Fall ADRC Directors Meeting

National Institute on Aging

Chicago, ILL

October 20, 2022

"Division of Neuroscience Update"

Eliezer Masliah, M.D.

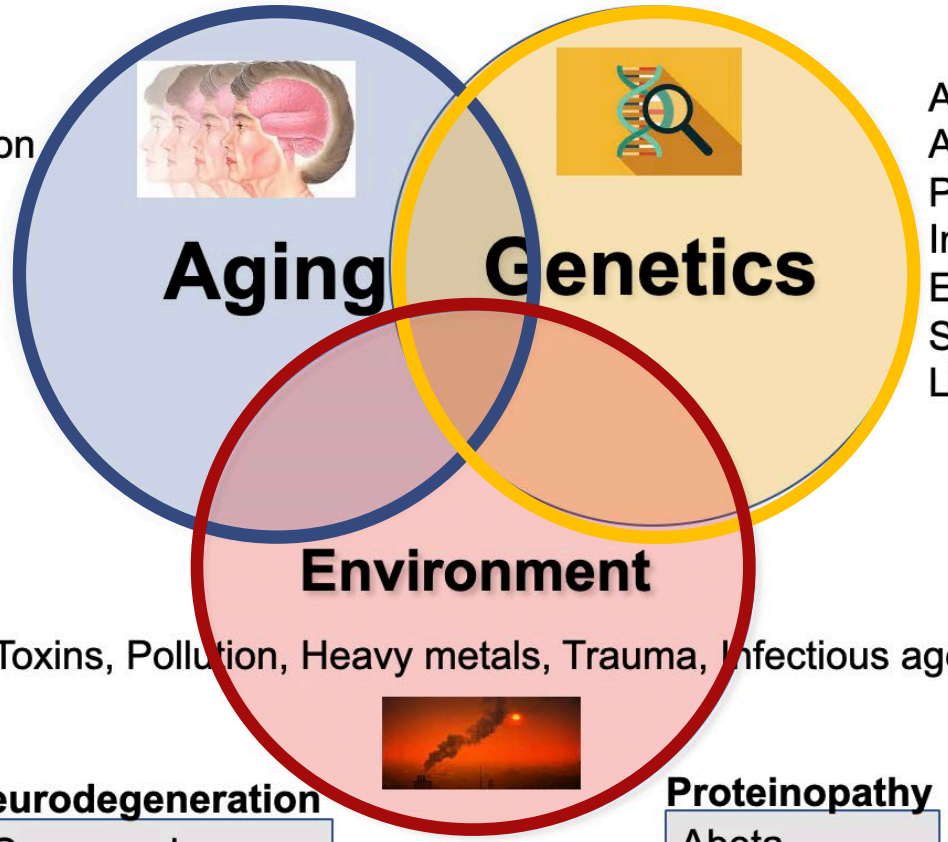
Director, Division of Neuroscience,

National Institute on Aging, NIH

NIA Approach to AD/ADRD reserach

Aging Genetics

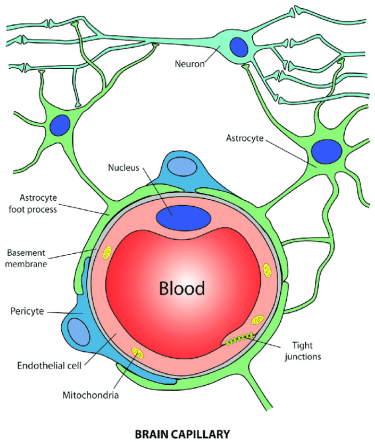
- Proteostasis defects
- Mitochondria dysfunction
- Oxidative stress
- Epigenetic alterations
- DNA damage
- Senescent cells
- Immune surveillance



- APP/Abeta
- APOE4
- Presenilin
- Inflammation genes
- Endosomal genes
- Synaptic genes
- Lipid metabolism genes

Accounts for 70% of the variance

Toxins, Pollution, Heavy metals, Trauma, Infectious agents



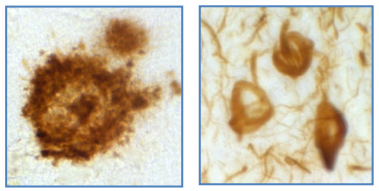
BRAIN CAPILLARY

Neurodegeneration

- Synapse damage
- Neuronal loss
- Vascular damage
- Inflammation

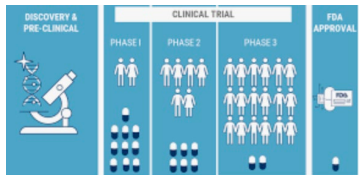
Proteinopathy

- Abeta
- Tau
- Synuclein
- TDP43



Diagnosis → **MCI/Dementia** ← **Therapeutics**

Progress in AD/ADRD research at a time of increased funding



NIA funded over 400 clinical trials

Lecanemab and other Mabs

2025

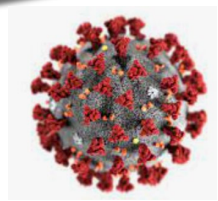
Precision Medicine

AD Knowledge Portal

NIA supported data sharing and harmonization

Inclusion of DIVERSITY in research

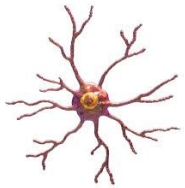
COVID19



Plasma biomarkers

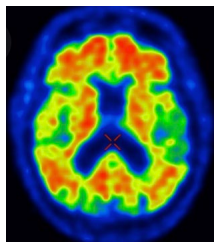
Immune, endosome Synaptic, Lipid metabolism, APP, Signaling pathways

