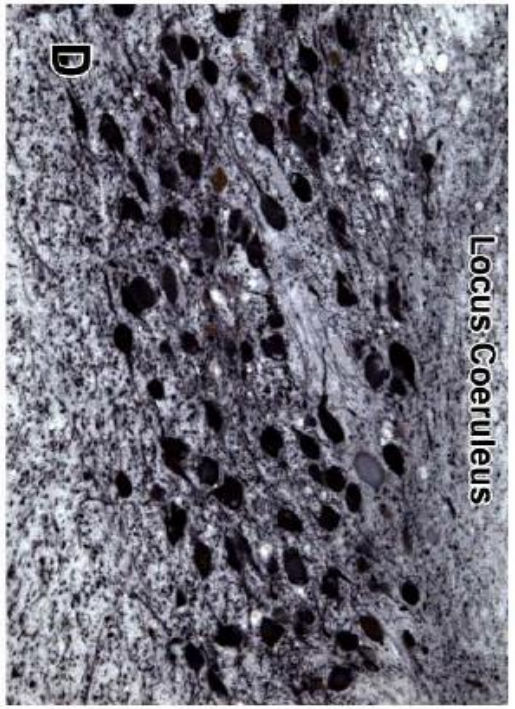
Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies

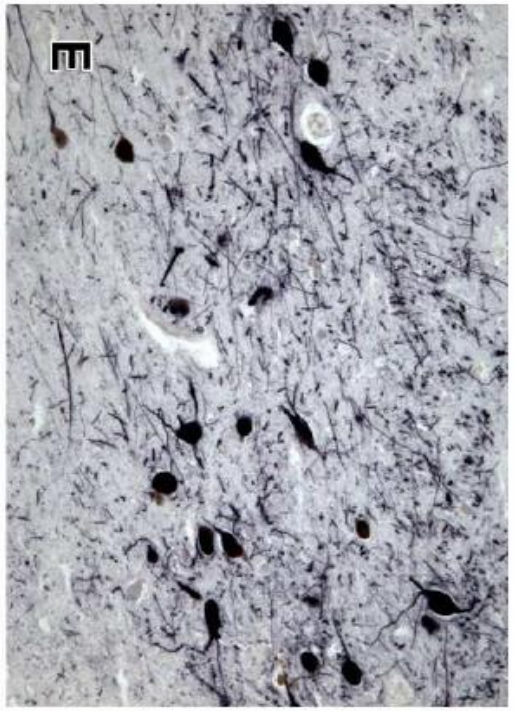


Boyle PA, et al. *Annals Neurology.* 2013;74:478-89

Neural reserve, neuronal density in the locus coeruleus, and cognitive decline

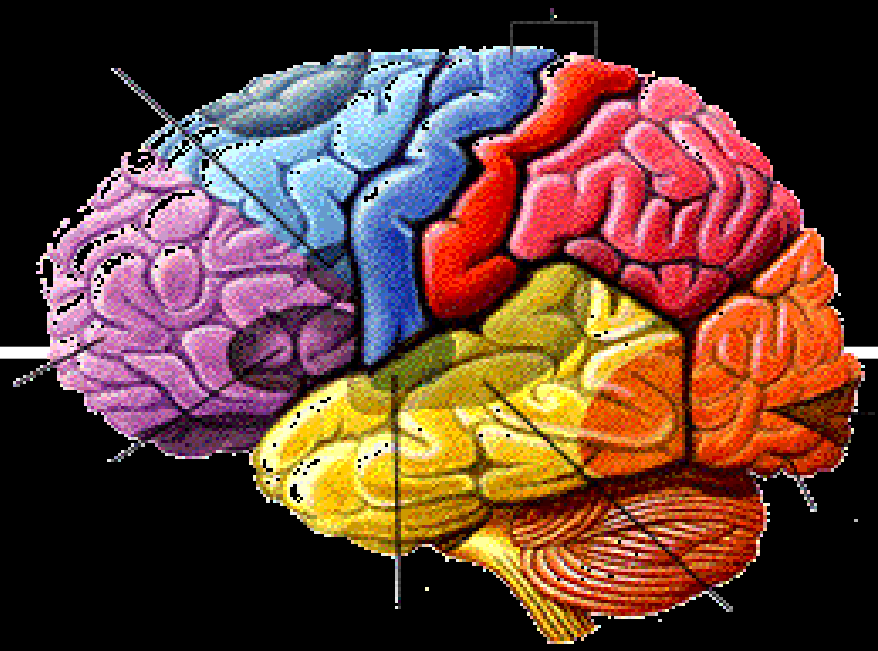






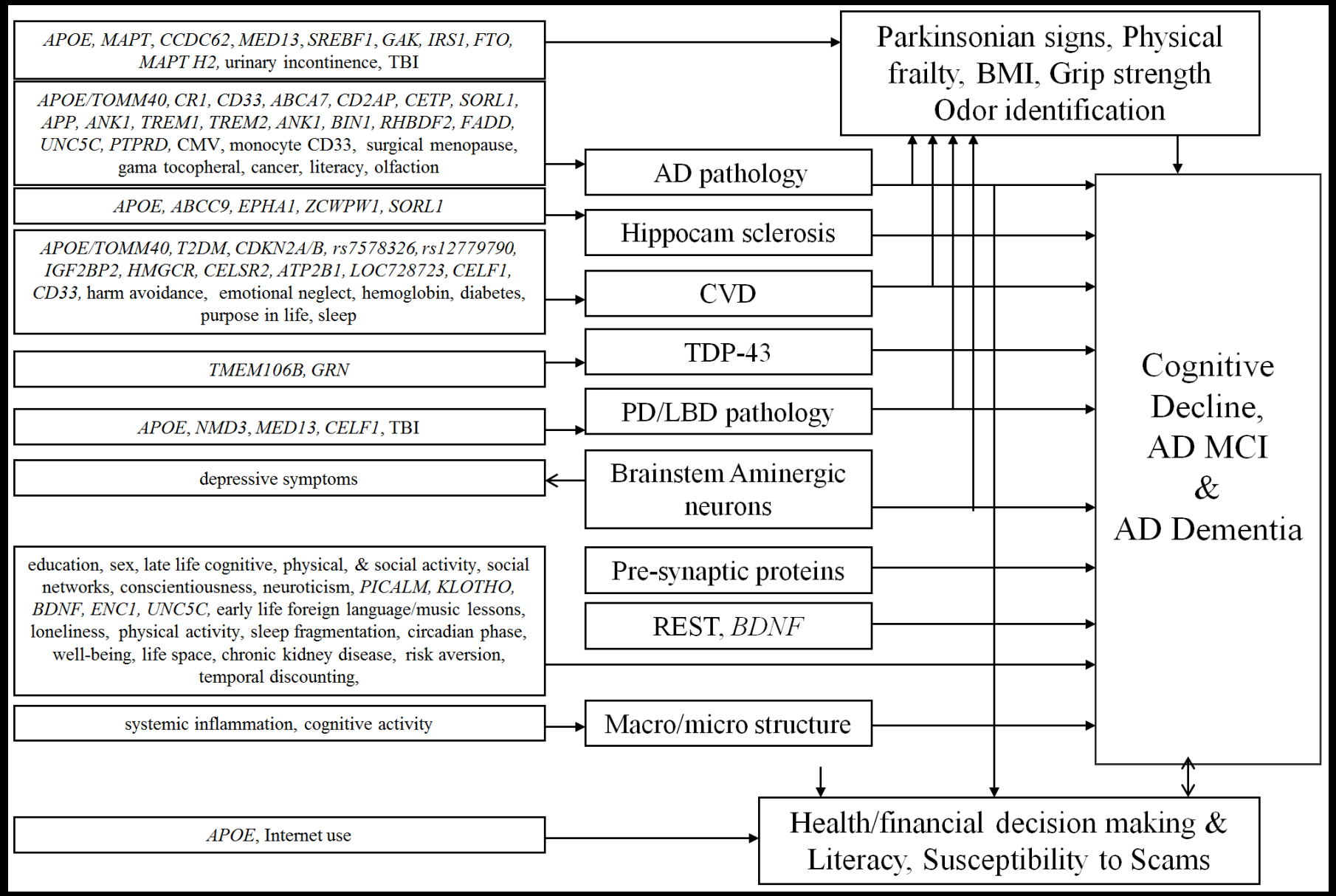
Wilson RS, et al. *Neurology*. 2013;80:1202-1208.

