Alzheimer's Disease and Related Dementias: Late-Breaking Research Findings.

Jorge J Llibre Guerra. MD,MSc
Assistant Professor of Neurology
Associate Medical Director,
Dominantly Inherited Alzheimer's Network Trials Unit

1

Disclosure

Sources of Research Support:
NIH K01AG073526
NIH U19AG032438 (DIAN)
NIH U01AG042791 (DIAN-TU)
NIH R56AG053267 (DIAN-TU NexGen)
NIH R01AG053267 (DIAN-TU NexGen)
NIH R01AG068319 (DIAN-TU Tau NexGen)
NIH U01AG059798 (DIAN-TU Primary Prevention)
NIH R01AG064778 (CADAS)

Alzheimer's Association (AARFD-21-851415, SG-20-690363), the Michael J. Fox Foundation (MJFF-020770), the Foundation for Barnes-Jewish Hospital and the McDonnell Academy.

Editorial Board: The Journal of Prevention of Alzheimer's Disease, Journal of applied cognitive neuroscience, Journal of Alzheimer Disease.

-I own no stocks or equity in any pharmaceutical company
-All financial relationships have been mitigated

The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other funding agencies.

2

2

Agenda:

Recent Developments in Alzheimer's Research (Late-breaking findings from AAIC 2024.)

- **Addressing Risk Factors and dementia trends**
- **Genetic Insights in Alzheimer's Disease**
  - Key results from the Alzheimer's Disease Sequencing Project (ADSP).
  - The critical role of genetic diversity in research.
- **Emerging Biomarkers for Alzheimer's**
  - Innovations in blood-based biomarkers for diagnosis.
  - Utilization of biomarkers in clinical settings and trials.
- **Prevention and Treatment Advances**
  - Overview of current strategies for prevention.
  - Preventive strategies to mitigate risk.
  - Recent advancements in therapeutic developments and clinical trials.

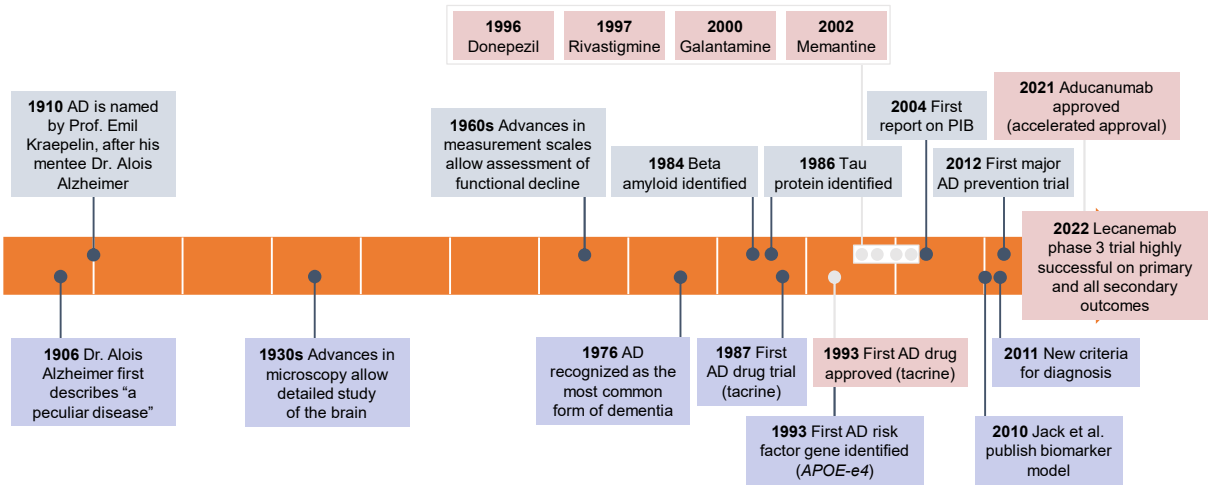
3

Alzheimer's disease – the challenge

- The most common form of dementia
- No cure (**but now disease-modifying treatments!**) currently for Alzheimer's (universally fatal)
- Personal and societal impact
  - >**30 million patients** suffering from Alzheimer's worldwide.
  - **6th leading cause of death** and the only increasing major cause of death
  - **>$200 billion** annual cost in US

4

100+ years of Alzheimer's disease (AD)



Modified - Courtesy of Ali Atri

5

Alzheimer's disease key areas of focus:

Clinical & Cognitive

Global and diverse cohort

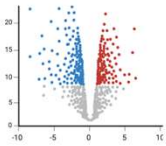
Exposome:

-Multimodal methods to assess risk and protective factors.
-Cross-population comparisons.

Fluid Biomarker

- On-site collection: CSF & Blood.
- At home collection collection: Blood

- Gold standard protein biomarker.
- Novel non-protein biomarker



Understanding AD and mechanistic links to therapeutic targets

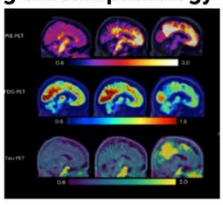
Sequencing

WGS, Epigenetics, Multi-omics

Immune response in AD and neurodegeneration

Deep phenotyping via neuroimaging & neuropathology

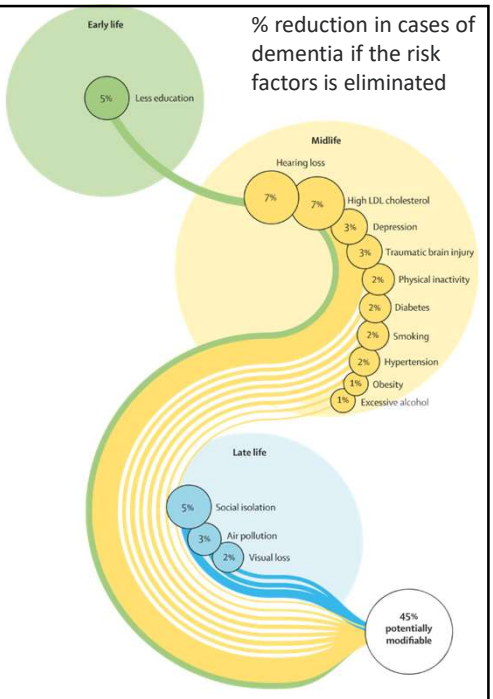
Multimodal methods to assess AD pathology, neurodegeneration, and neuroinflammation