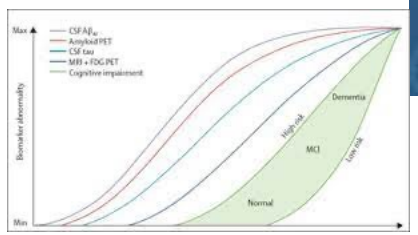
NAPA and increased NIH funding for AD/ADRD



PET imaging,

CSF biomarkers

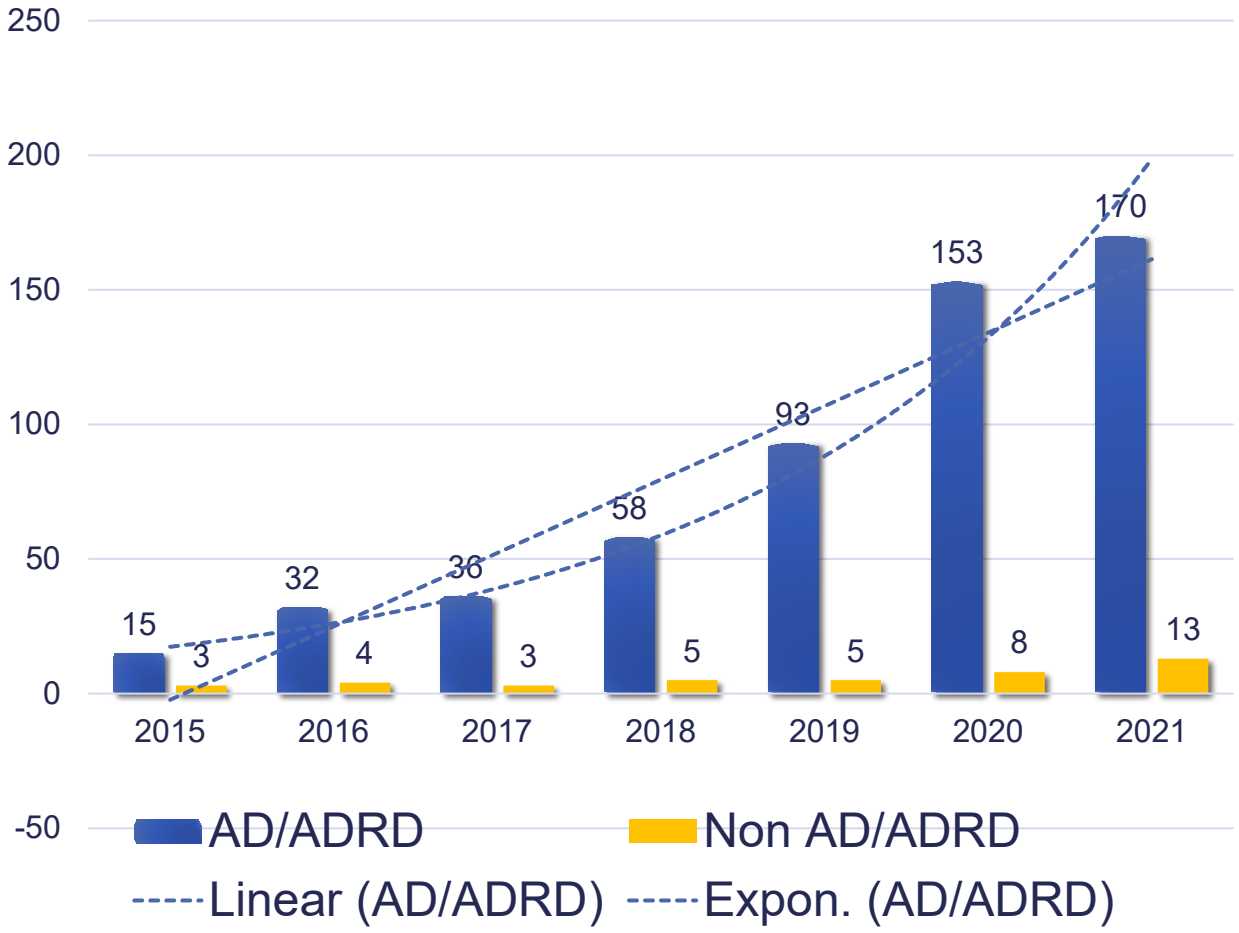




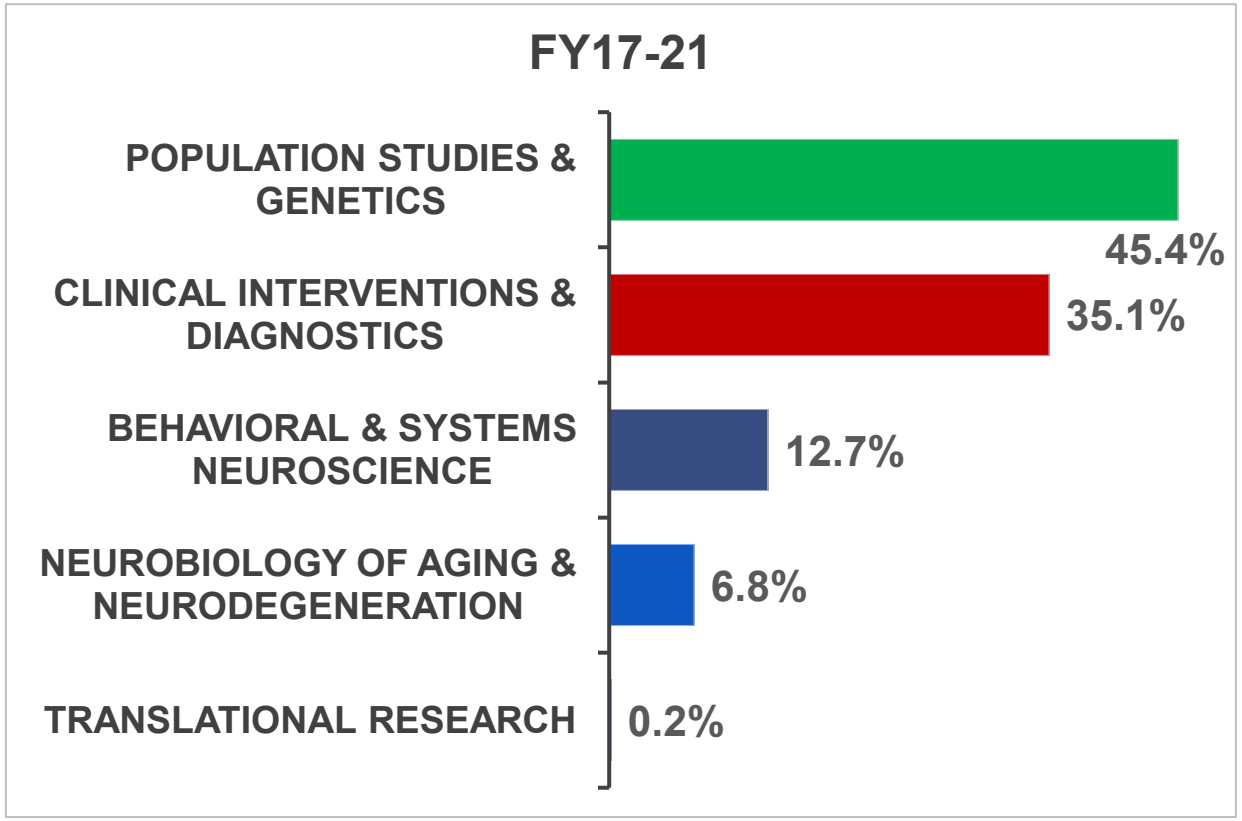
Division of Neuroscience NIA Diversity awards

Total number of all applications (competing, non-competing, supplements, centers, training and research) = **598**
Total number of all new applications (Types 1,2,3) = **291**

DN Awards by Fiscal Year



% of Awards by area of research



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Prioritizing Diversity & Inclusion in Research

NIA released the *National Strategy for Recruitment and Participation in AD/ADRD Clinical Research* and expanded efforts to include diverse populations in NIA-funded research

Increasing Diversity in AD/ADRD Research

(example studies)