Risk Factors



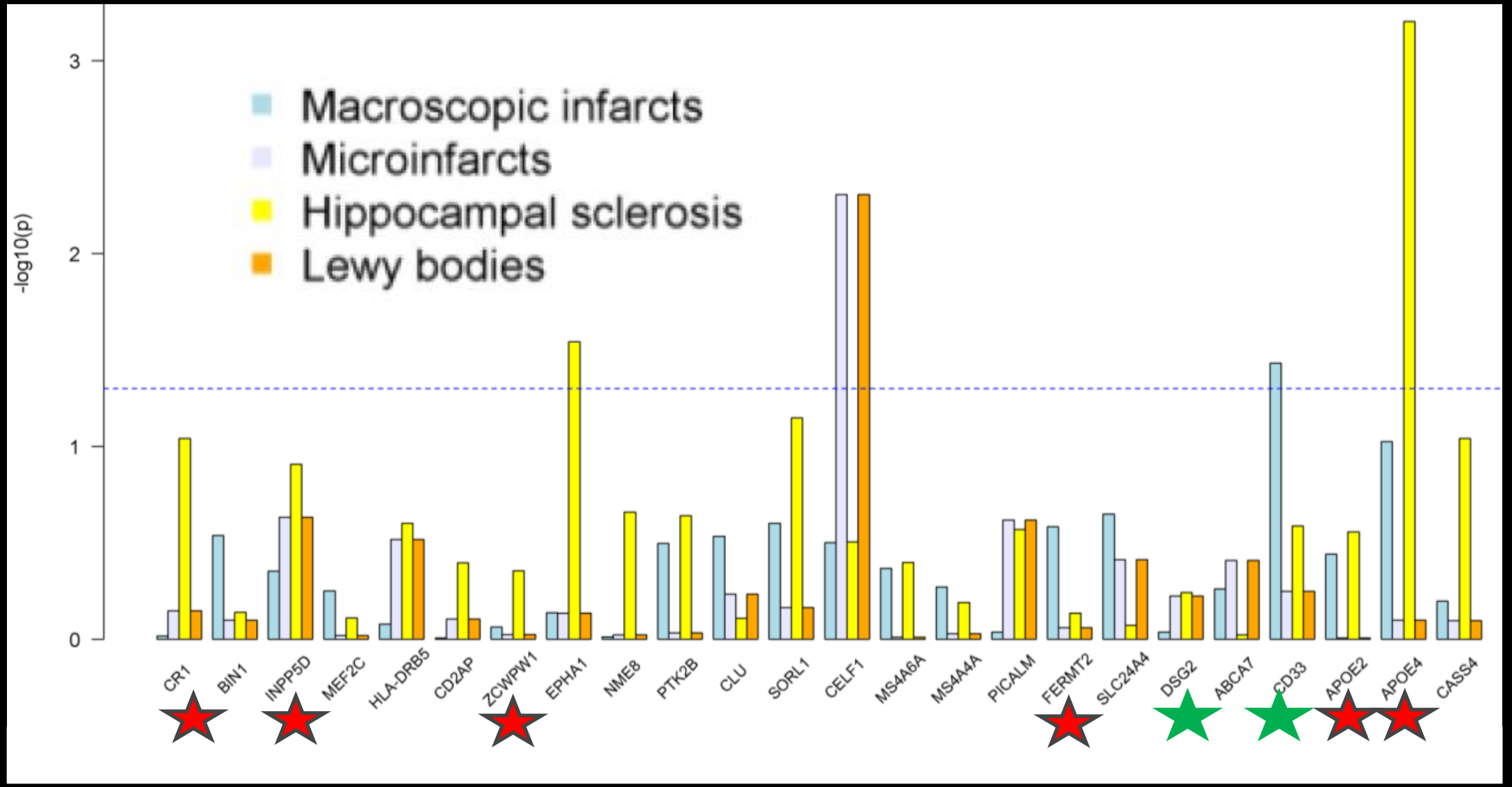
Alzheimer's Dementia

Religious Orders Study and Rush Memory and Aging Project



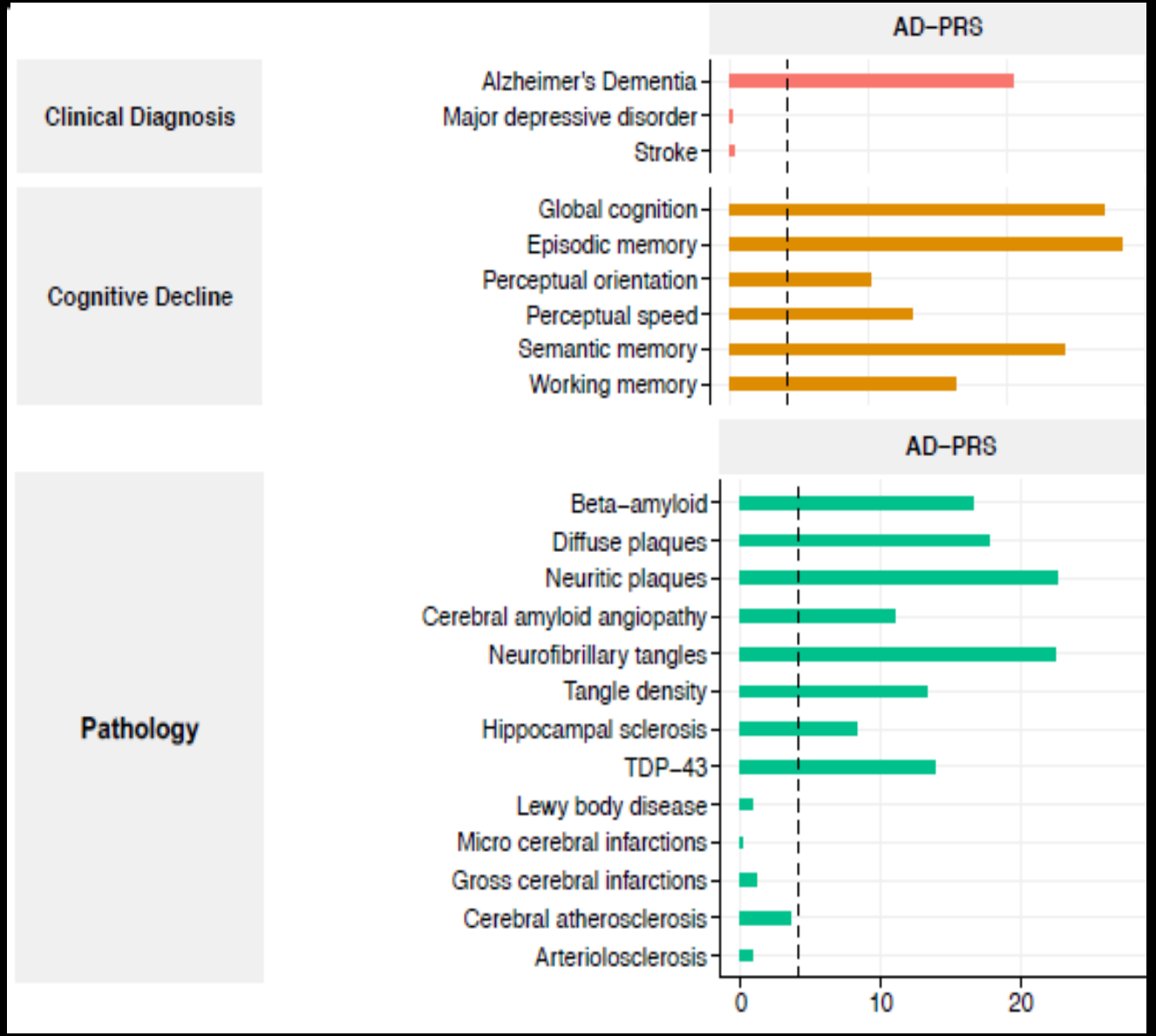
Bennett DA, et al. *J Alz Disease.* 2018;64:S161-S189.

Relation of genomic variants for Alzheimer disease dementia to common neuropathologies



Farfel JM, et al. *Neurology*. 2016;87:489-496.

The Molecular and Neuropathological Consequences of Genetic Risk for Alzheimer's Dementia



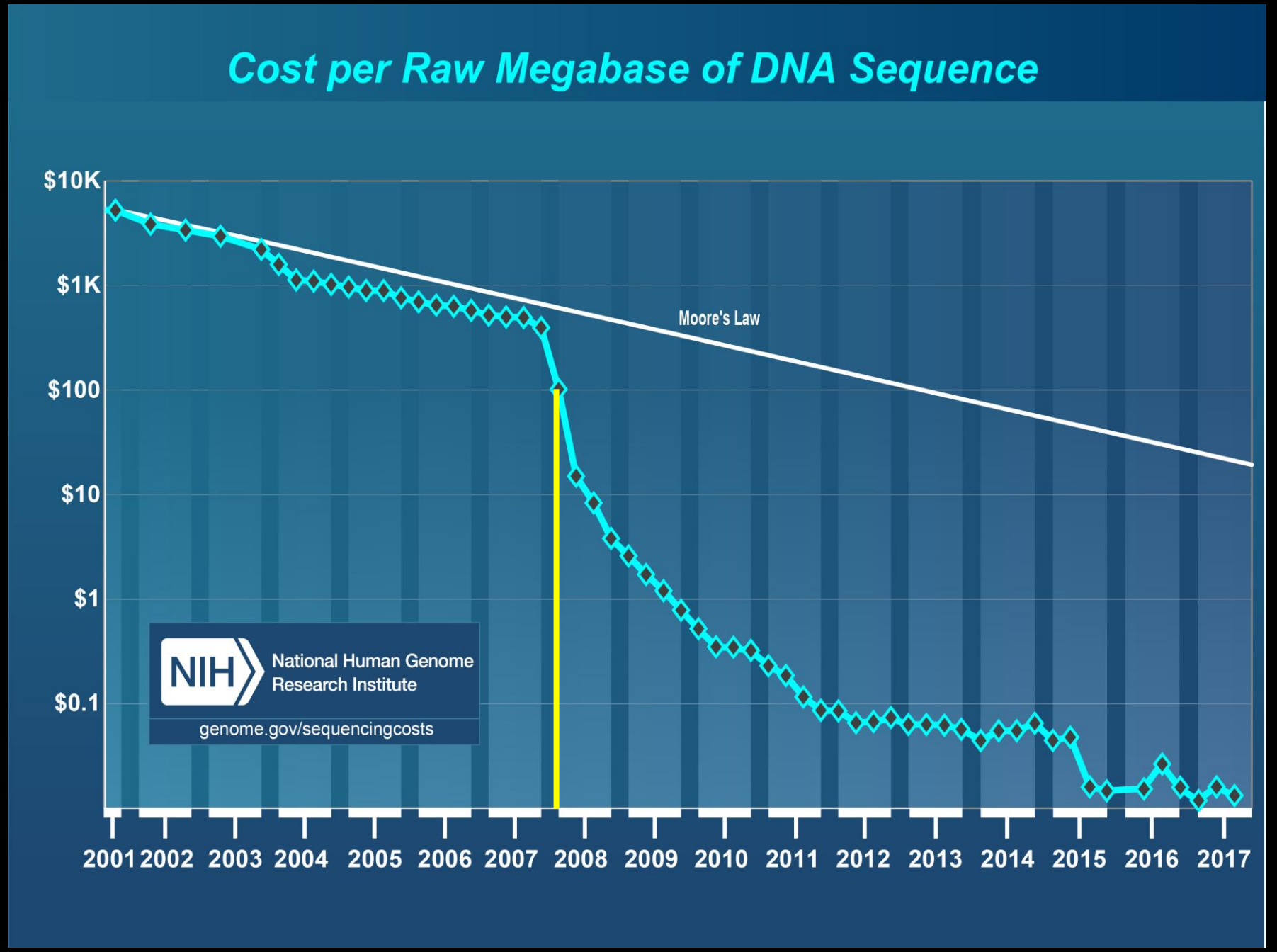
Tasaki S, et al. *Frontiers Neurosci*. 2018;12:699.

Summary

- Loss of cognition with age is a complex function of multiple brain pathologies adding to and interacting with multiple resilience markers
- Numerous genomic, experiential, psychological, and medical factors are associated with cognitive decline that are not associated with any pathology or biology measured to date
- Risk factors for Alzheimer's dementia are often NOT risk factors for Alzheimer's disease (defined biologically in new Framework)

Objectives

- Motivating questions
- Risk factors, pathology, cognitive decline and Alzheimer's dementia
- Identifying the molecular basis of dementia