6

Risk factors for dementia — 2024 update

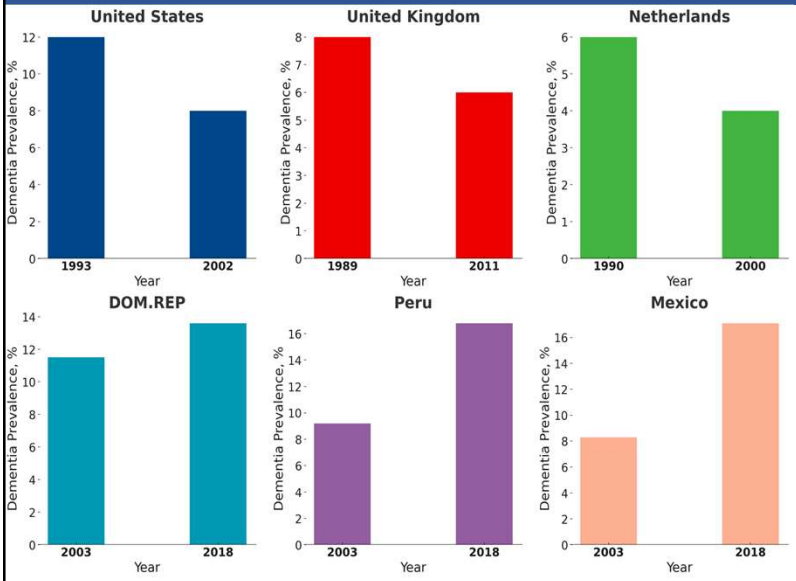
- Evidence is increasing and is now stronger than before that tackling the many risk factors for dementia reduces the risk of developing dementia.
- 45% of cases of dementia could potentially be delayed or reduced.



Livingston G et al. Lancet. 2024; 390: 2673-2734

7

Recent Trends in Dementia:



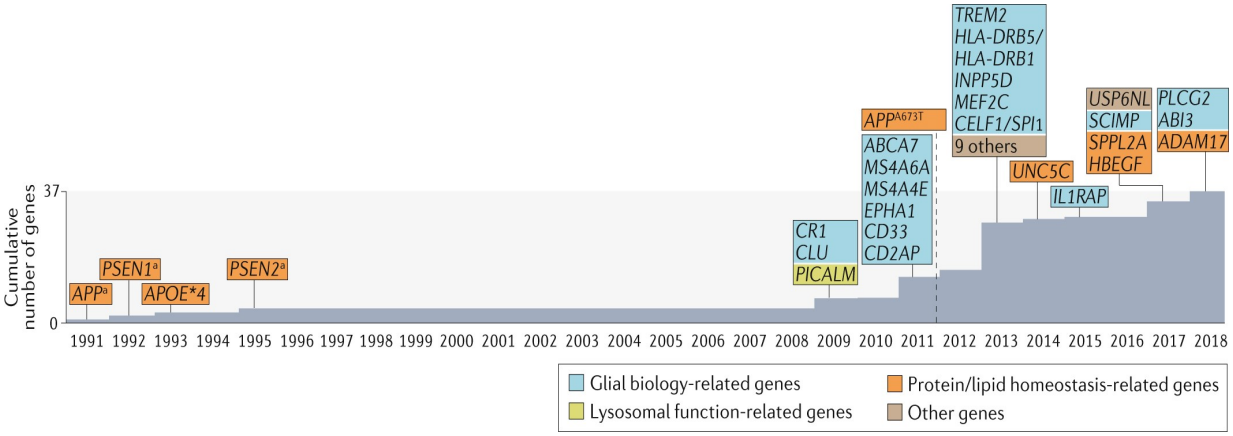
Lower or stable incidence of cognitive impairment or dementia in several countries <u>but not across all populations or ethnic groups.</u>

Langa et al, *Alzheimer's & Dementia,* 2008; Shrijvers et al, *Neurology,* 2012; Qiu et al, *Neurology,* 2013; Matthews et al, *The Lancet,* 2013; Llibre et al, The Lancet, 2024 (under review)

8

Alzheimer's Disease gene Discovery timeline:

- Accelerating Therapeutic Development: A Global Commitment by the Alzheimer's Disease Sequencing Project (ADSP).



Llibre-Guerra: Dementia Prevention and Treatment.

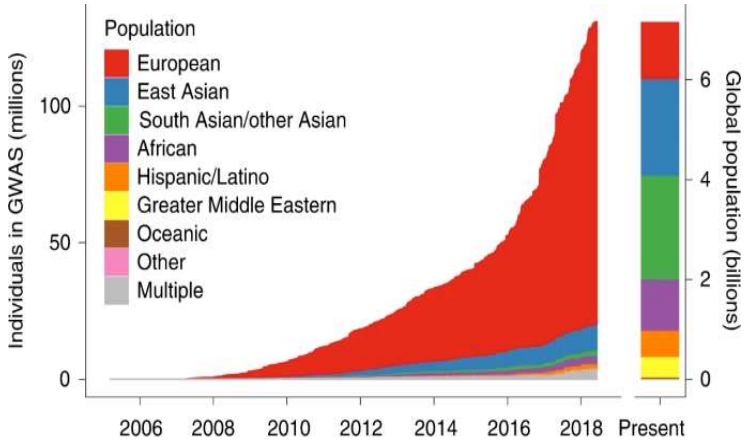
9

Alzheimer's Disease gene Discovery timeline:

The recent development of PRS to identify individuals at risk for dementia in are very promising, but they lack validation in more heterogeneous populations.

- Poor generalizability of genetic studies across populations
- To realize the full and equitable potential of PRS, greater diversity must be prioritized in genetic studies.

Expected to increase via the Alzheimer's Disease Sequencing Project (ADSP).



Martin et al Nature Genetics **volume 51**, pages584–591(2019)

Llibre-Guerra:.

10

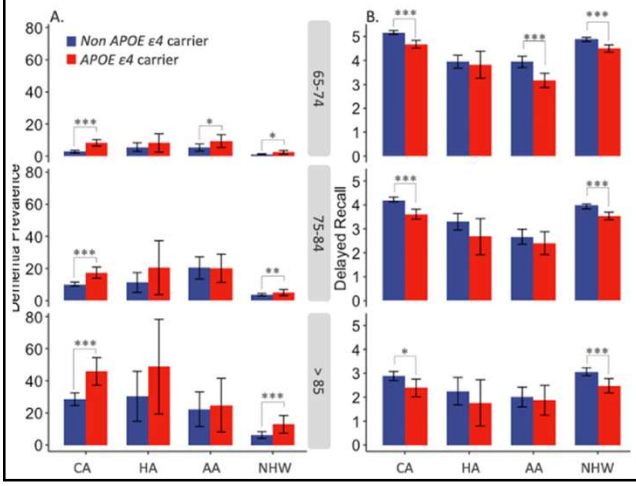
ApoE4 and genetic ancestry:

DOI: 10.1002/alz.12699

RESEARCH ARTICLE

Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Apolipoprotein E (*APOE*) genotype, dementia, and memory performance among Caribbean Hispanic versus US populations



APOE-ε4 allele frequencies were similar in NHW, HA and CH, but ε4 frequency was substantially higher in AA ($p<0.001$)

Frequency of E4 increase in CH and HA with higher AA.