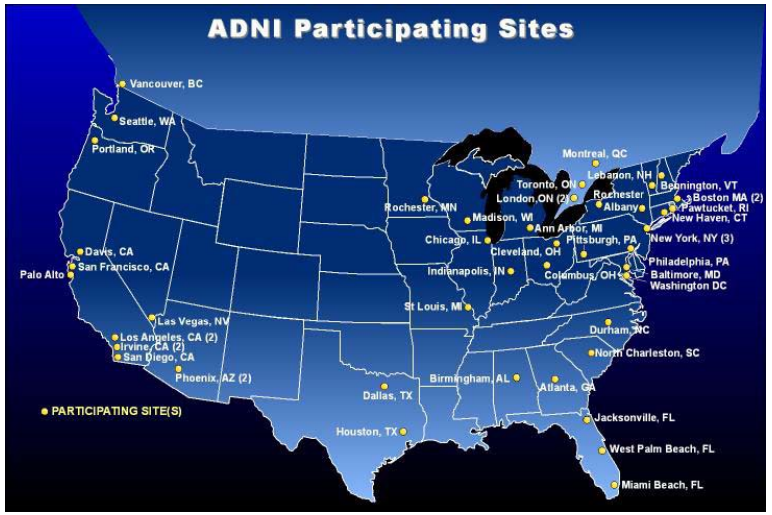
- Alz Disease Neuroimaging Study (ADNI-4) (AA, HL,A)
- Health and Aging Brain Study-HD (HABS-HD) (AA, HL)
- Health and Retirement Study (AA, HL)
- Stress and Resilience in Dementia (STRIDE) Study (AA, AI/AN)
- Alz Disease Sequencing Study (ADSP) (AA, HL, A)
- Study to expand Registry Participation of Underrepresented Populations (STEP-UP) (AA, HL)
- Strong Heart Study (AI/AN)
- Diabetes Prevention Program Outcomes (DPPOS) (AA, HL)

AA: African American
AI/AN: American Indian/Alaska Native
HL: Hispanic/Latino
A: Asian

ADNI-4 Increasing Generalizability by Enrollment of a Diverse Population

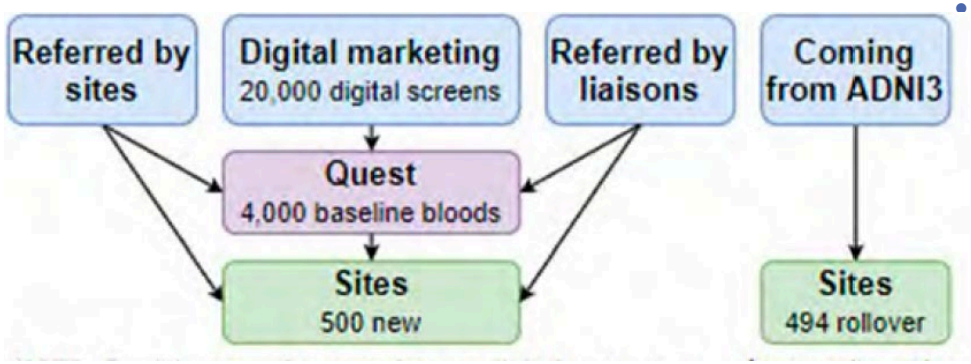
PI: Mike Wiener, UCSF
NIA Program Directors: John Hsiao, Laurie Ryan

Goal: ***500*** *rollover participants and* ***500*** *new participants" 40% MCI, 40% CN, 20% Dem (50-60% diverse populations)*



- **> 59 sites**
- **Clinical, blood, LP**
- **Cognitive Tests**
- **MRI: all types**
- **FDG/amyloid/tau PET**
- **LP: CSF Ab/tau**
- **Genetics**
- **Neuropathology**

All data in public database: USC/LONI/ADNI: No embargo of data



- **NEW Engagement Core**- Drs Rivera-Mindt and Okonkwo PI's
- **Enroll 50-60 %** of new participants from URPs (African-American, Latino, Asian)
- Facilitate **"Community Engaged Research"** expanded Community Science Partnership Board
- **At least 15 "hub sites"** with full time recruiters
- **Digital marketing-social media** enroll 20,000 into an on-line screener.