Cost per Raw Megabase of DNA Sequence
$10K
$1K
$100
$10
$1
$0.1
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
2002
2003
2004
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2006
2007
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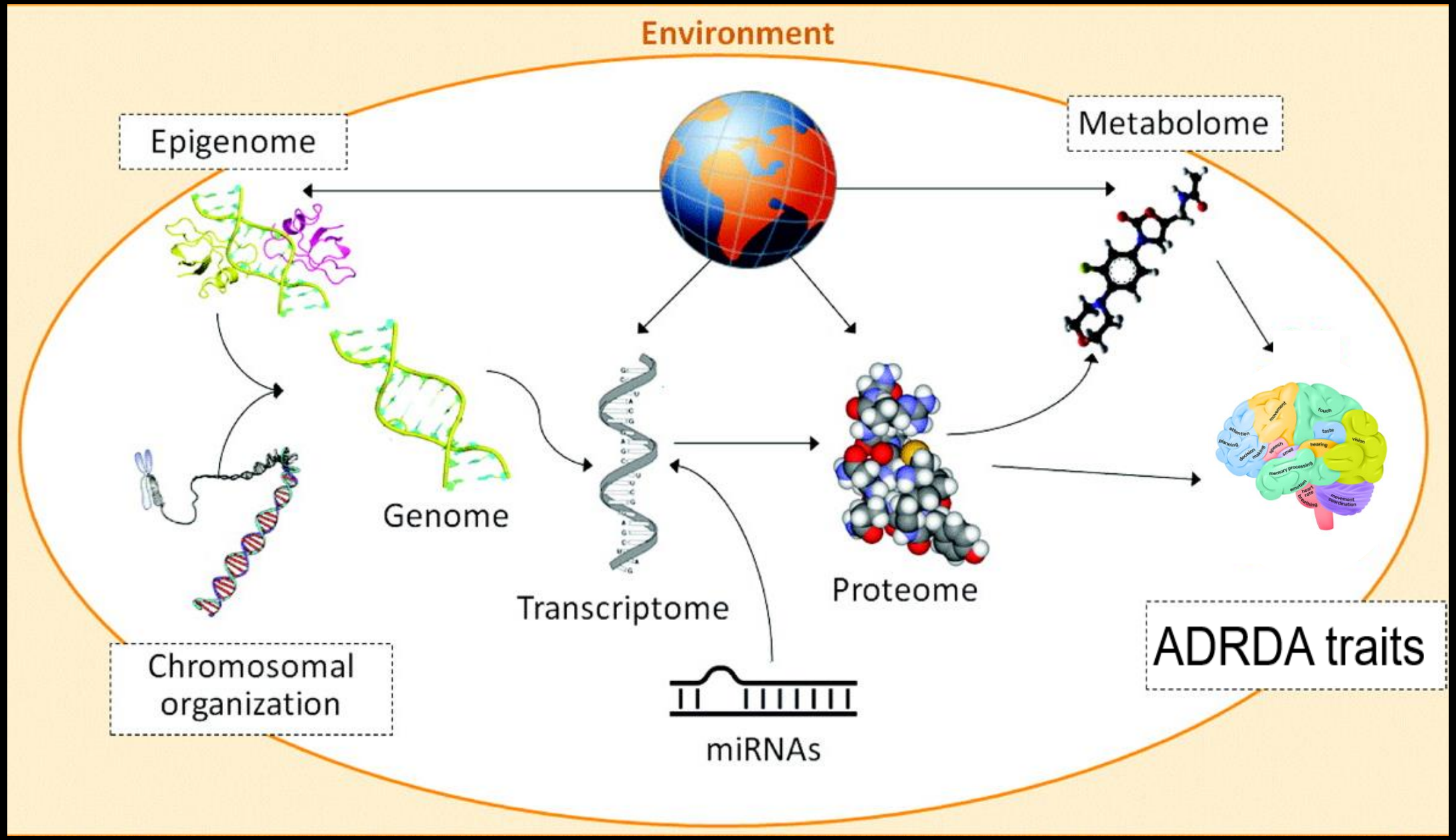
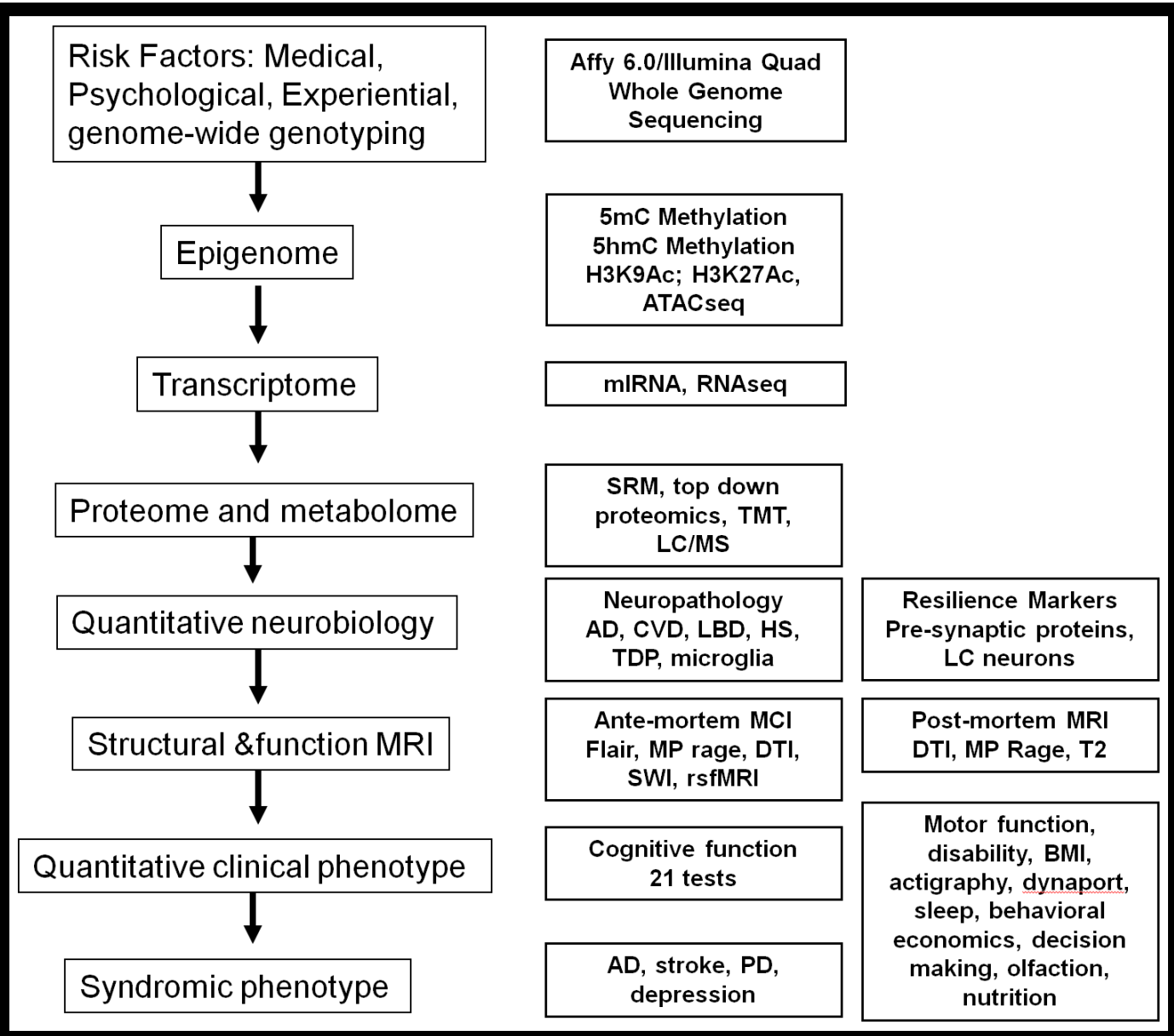
2016
2017


Environment
Epigenome
Metabolome
Genome
Transcriptome
Proteome
Chromosomal organization
miRNAs
ADRDA traits

Religious Orders Study and Rush Memory and Aging Project



6mA
DLPFC

Bulk RNAseq
DLPFC
PCC
AC
Nuc Accumbens
Lat Hypothal
snRNAseq
DLPFC
Hippocampus
Watershed
m6A

Bennett DA, et al. *J Alz Disease.* 2018;64:S161-S189.

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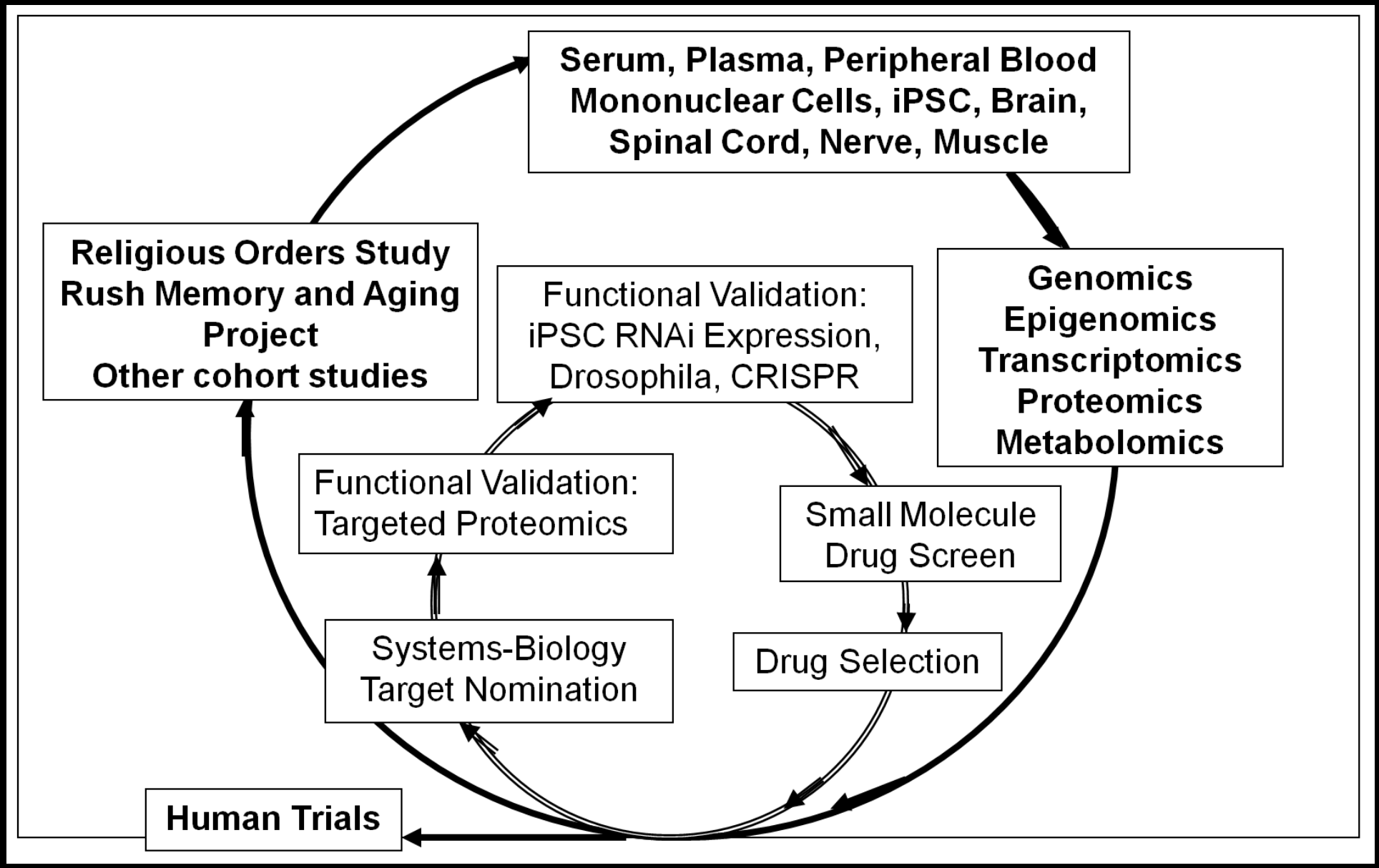