Across all ethnic groups, APOE-ε4 carriers had higher dementia prevalence, but only significant in NHW and CA.

11

ApoE4 and genetic ancestry:

	1 e4 allele	2 e4 alleles
Peruvian[1]	--	5.0 (2.3-12.5)
Ecuatorian[2]		7.286 (2.824–18.799)
Cuba, Dominican Republic and Puerto Rico[3]	1.64 (1.30-2.67)	2.84 (1.51-5.35)
Yoruba[4]	1.21 (0.88-1.67)	2.95(1.67-5.19)
Caucasian[5]	2.7 (2.2-3.2)	12.5 (8.8-17.7)

[1]*Cornejo-Olivas et al. BioRxiv 2020*
[2] *Montufar S et al. Int J of Alz Disease 2017*
[3] *Llibre et al. Dementia & Neurop*
[4] *Hendrie HC et al. Int Psychogeriatr. 2014*
[5]*Farrer et al.* Meta-analysis. *JAMA.* 1997

Blacks Caribbean Hispanics are about 1.4 times more likely than whites to carry APOEe4 gene variant. However, the association between APOE genotype and dementia is weaker in those self-identify as blacks.

12

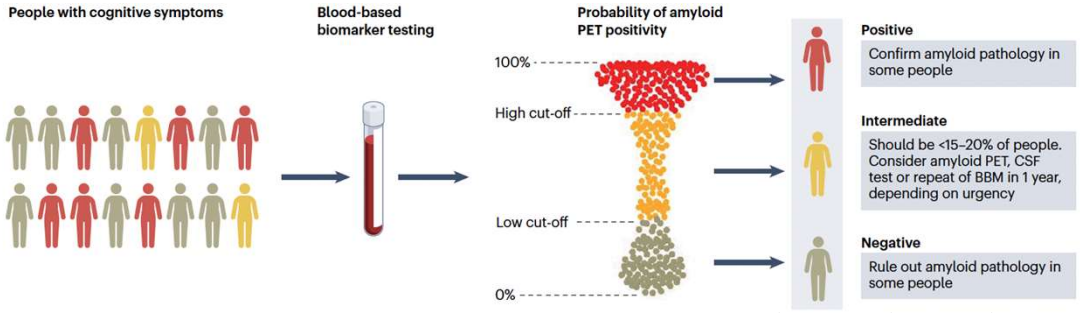
A blood test for AD brain pathology:

- **Scientific advantages of a blood test**
  - Multiple proteins can be measured with a single blood sample.
  - Results are a number, rather than a more subjective "read," facilitating interpretation.
- **Potential impact of a blood test on clinical trials and clinical practice**
  - Participants in clinical trials could be screened/recruited more rapidly and cost-effectively
  - A blood test is likely be more widely used in the clinic compared to amyloid PET or CSF biomarkers.
  - Anti-amyloid treatments for early symptomatic Alzheimer disease have recently become clinically available in some countries, which has greatly increased the need for biomarker confirmation of amyloid pathology.

13

Blood Biomarkers from Research Use to Clinical Practice:

- Timely detection of cognitive impairment, and accurate etiologic diagnosis are notoriously poor in primary care clinics.
- In many areas, most AD care is still provided by non-memory specialists, even more so in regions with low access to specialty care.
- As more AD-specific treatments (e.g., anti-amyloid) are approved and become widely accessible, the need for detection and accurate diagnosis will be amplified.



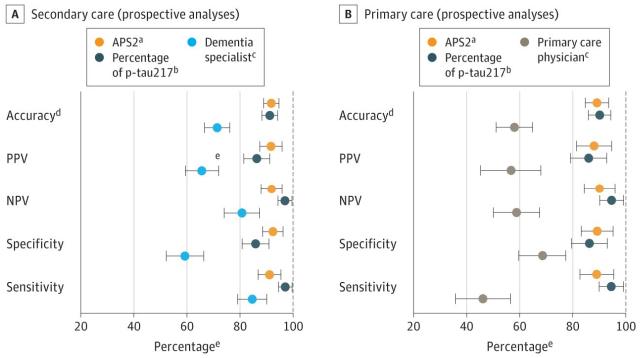
Schindler S et al, Nature Reviews Neurology | Volume 20 | July 2024 | 426–439

14

Blood Biomarkers from Research Use to Clinical Practice:

- A blood test was around 90% accurate in identifying Alzheimer's disease in patients with cognitive symptoms seen in primary care and at specialized memory care clinics.
  - In the research study, primary care physicians were 63% accurate and specialists were 73% accurate when not using the blood test.

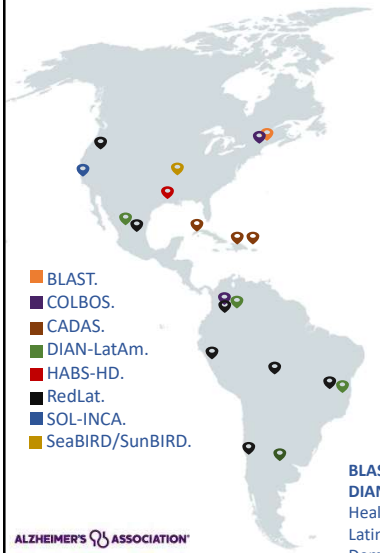
Once confirmed, blood tests could enhance recruitment for Alzheimer's clinical trials and clinical practice.



Palmequist et al. 2024 JAMA

15

AD biomarkers in diverse populations (Ongoing efforts):



A simple, inexpensive, non-invasive test for AD can accelerate observational epidemiological, genetic, and clinical trial research in diverse populations.