4000 of these will have blood drawn at local Quest Centers for blood testing

"**Telephone help desk"** to facilitate URP participation

http://adni.loni.usc.edu/

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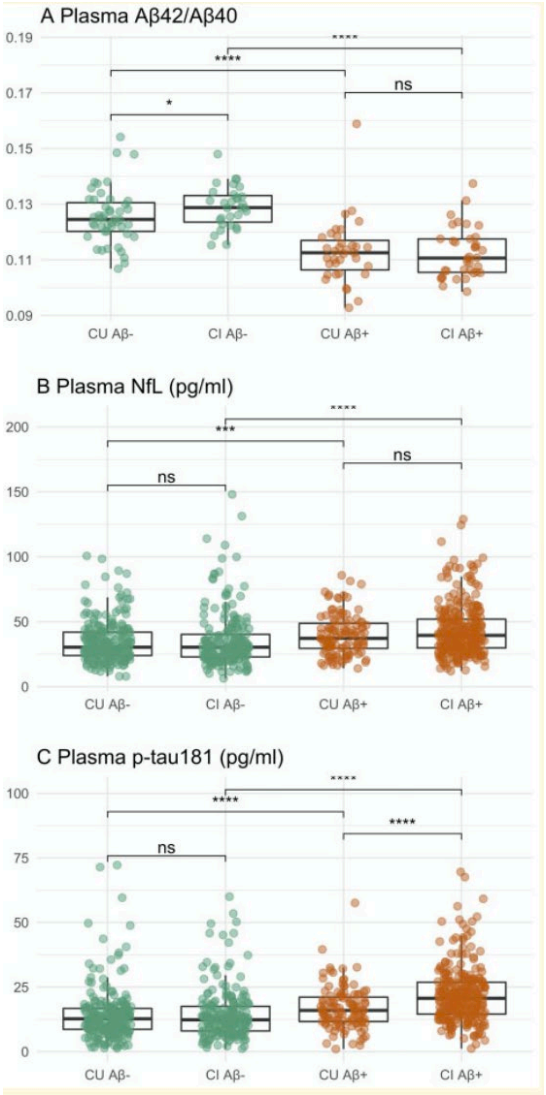
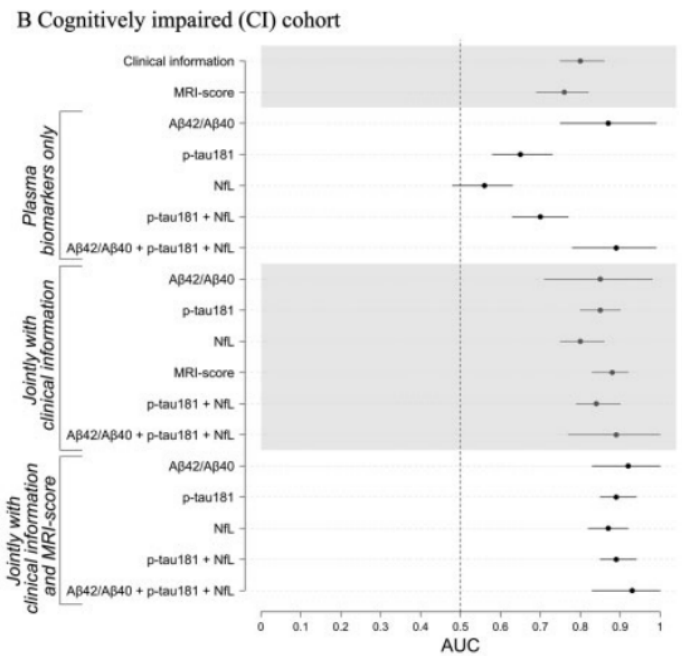
Plasma biomarkers in ADNI

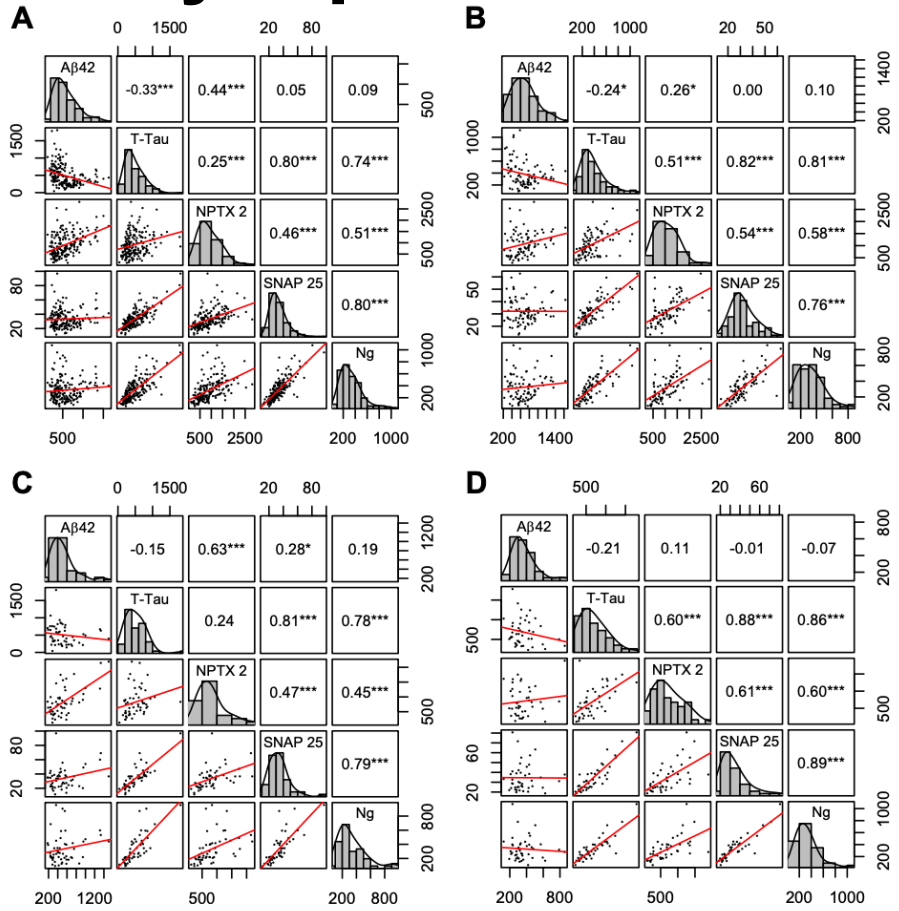




- *Combined clinical information, plasma p-tau 181 and Nfl and an MRI-score identify Abeta cognitively unimpaired and impaired (area under curve, 0.80–0.90)*
- *Plasma Abeta improves with age and APOE*