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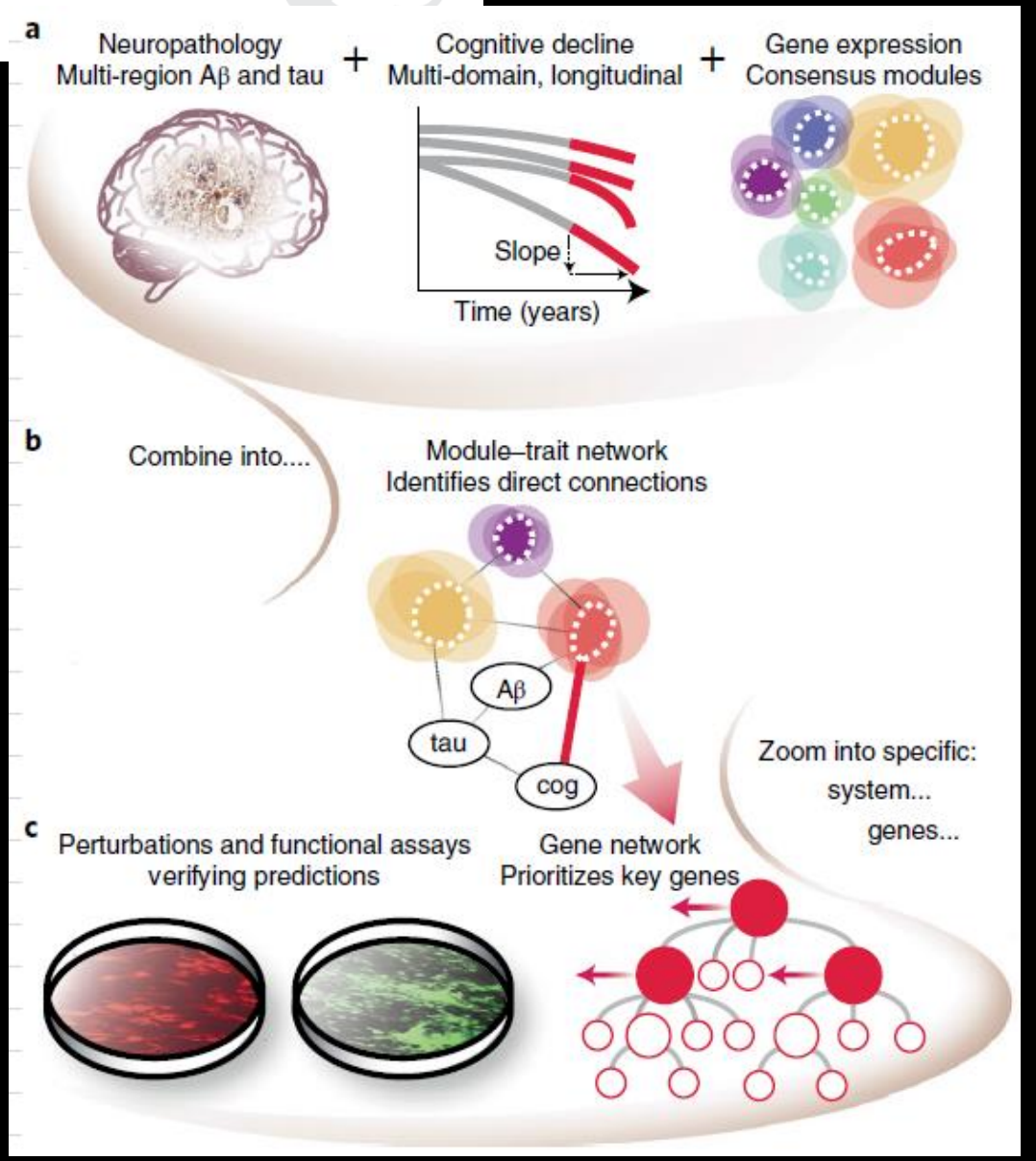
A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease



Mostafavi S, et al. *Nature Neuroscience*. 2018;21:811-819.

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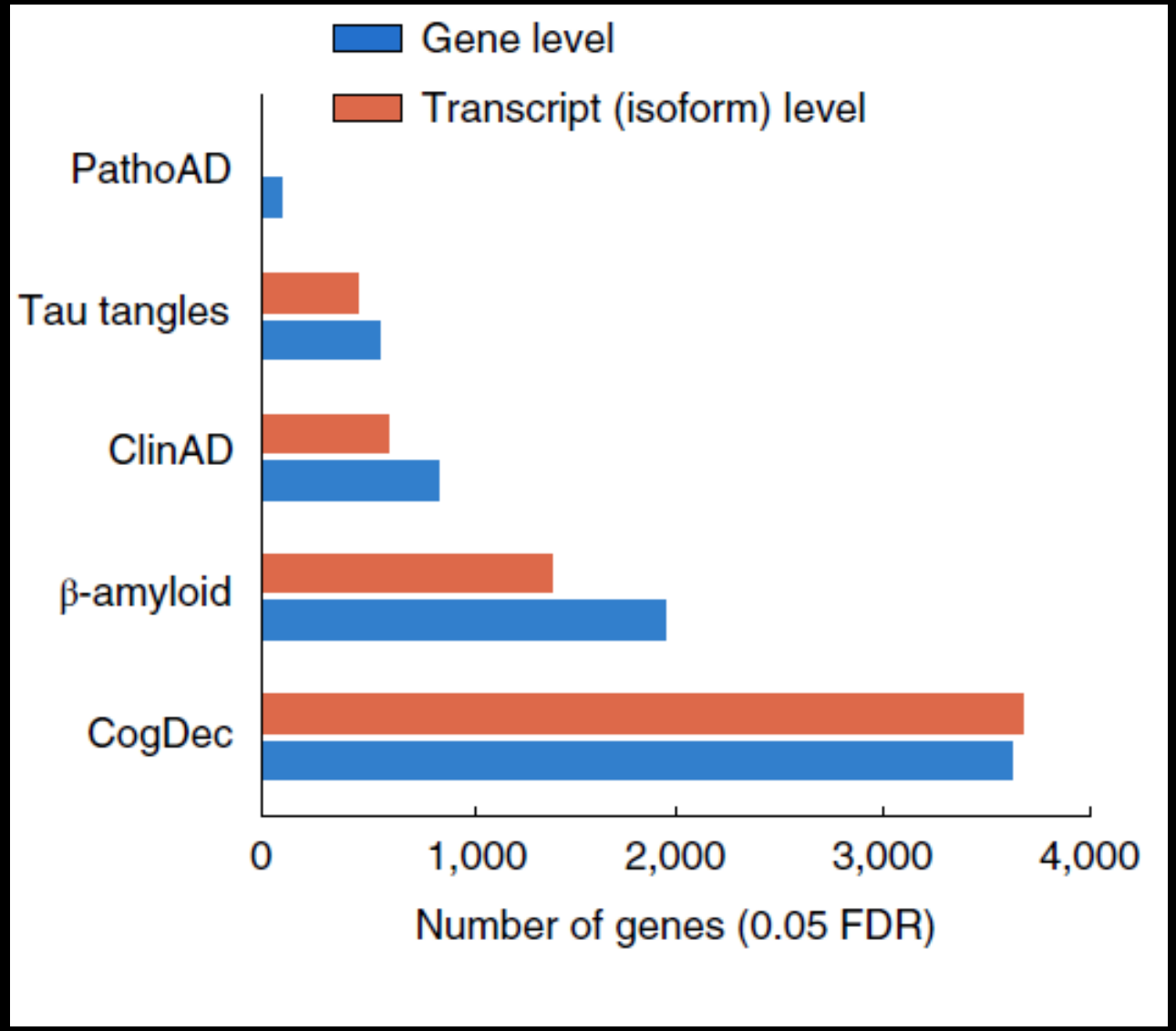

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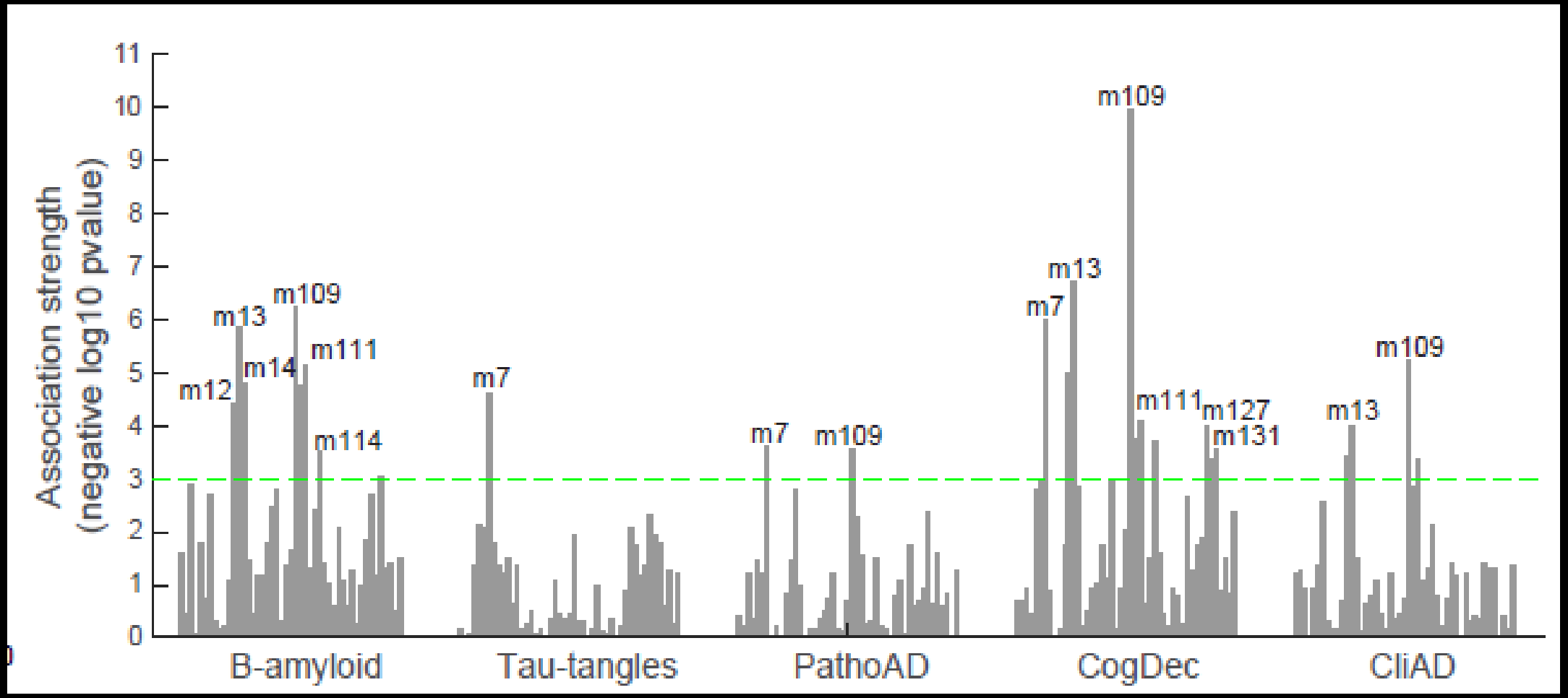

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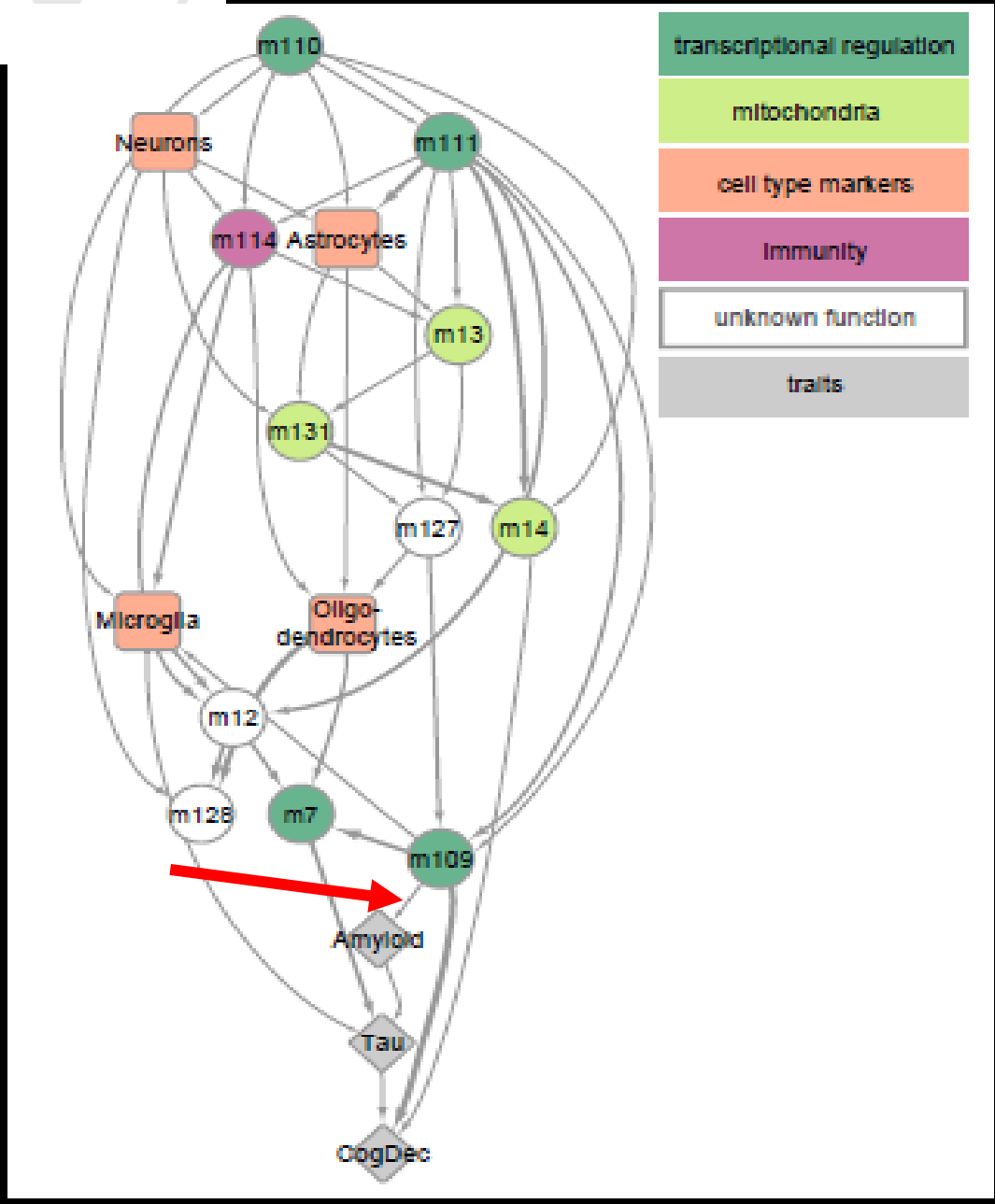
47 co-expression networks
53 ADRD phenotypes