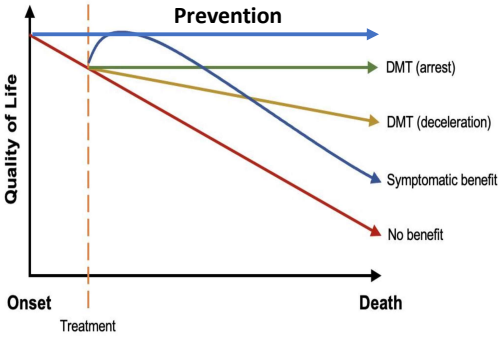
Factors governing the clinical robustness of a biomarker:

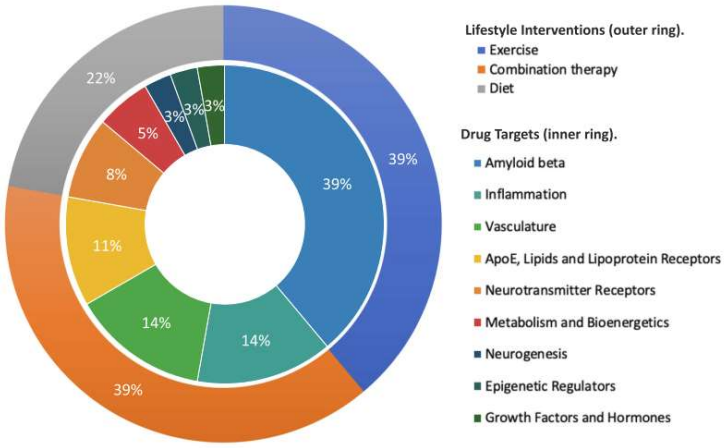
- Age
- Sex
- Ethnicity and ancestry
- Genetics (e.g., *APOE* genotype)
- Obesity
- Comorbidities (e.g., kidney dysfunction)
- Cardiovascular Risk factors

BLAST. Boston Latino Aging Study, **COLBOS.** Colombia-Boston biomarker study, **CADAS.** Caribbean Aging and Dementia Study, **DIAN-LatAm.** Dominantly Inherited Alzheimer Network Latin America Initiative, **HABS-HD.** The Health & Aging Brain Study - Health Disparities **RedLat.** Multi-Partner Consortium to Expand Dementia Research in Latin America, **SOL-INCA.** Study of Latinos-investigation of Neurocognitive aging. **SeaBIRD/SunBIRD.** Study to Evaluate Amyloid in Blood and Imaging Related to Dementia.

16

Treatment in Neurodegeneration:

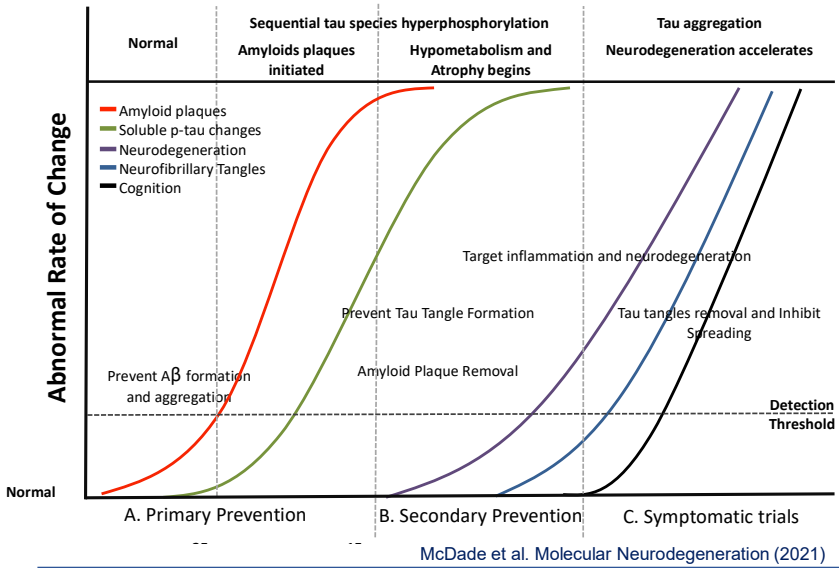




Llibre-Guerra: Dementia Prevention and Treatment.

17

Timing of AD prevention trials related to core pathology and symptom



McDade et al. Molecular Neurodegeneration (2021)

Llibre-Guerra: Dementia Prevention and Treatment.

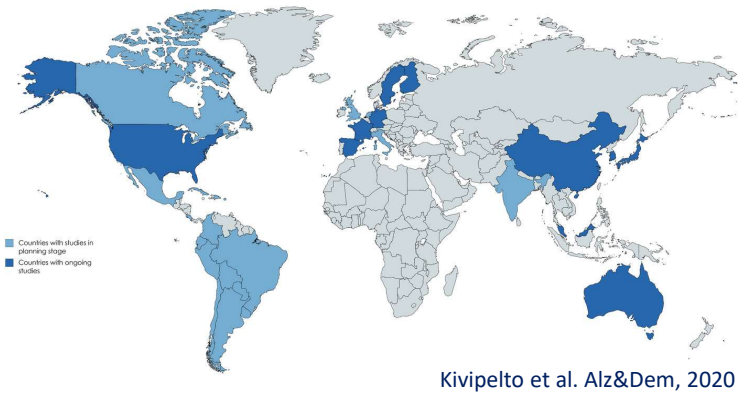
18

World-Wide FINGERS Network: A global approach to risk reduction and prevention of dementia.

- **U.S. study to Protect Brain Health through a Lifestyle Intervention to Reduce Risk (U.S. POINTER)**

1. 2000 cognitively normal adults at risk for cognitive decline and dementia in later life.
2. Randomly assigned to a self-guided or structured lifestyle intervention program.
3. The primary outcome is change in global cognition.