Tosun et al in Brain Comm 2021

CSF Synaptic biomarkers



- *CSF synaptic biomarkers, particularly NPTX2, relate to cognition and predict progression in AD beyond Ab1-42 and Tau.*

Galasko et al in Alz Dem 2019

Health Disparities

- **Total= 3500 participants**
- **1,500 Mexican Americans** (>1,000 enrolled)
- **1,500 Blacks/African Americans** (>700 enrolled)
- **1,500 non-Hispanic whites** (>1,000 enrolled)
- **24-month follow-up intervals** (>1,000 V2 completed)
- **Community-based** research approach.
- **Engage community** leaders, organizations
- **"Give Back"** to the community
- Be part of the community, **always present**

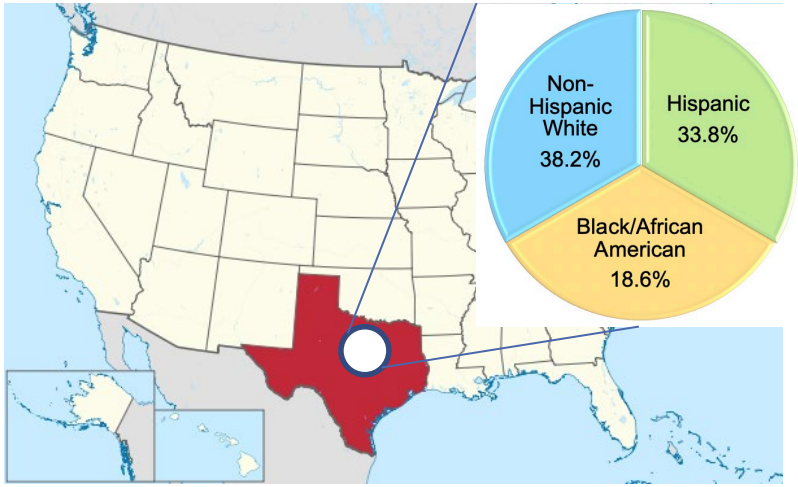
A. Admin
B. Neuro Imaging
C. Clinical
D. Omics
E. Disparities
F. Stats
G. Development

***1**. Diversity and ATN framework*

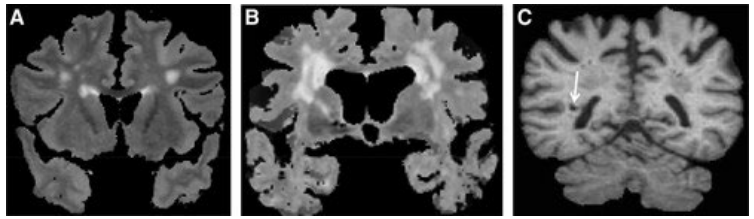
***2**. VMI and ATN*

***3**. Exposome and ATN*

PI', Sid O'Bryant, UNTHSC
NIA Program Directors: Damali Martin



Data sharing via LONI
https://apps.unthsc.edu/itr/request/hd



- *Functional exam*
- *Clinical labs*
- *Sociocultural, environmental and behavioral factors*
- *Item-level data entry*
- *Neuropsychological assessment*
- *Biorepository (n>500,000 aliquots available)*
- *Multi-level "omics"*
- *Amyloid and Tau PET Scans*
- *3T MRI*

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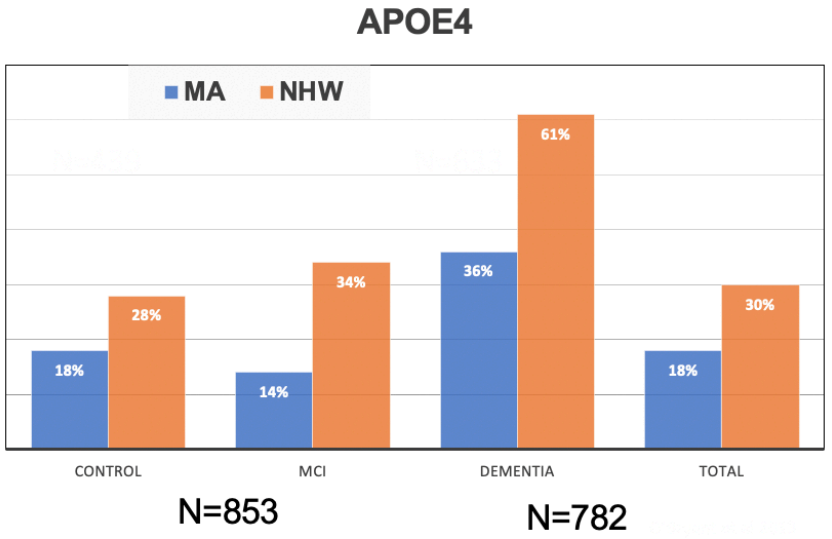
O'Bryant et al in preparation