Mostafavi S, et al. *Nat Neurosci*. 2018;21:811-9.

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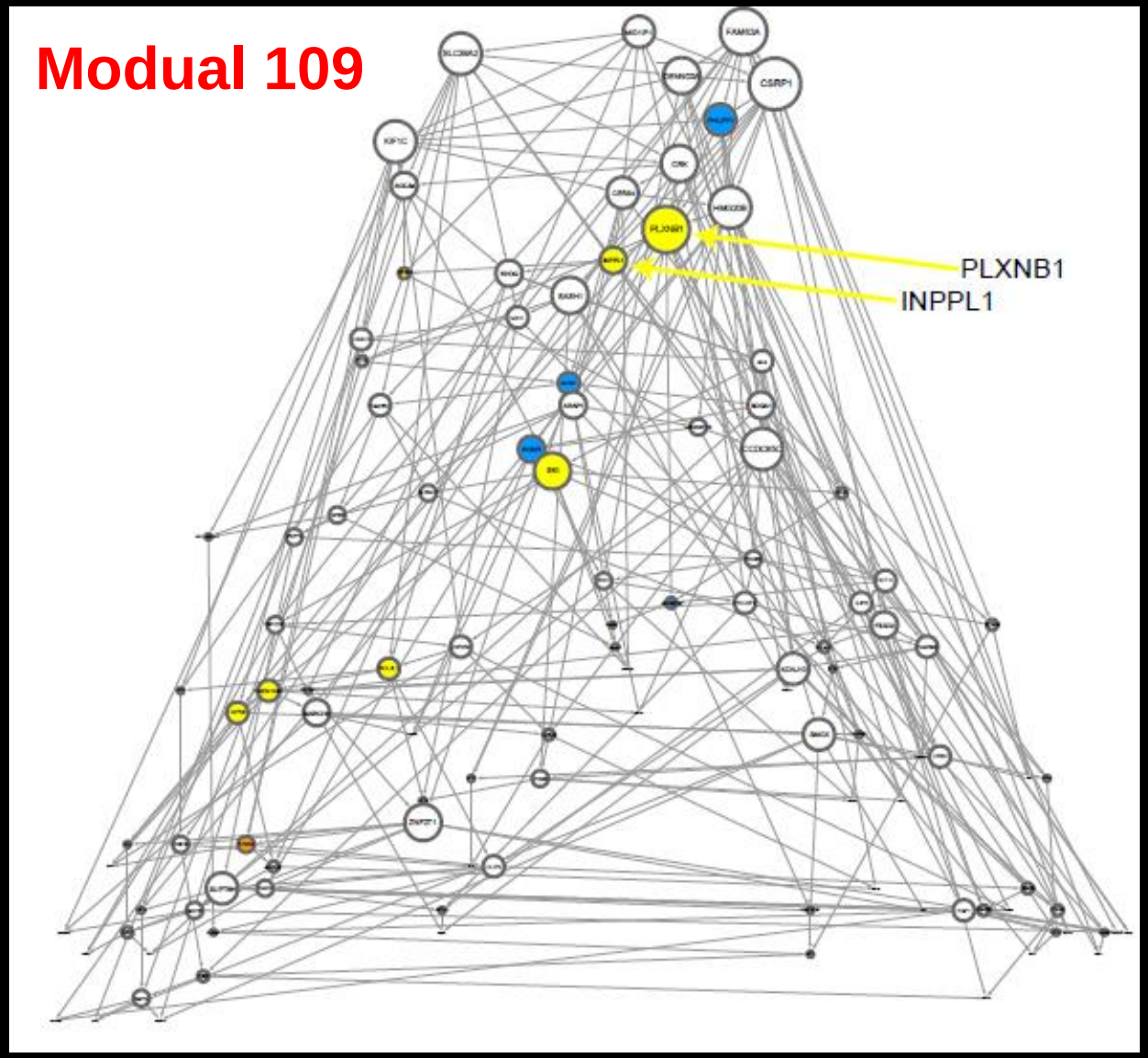
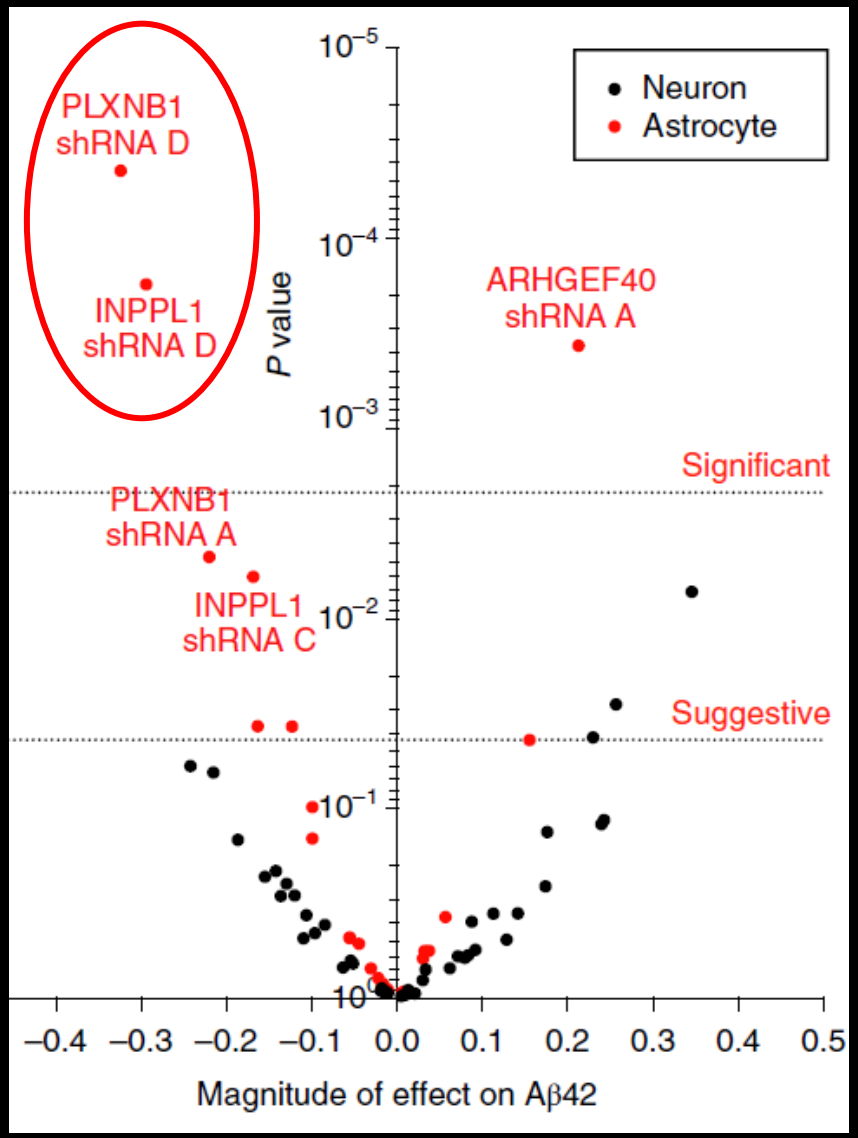
Knockdown experiments
Effect of construct on Aβ 42 secretion.





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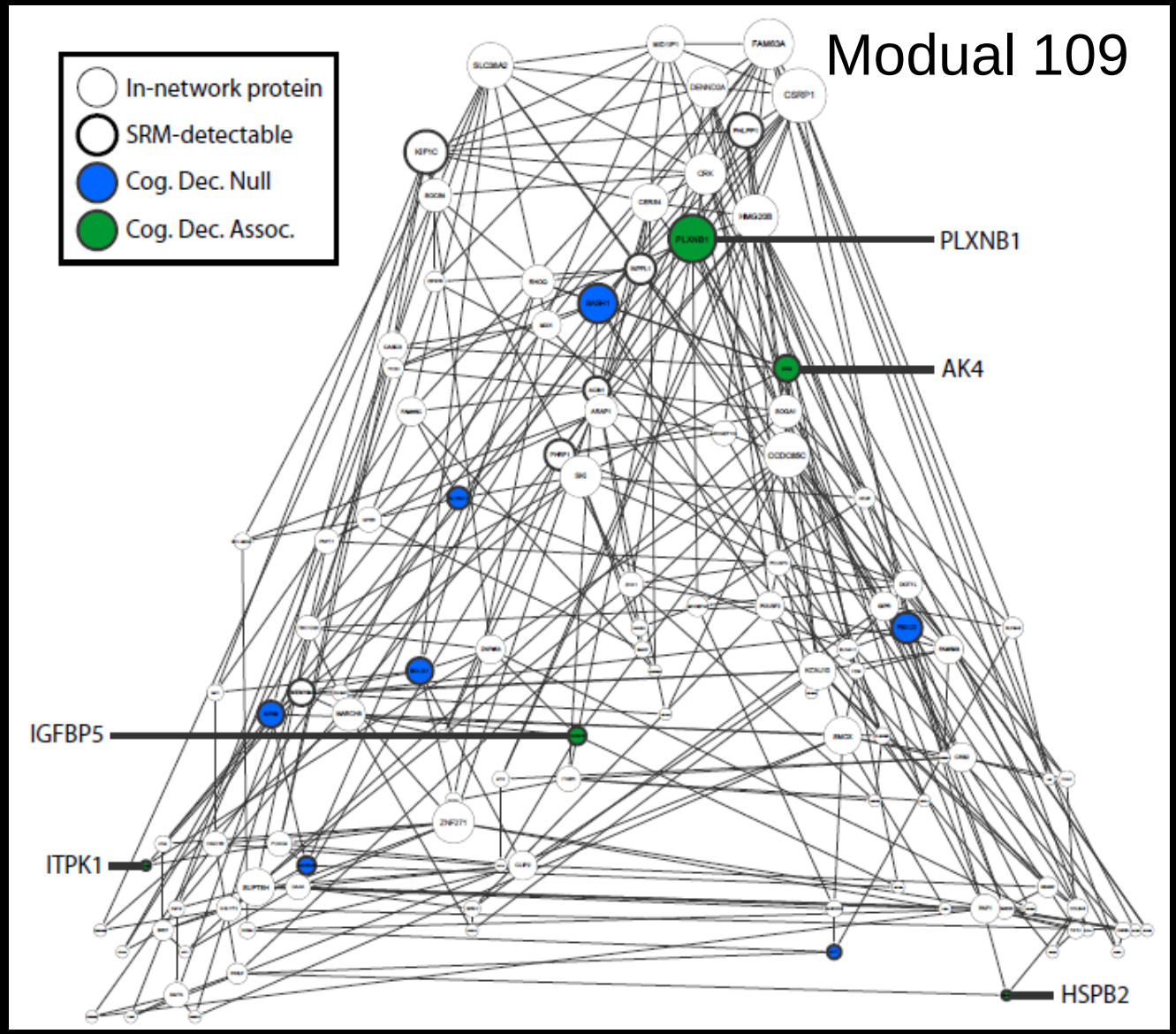
Targeted proteomics of human neocortex uncover multiple paths to Alzheimer's dementia



Yu L, et al. *Annals of Neurology*. 2018;84:78-88.