- **MIND-Europe**
- **MIND-China**
- **Australia—AU-ARROW**
- **LatAm FINGER**

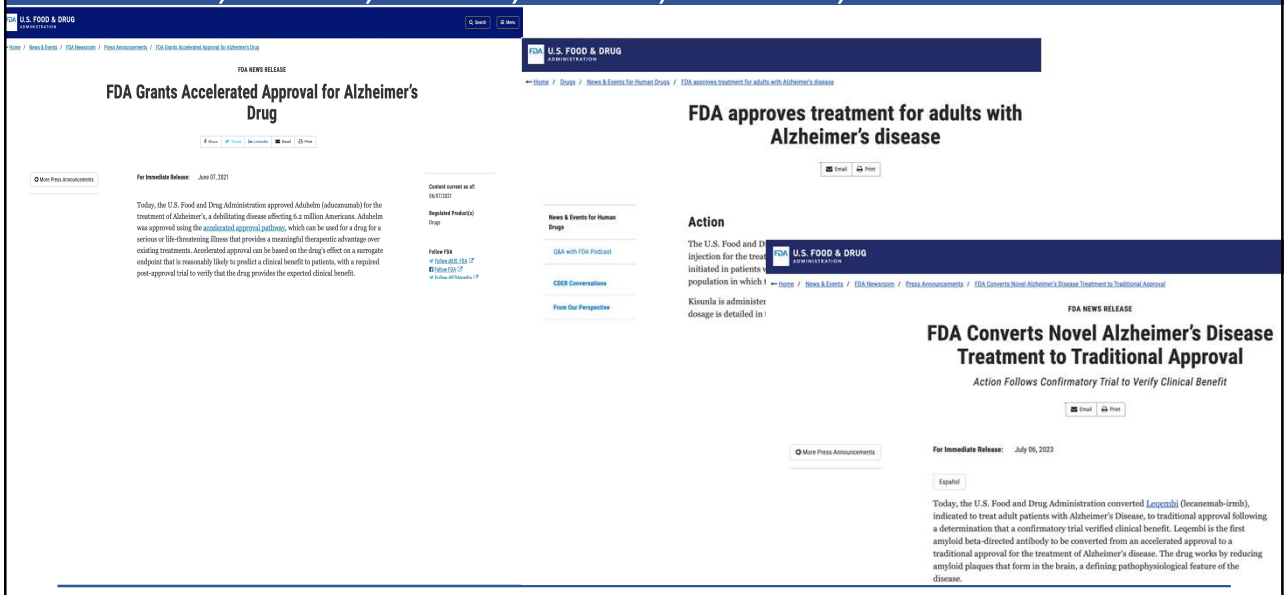


Kivipelto et al. Alz&Dem, 2020

ALZHEIMER'S ASSOCIATION AAIC 24

19

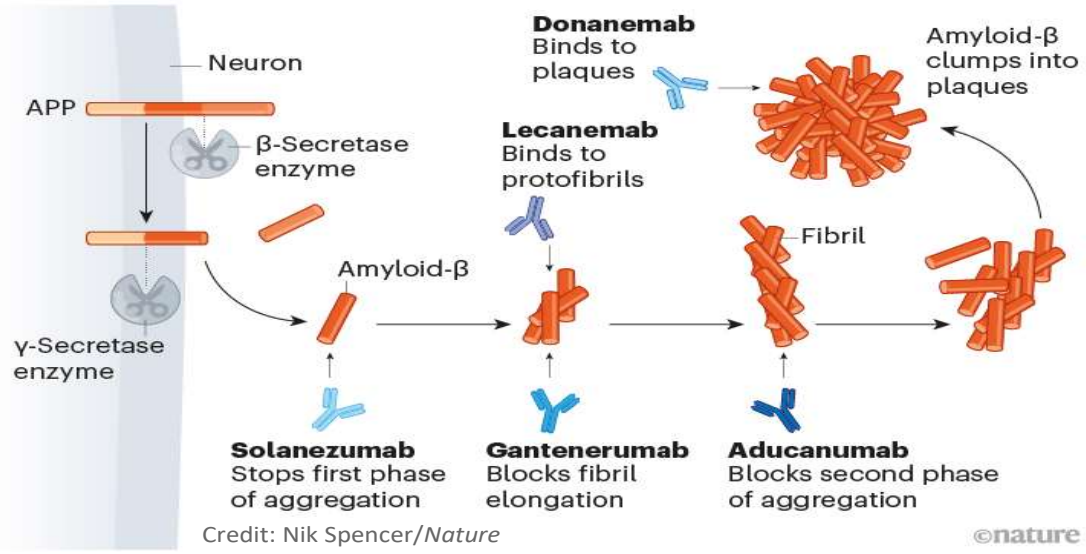
June 21, 2021, Jan 6, 2023, June 2, 2024



Llibre-Guerra: Dementia Prevention and Treatment.

20

Timing of AD prevention trials related to core pathology and symptom

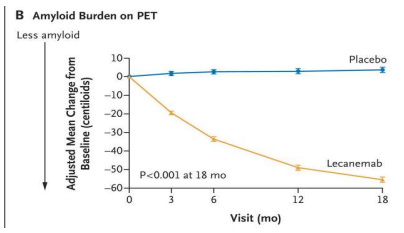


Llibre-Guerra: Dementia Prevention and Treatment.

21

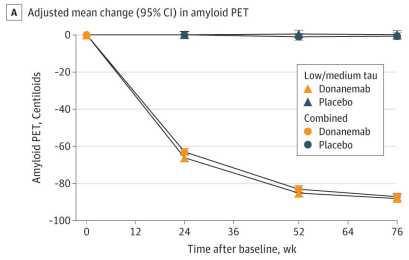
Significant Amyloid reduction slows cognitive decline

Lecanemab

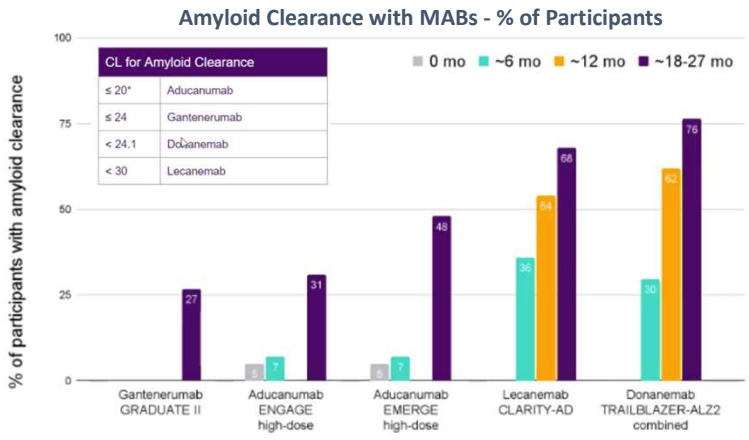


van Dyck CH, et al. *N Engl J Med.* Nov 29, 2022.

Donanemab



Sims, et al. *JAMA. 2023;330(6):512-527.*

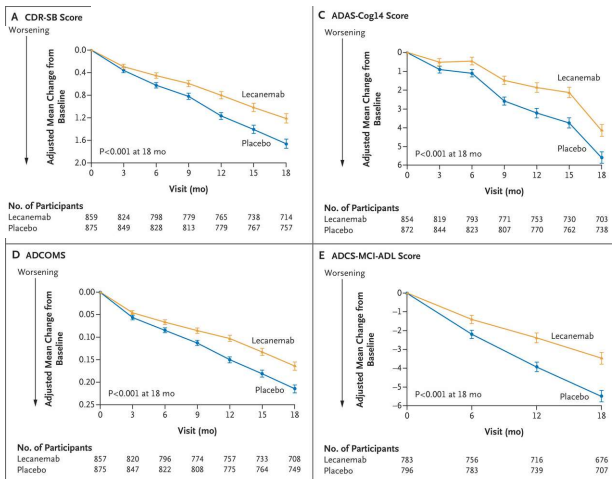


Alzheimer Association

22

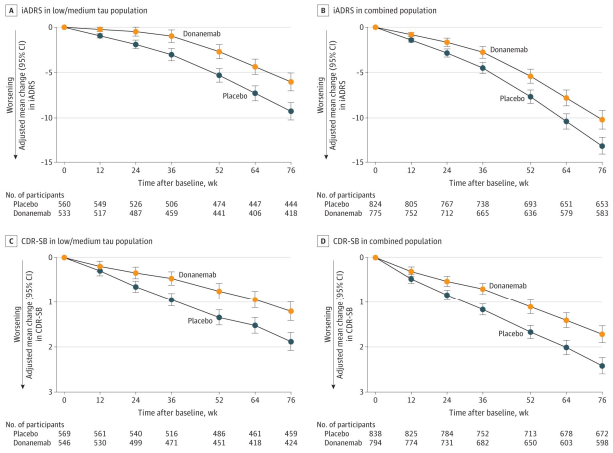
Amyloid reduction slows cognitive decline

Lecanemab



van Dyck CH, et al. *N Engl J Med.* Nov 29, 2022.