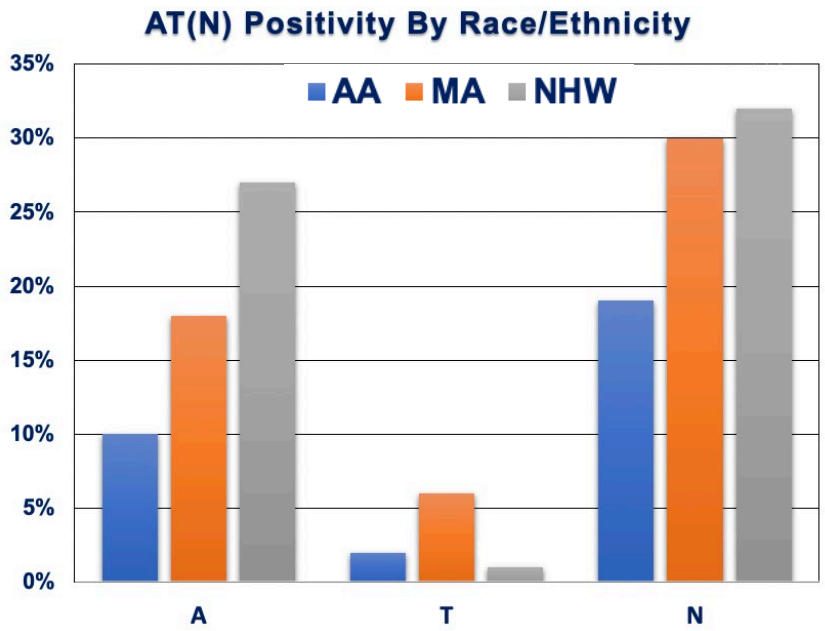
HEALTH & AGING BRAIN STUDY

Health Disparities

Visit 1	Total
Mexican American	1122
White	1094
African American	634
Visit 2	**Total**
Mexican American	544
White	595
African American	0
Visit 3	**Total**
Mexican American	119
White	115
African American	0

	Amyloid PET	Tau PET
White	654	383
Mexican American	489	249
African American	548	298
Total	**1,691**	**930**





- **ATN-biomarkers are** differentially <u>prevalent among diverse pop</u>
- **ATN-biomarkers are** differentially related to <u>clinical outcomes</u>
- **Clinical, demographic and sociocultural** factors are differentially related to ATN-defined and cognitive outcomes
- **Precision medicine** requires inclusion of diverse communities

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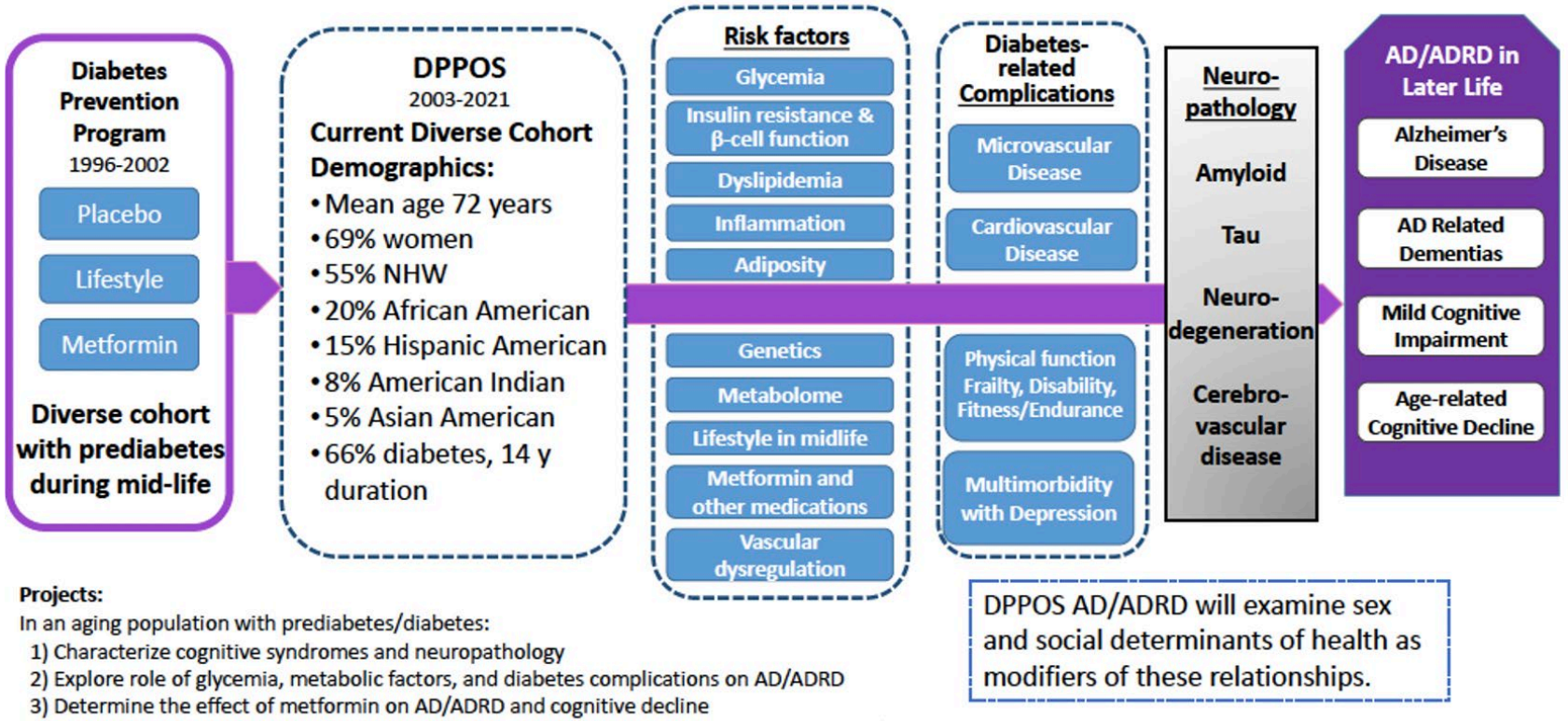
Diabetes Prevention Program Outcomes Study AD/ADRD Project