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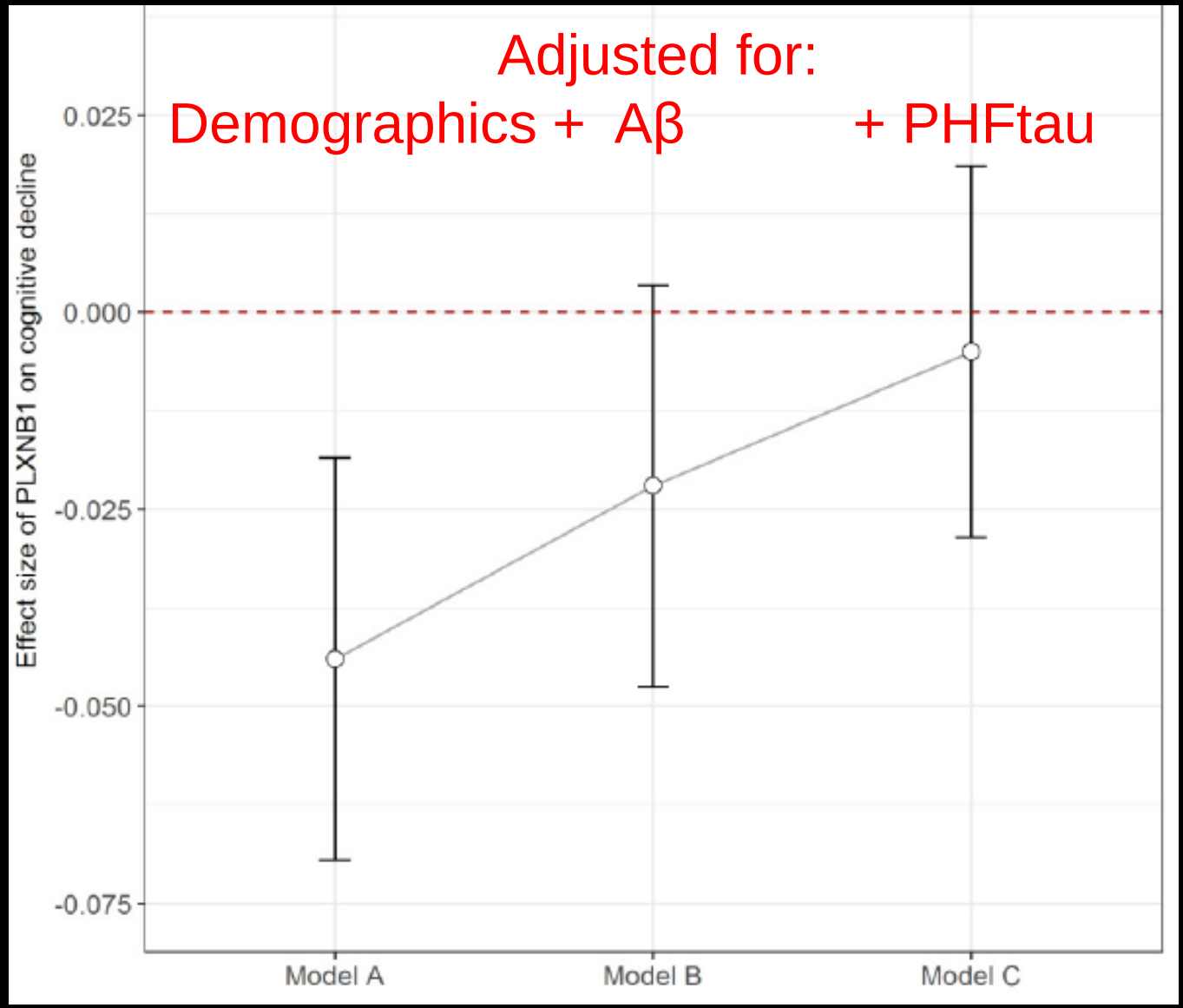
PLXNB1

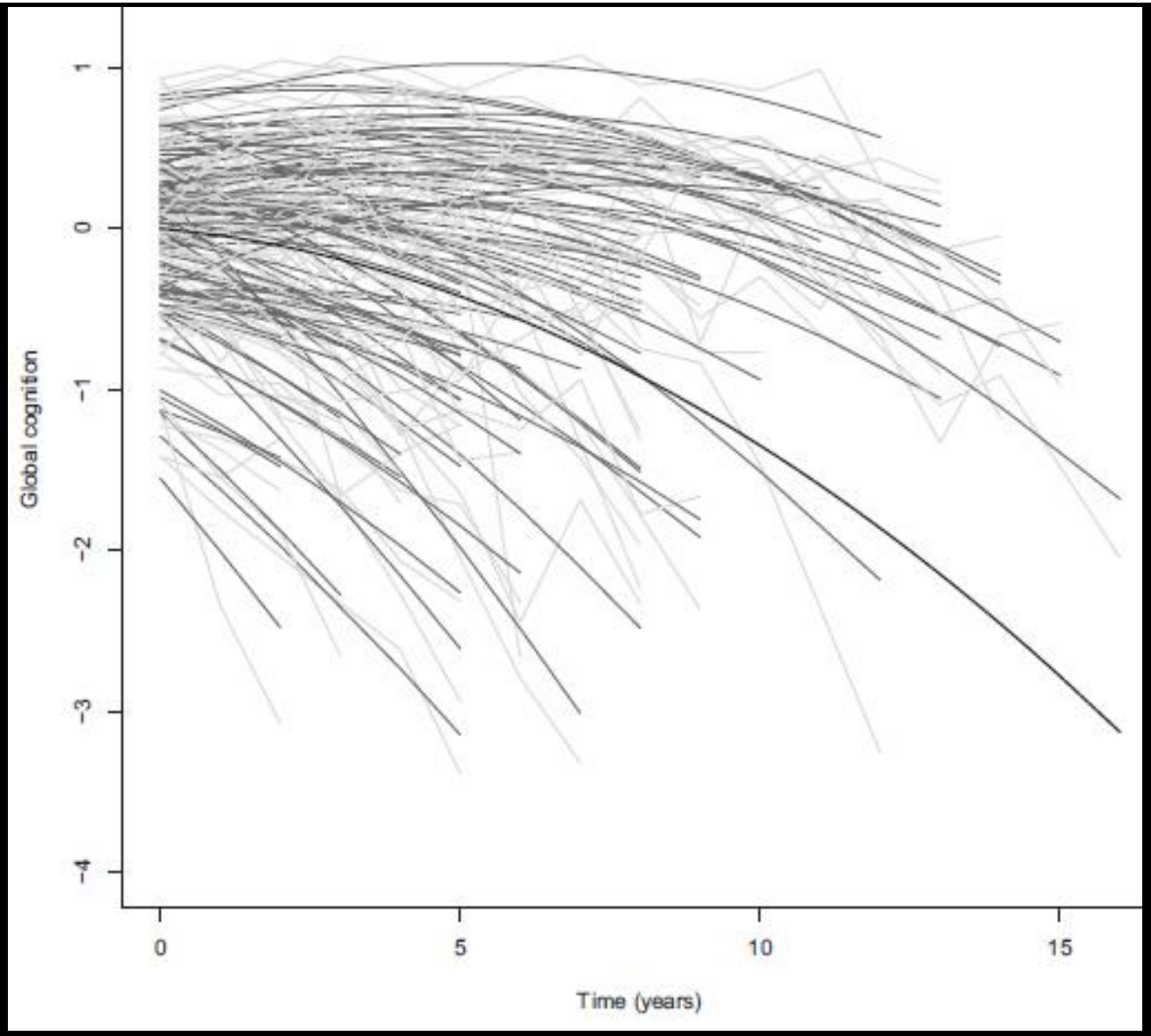


Yu L, et al. *Annals of Neurology*. 2018;84:78-88.

Summary

- Found mRNA coexpression networks related to AD
- Nominated genes in m109 as drivers of amyloid-beta
- Knockdown experiments *ex vivo* illustrates altered amyloid-beta production as predicted
- SRM proteomics quantified protein and showed its effect mediated by AD pathology as predicted

Residual Decline in Cognition After Adjustment for Common Neuropathologic Conditions



Yu L, et al. *Neuropsychology*. 2014;29:335-43.

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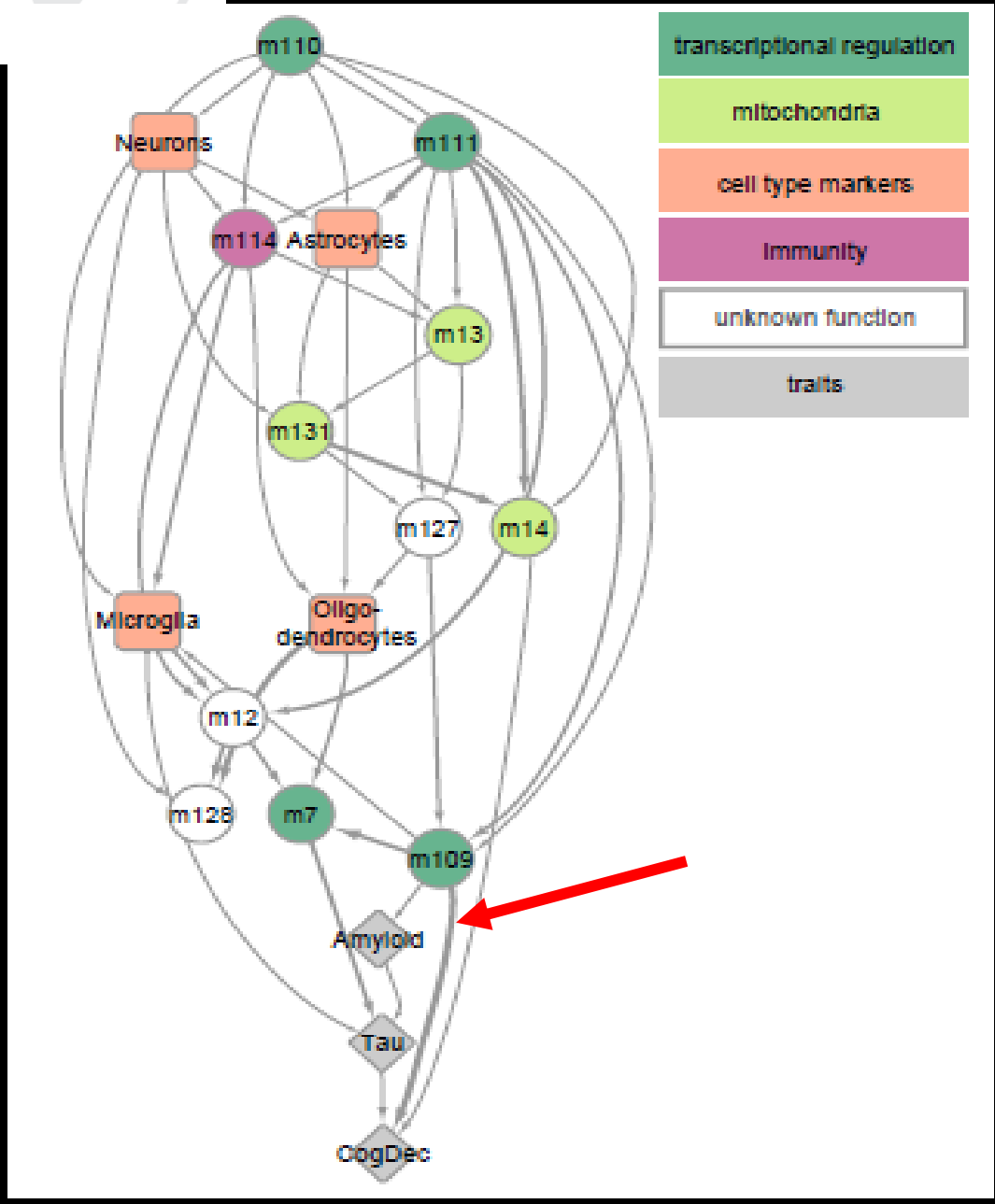