Donanemab



Sims, et al. *JAMA. 2023;330(6):512-527.*

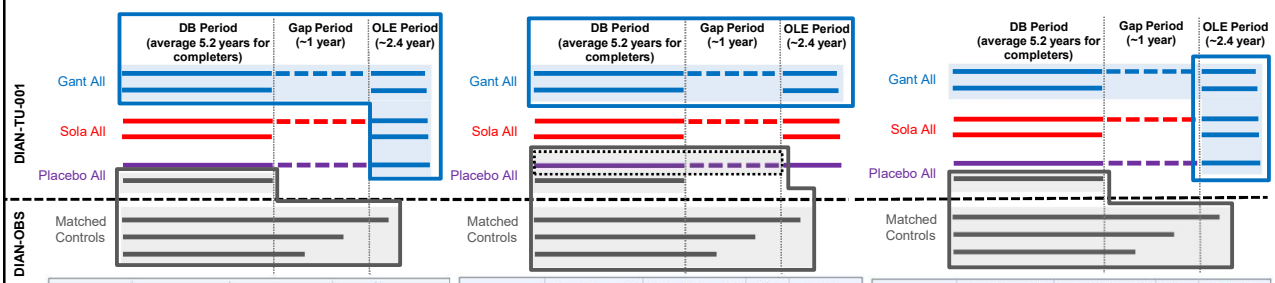
Llibre-Guerra: Dementia Prevention and Treatment.

23

Key Secondary (Clinical) Outcomes: Potential First Evidence of Dementia Prevention in the Asymptomatic Longest Treated Group

KNIGHT FAMILY DIAN TU

Gant Treated
Main Set Controls
Extended Controls



	Gant, N (event %)	Control, N (event %)	HR	95% CI
CDR Global	53 (5.4%)	74 (5.6%)	0.91	0.43, 1.95
CDR-SB	53 (12.4%)	74 (10.6%)	0.77	0.47, 1.27

	Gant, N (event %)	Control, N (event %)	HR	95% CI
CDR Global	22 (3.0%)	74 (5.6%)	0.48	0.16, 1.40
CDR-SB	22 (9.1%)	74 (10.6%)	0.55	0.29, 1.04

	Gant, N (event %)	Control + Extended, N (event %)	HR	95% CI
CDR Global	22 (3.0%)	86 (5.1%)	0.50	0.17, 1.46
CDR-SB	22 (9.1%)	86 (10.8%)	0.52	0.28, 0.95

	Gant, N (event %)	Control, N (event %)	HR	95% CI
CDR Global	40 (7.6%)	74 (5.6%)	0.90	0.32, 2.49
CDR-SB	40 (15.8%)	74 (10.6%)	1.32	0.64, 2.70

Output based on Cox proportional hazard model
- CDR global: time to first progression
- CDR SB: time to recurrent progression
- Event % is the event rate per person year.

Note: OLE analysis has several potential biases including selection bias and difference in duration of follow-up.

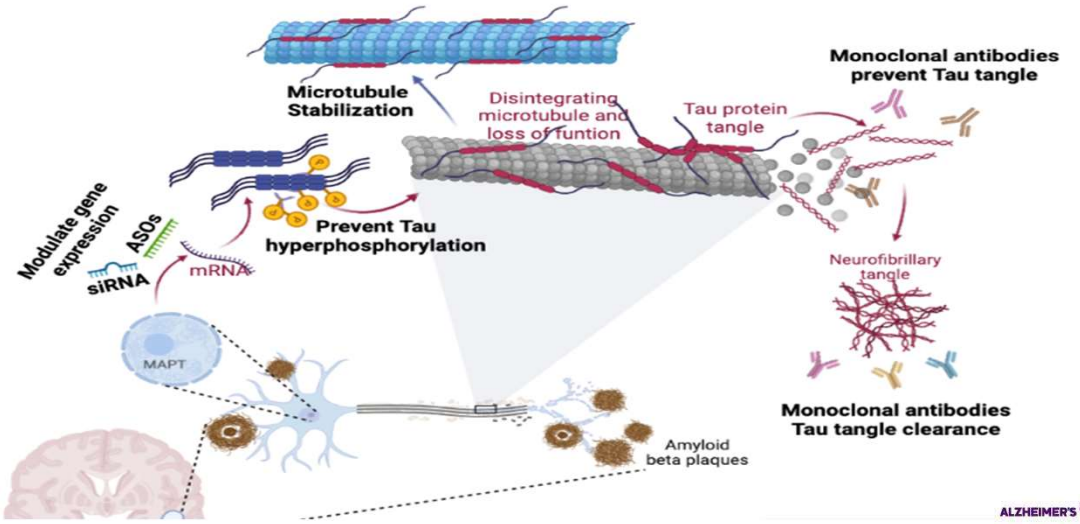
Removing amyloid plaques for an average of 8 years before symptom onset may provide a 50% decrease in the risk of conversion to symptomatic dementia and dementia progression rate.

ALZHEIMER'S ASSOCIATION AAIC 24

Modified - Courtesy of Randall Bateman

24

Prime time to target Tau pathology:



ALZHEIMER'S ASSOCIATION AAIC 24

25

Timing of AD prevention trials related to core pathology and symptom

Wrong target?

Which Aβ species, tau species, other? Not all targets may be safe to maximal effect (e.g., general gamma secretase inhibitors).

Too little?

Biomarker engagement in the human CNS of the mechanism of action has been inconsistently shown in many trials. No drug has completely "normalized" AD biomarkers.

Too late?

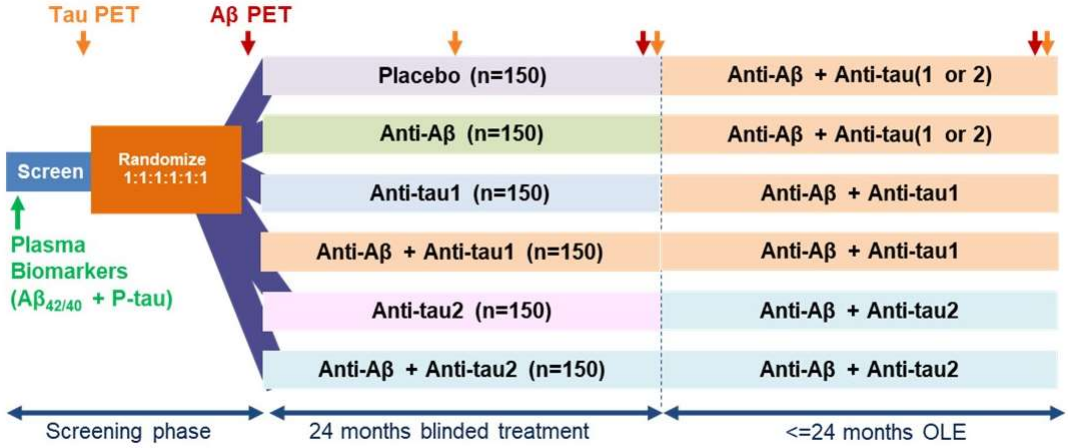
Focus on earlier stages of the disease including secondary prevention.