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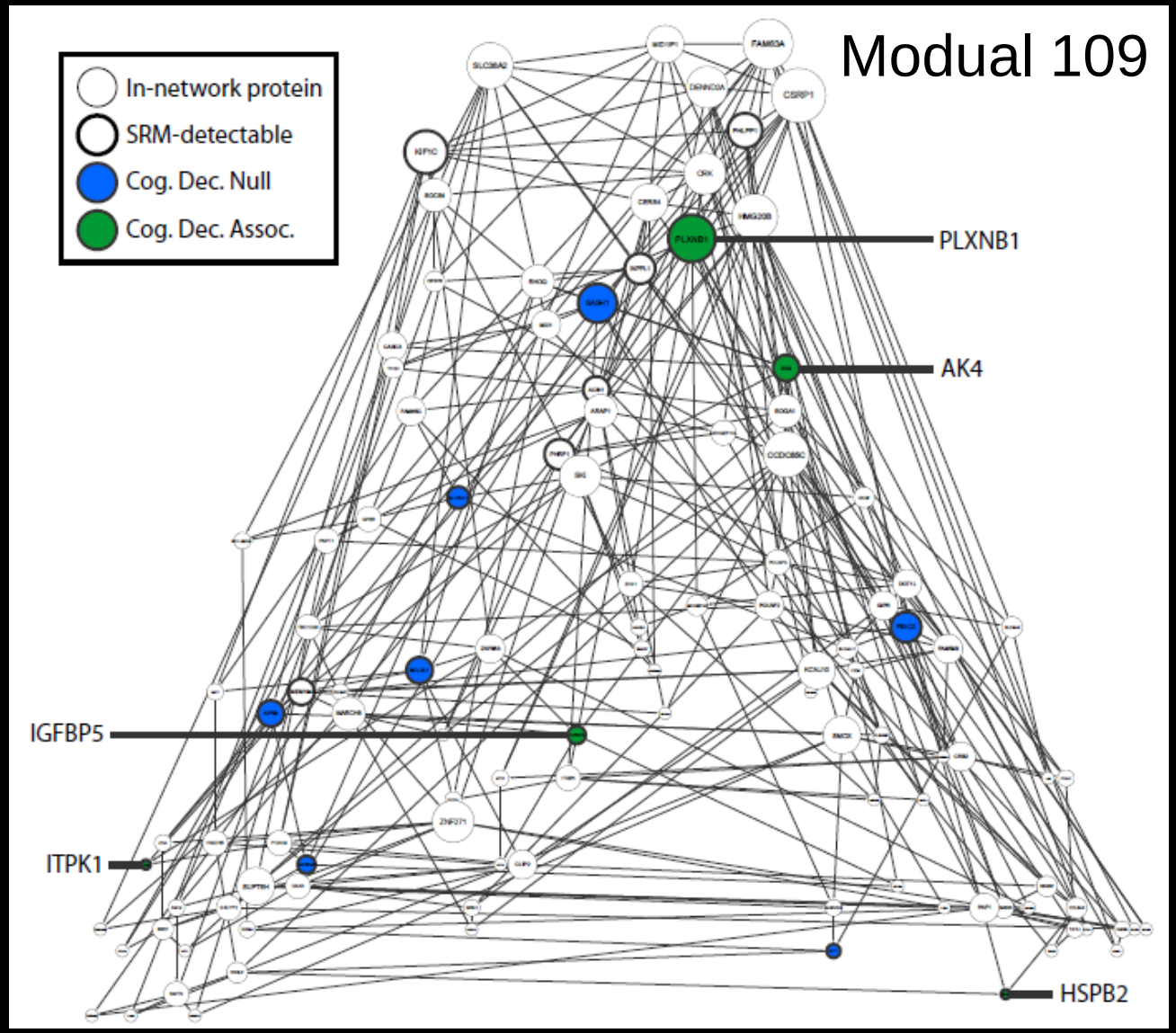

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Protein	Cog Decline Est	P value
AK4	-0.090	7.3×10^{-6}
ANKRD40	-0.0009	0.922
BCL2L1	-0.012	0.576
FBXO2	-0.023	0.033
HSPB2	-0.048	7.4×10-6
IGFBP5	-0.063	1.2×10-16
ITPK1	0.056	7.8×10-5
KIF5B	0.006	0.606
SASH1	0.006	0.512
SLC6A12	-0.034	0.006
VAT1	-0.023	0.017

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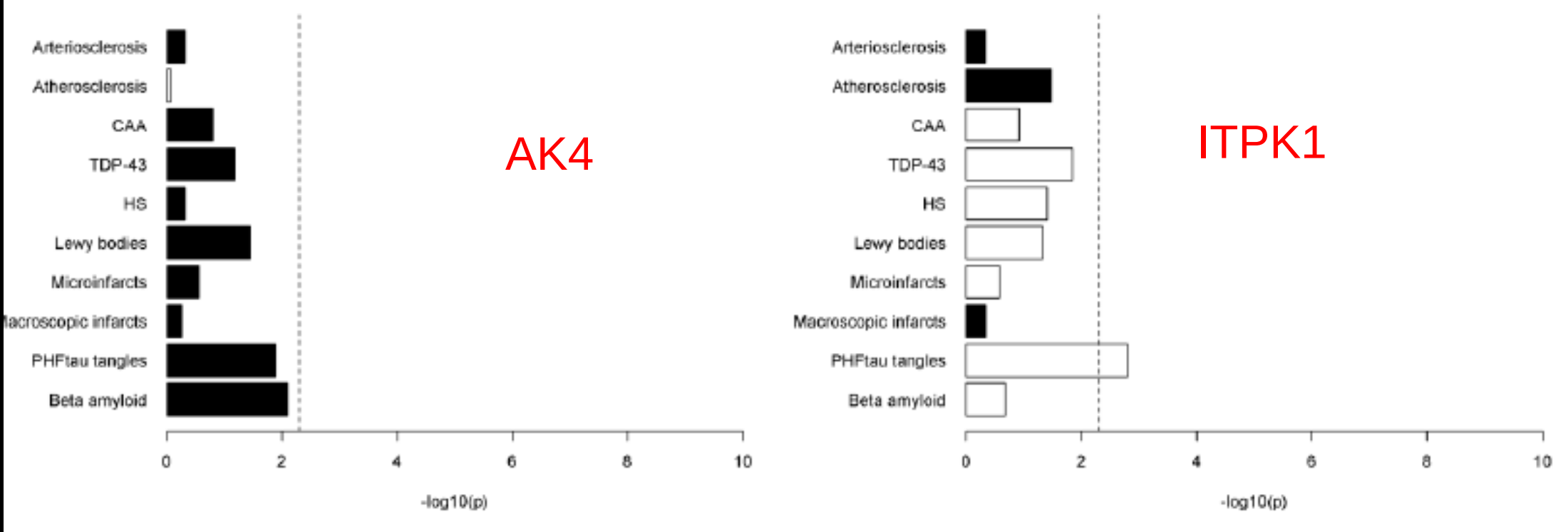

Black is positive and white is negative association

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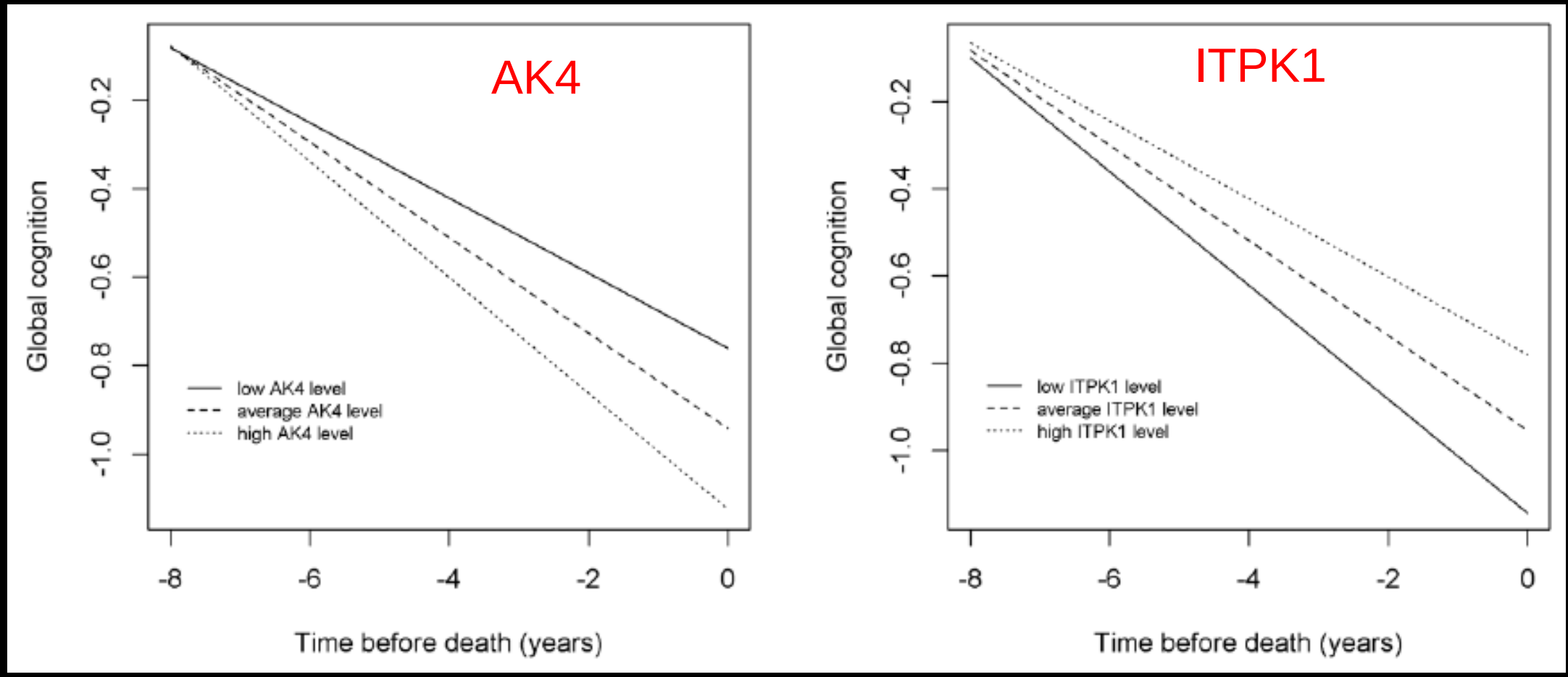