Llibre-Guerra: Dementia Prevention and Treatment.

26

Timing of AD prevention trials related to core pathology and symptom

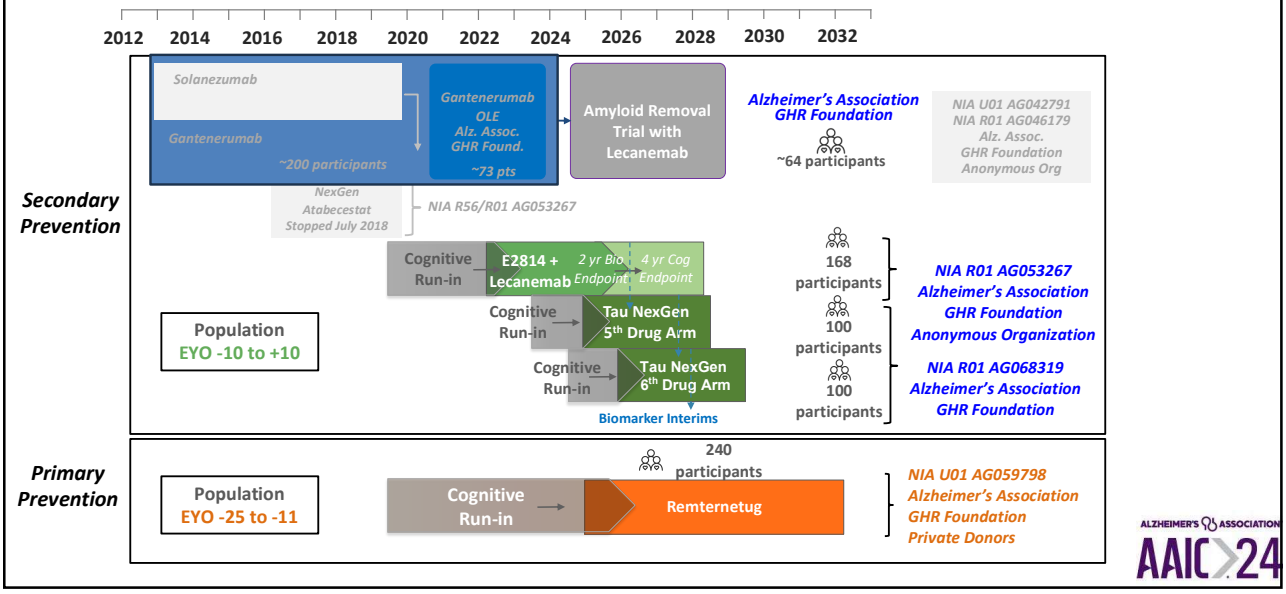
- The ATP is a six arm factorial design platform trial that is planned to begin in late 2024 or early 2025 that will support efficient development of tau and combination therapies for early, sporadic AD.



27

Timing of AD prevention trials related to core pathology and symptom

DIAN-TU AD Prevention Trial Platform



28

Summary of comparisons of DIAD vs. SAD trials

Population	Sporadic AD	Dominantly Inherited mutations (DIAN-TU, API)	Comparison of Clinical and Biomarker Results between DIAD and SAD
Soluble Aβ antibody	Solanezumab (A4) - little effect on plaques, clinical trend towards worsening	Solanezumab (DIAN-TU) – little effect on plaques, clinical trend towards worsening	DIAN-TU = SAD A4 (negative clinical and biomarker) DIAN-TU=SAD Expedition 3 (negative clinical and biomarker)
Oligomeric Aβ antibody	Crenezumab (CREAD) – little effect on plaques or clinical progression	Crenezumab (API) – little effect on plaques or clinical progression	API Crenezumab = SAD CREAD (negative clinical and biomarker)
	Lecanemab - AHEAD (A45) – Pending Results	Lecanemab - DIAN-TU prevention trials - Pending Results	AHEAD A45 ?= DIAN-TU lecanemab trial TBD
Fibrillar Aβ antibody	Graduate 1 & 2 trials – moderate effect on plaques – minimal clinical effect	Gantenerumab – moderate effect on plaques in symptomatic – minimal clinical effect	DIAN-TU= SAD Graduate in symptomatic (negative clinical and moderate biomarker)
	Lecanemab - AHEAD (A45) – Donanemab – Trailblazer4 – Pending Results	Gantenerumab – large effect on plaques in pre-symptomatic – possible clinical effect	DIAN-TU amyloid removal in asymptomatic suggests 50% risk reduction ?= Sporadic AD TBD

AAIC July 2024

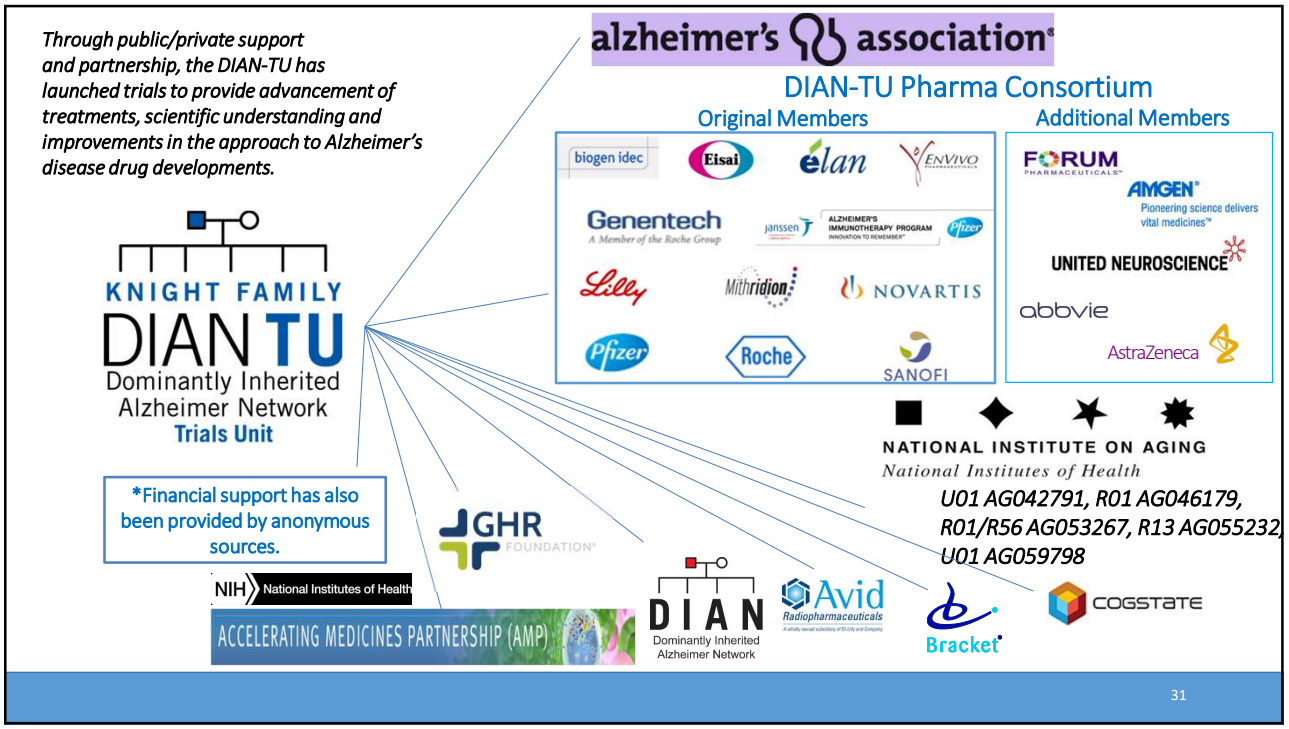
29

29

Take home message:

- Recent trends show lower or stable incidence of cognitive impairment or dementia in several countries but not across all populations or ethnic groups.
- Evidence is increasing and is now stronger than before that tackling risk factors for dementia (ie, lower education, hypertension, smoking, obesity, depression, physical inactivity, diabetes, among others) reduces the risk of developing dementia.
- Timely and accurate diagnosis of Alzheimer's disease (AD) in clinical practice remains challenging, BUT emerging blood-based markers have the potential to be accurate, cost-effective, and easily accessible for widespread clinical use, and could facilitate timely diagnosis.
- Significant Amyloid reduction slowed cognitive decline, leading to the approval of Anti-amyloid treatments for early symptomatic Alzheimer disease. In pre-symptomatic autosomal dominant AD, removing amyloid plaques for an average of 8 years before symptom onset may provide a 50% decrease in the risk of conversion to symptomatic dementia and dementia progression rate.
- It is prime time for anti-Tau therapies and the Next Generation of combination trials in AD, aimed at stopping or significantly delaying disease onset and progression.

30



31

SA0

The Knight Family DIAN-TU Administrative and Clinical Operations

Randall Bateman – Director and PI | Eric McDade, Co-Director
David Clifford, Associate and Medical Director | Jorge Llibre-Guerra, Assistant Medical Director
S. Alexander, E. Andrews, N. Angeloff, J. Bartzel, J. Beatty, J. Bur, D. Burgdorf, T. Carril, R. Carrow, E. Cook, K. Ferguson, A. Fuqua, E. Gruebbeling, A. Hageman, E. Hart, R. Hawley, M. Jany, M. Jorke, B. King, N. Landers, J. Mallmann, T. Mayhew, K. McCann, I. Meshulam, D. Morrison, J. Murphy, M. Nies, J. Portell, M. Qassem, L. Sawicki, J. Schillizzi, W. Simpson, A. Stiebel, A. Stueve, S. Sweeney, E. Ziegemeier

Cores

Administrative: *R.J. Bateman, C. Supnet-Bell, A. Santacruz and team*
Clinical: *D. Clifford, J. Llibre-Guerra, E. McDade*
Clinical Operations: *S. Mills, S. Belyew and team*
Biomarkers: *L. Ibanez, S. Preminger, J. Stauber and team*
Biostatistics: *G. Wang, Y. Li , C. Xiong and team*
Cognition: *J. Hassenstab, A. Aschenbrenner, J. Smith and team*
Genetics: *C. Cruchaga, A. Renton and team*
Imaging: *T. Benzinger, B. Gordon, R. Hornbeck and team*
Neuropathology: *R. Perrin, E. Franklin and team*

Collaborators

Project Arm Leaders: *A. Atri, L. Schneider, O. Hansson, A. Porsteinsson (Former S. Salloway, M. Farlow)*
DIAN-TU Therapy Evaluation Committee: *P. Aisen, R. J. Bateman, J. Chhatwal, D. Clifford, D. Cribbs, K. Dineen, N. Fox, D. Holtzman, J. Kelly, C. Lemere, J. Llibre-Guerra, E. M. McDade, S. Mead, C. Mummery, E. Musiek, E. Roberson, C. Supnet-Bell, R. Vassar*
DSMB Members: *S. Evans, S. Greenberg, S. Kim, D. Knopman, K. Yaffe (Former: G. Cutter, K. Kiebertz)*
ADCS: *R. Thomas*
ATRI: *P. Aisen*
University of Michigan: *R. Koeppe*
Mayo Clinic: *C. Jack*

We gratefully acknowledge the DIAN and DIAN-TU participants and family members, DIAN Team, DIAN Steering Committee, Knight ADRC, Alzheimer's Association, ADAD Forum, NIA/NIH U01AG042791, R01AG046179, R01/R56AG053267, R01AG068319, U01AG059798, R13AG055232, DIAN-TU Pharma Consortium, GHR Foundation, Anonymous Organization, Industry Partners (Eli Lilly & Co., Roche/Genentech, Janssen, Eisai, Avid Radiopharmaceuticals, Lantheus, Cogstate), and Regulatory Representatives.

32

32

Slide 32

SA0 Should we include Lantheus and Flywheel?
Alexander, Silvy, 2024-07-18T17:27:21.050

MS0 0 [@Santacruz, Anna] - do we want all trial vendors or was there a rationale for which ones to include here?
Mills, Susan, 2024-07-24T14:19:32.709

0 1 [@Mills, Susan] I personally think we should remove - in addition to the consultants. This started with adding IQVIA and maybe Cogstate and Signant (Bracket at the time) several years ago because they wanted recognition as collaborators. I think because they were giving us some services "pro bono". But I agree that if we are going to list some, we should list all. Some consultants may be good because they actually contribute to our design (mainly Berry and Janice). For the OLE related slides, we should probably keep Berry and Janice, but remove them for future presentations.
Santacruz, Anna, 2024-07-24T14:28:05.926

MS0 2 removed
Mills, Susan, 2024-07-26T18:19:08.714

33