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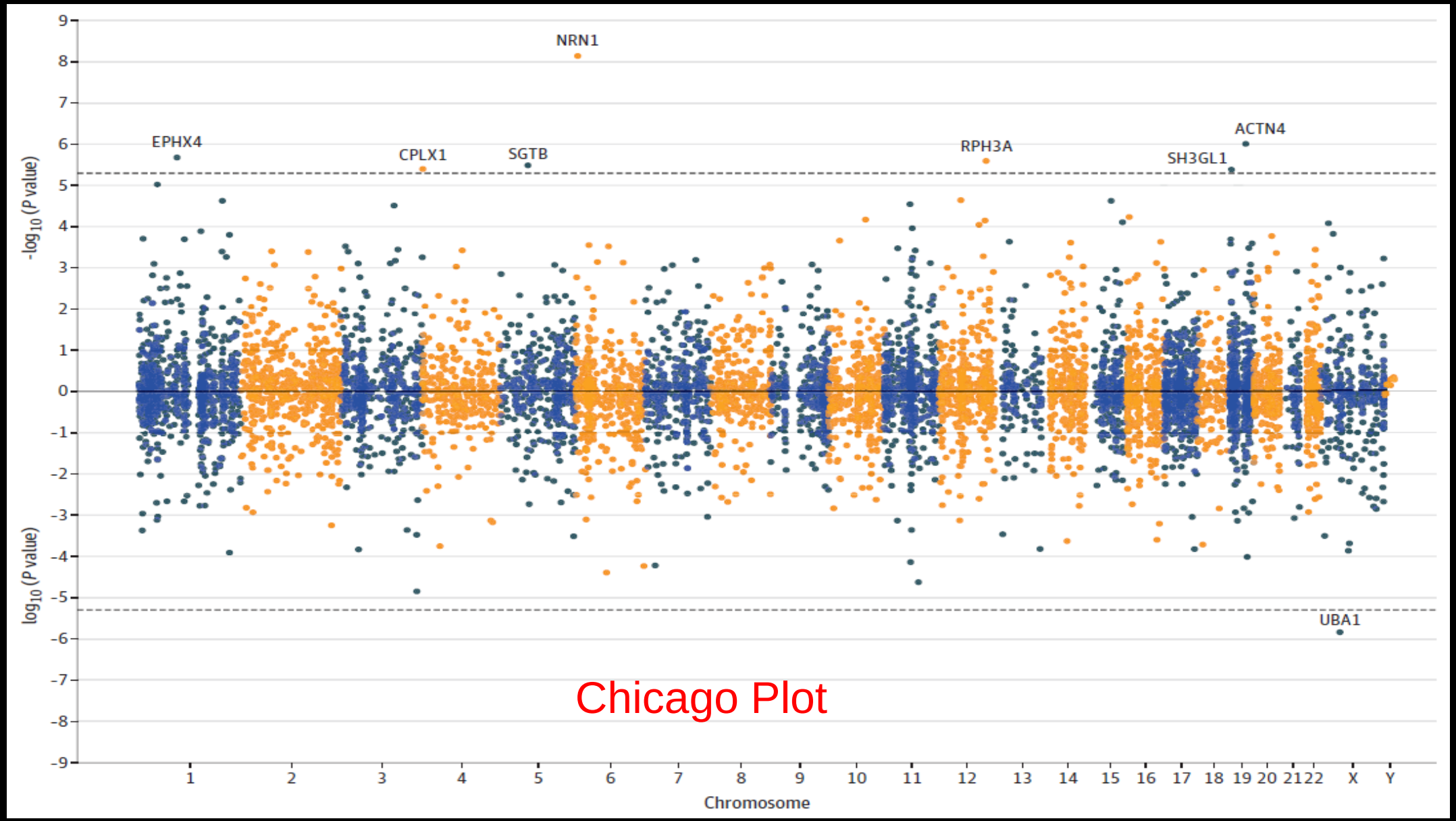
Cortical Proteins Associated With Cognitive Resilience in Community-Dwelling Older Persons



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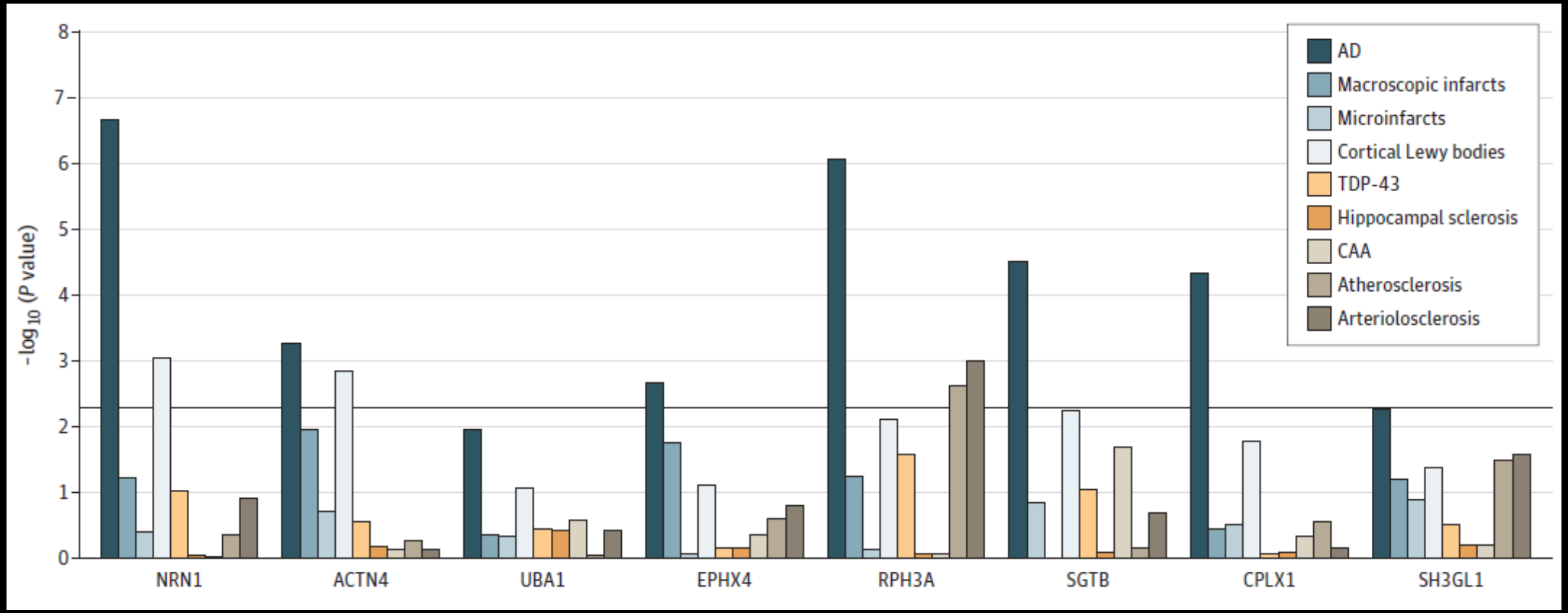

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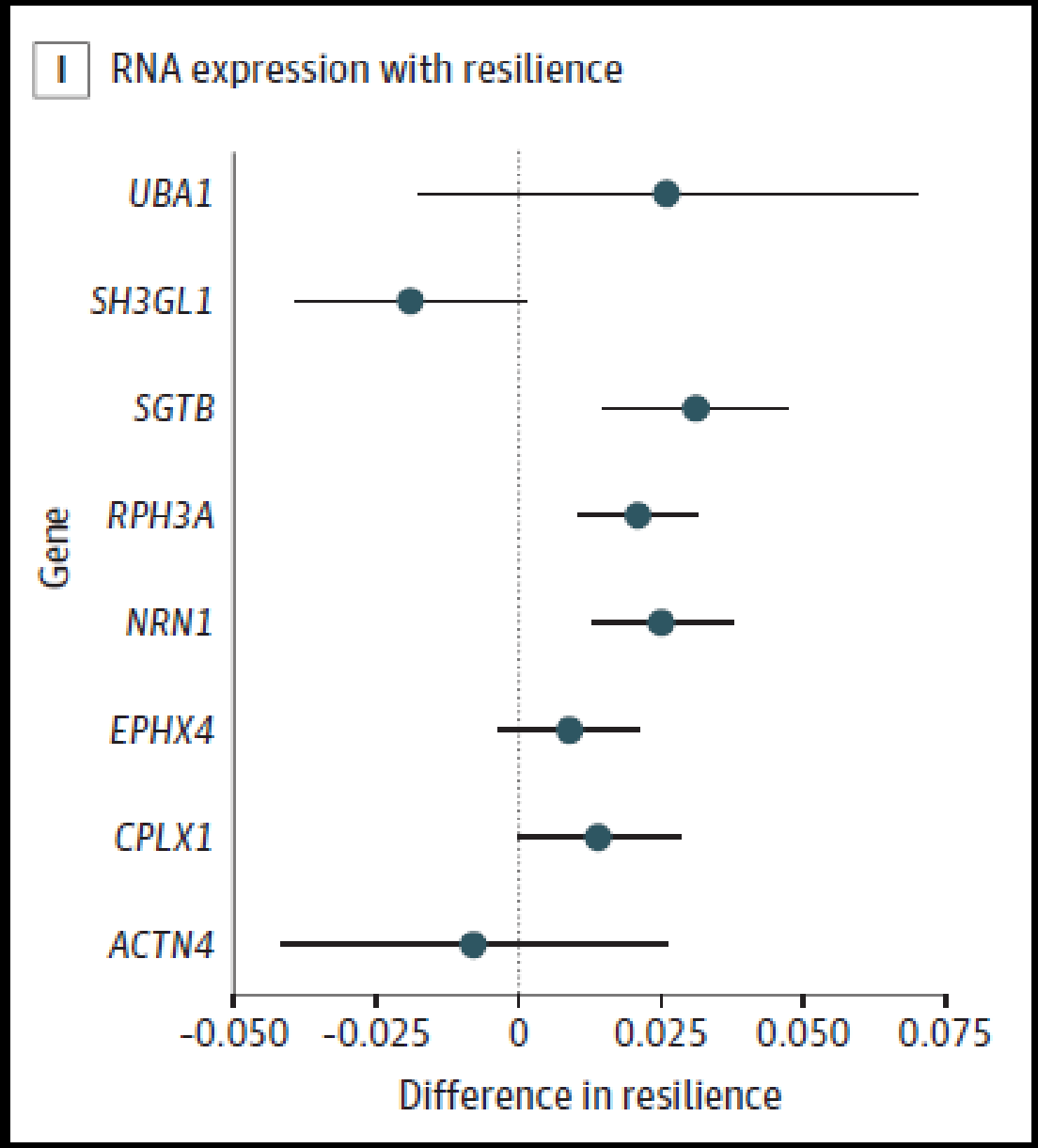

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Summary

- Using residual cognitive decline as a continuous measure of high and low resilience to common brain pathologies, we can use the same pipeline aimed at
  - identifying molecular genomic indices related to common dementing neuropathologies,
  - to identify molecular genomic indices related to high and low resilience

RADC Research Resource Sharing Hub

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