PI's: Jose Luchsinger (Columbia U), David Nathan, Marinella Temprosa
NIA Program Directors: Dallas Anderson, Molly Wagster, Marcell Salive

Main objective: What are the determinants and mechanisms of AD/ADRD among persons with PreD and T2D?



Projects:
In an aging population with prediabetes/diabetes:
1) Characterize cognitive syndromes and neuropathology
2) Explore role of glycemia, metabolic factors, and diabetes complications on AD/ADRD
3) Determine the effect of metformin on AD/ADRD and cognitive decline
4) Evaluate trajectories of physical activity, physical function and frailty on pathways to AD/ADRD

DPPOS AD/ADRD will examine sex and social determinants of health as modifiers of these relationships.

- 25 clinical sites and core functions across > 30 institutions in the US
- NACC UDS clinical measures
- Legacy DPPOS measures
- MRI and Abeta PET in a third of participants (one wave in 650 of 1900 participants)
- Plasma AD biomarkers in all participants
  - Amyloid beta 40 and 42
  - ptau-231
  - GFAP
  - NFL

Data sharing via NACC and NIDDK

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PreD and T2D clinical AD/ADRD Studies in a diverse US population

Excellent retention 48% underrepresented minorities

Table 1. Characteristics of the DPPOS cohort through in the last 25 years and projected for DPPOS AD/ADRD

	DPP	DPPOS Phase 1	DPPOS Phase 2	DPPOS Phase 3	DPPOS AD/ADRD@
Calendar Years	1996-2002	2002-2009	2009-2015	2015-2022	2022-2027
DPPOS Years	-	1-7	8-13	14-19	20-24
Total enrolled participants	3234	2766 (86%)#	2493 (93%)#	2261 (96%)#	~1979
Withdrew consent	42	27	31	10	0
Died during period**	28	97	144	277	-
Mean age in years+	53	61	67	72	77
Age ≥ 65 years (%)+	10%	26%	48%	74%	93%
Sex (% women)	2191 (68)	1878 (68)	1694 (68)	1572 (70)	1402 (71)
Ethnic and racial group (%)					
Hispanic	508 (16)	424 (15)	368 (14)	347 (15)	312 (15)
Non-Hispanic White	1768 (54)	1506 (54)	1350 (54)	1194 (52)	1030 (52)
Non-Hispanic Black	645 (20)	559 (20)	511 (20)	472 (20)	406 (20)
American-Indian	171 (6)	153 (5)	148 (5)	144 (6)	132 (6)
Asian American/Pacific Islander	142 (5)	124 (4)	116 (4)	104 (5)	99 (5)
Diabetes (%)+	851 (26)	1338 (48)	1501 (60)	1504 (67)	--
Diabetes duration (years)+^	1.6	5.8	10	14.3	~19

Apolipoprotein E genotype and in vivo amyloid burden in middle-aged Hispanics

Priya Palta, PhD, Brady Rippon, MS, Christiane Reitz, MD, Hengda He, MS, Greysi Sherwood, BS, Fernando Ceballos, MD, Jeanne Teresi, EdD, PhD, Qolamreza Razlighi, PhD, Herman Moreno, MD, Adam M. Brickman, PhD, and José A. Luchsinger, MD

Correspondence
Dr. Palta
pp2464@cumc.columbia.edu

Neurology® 2020;95:e2086-e2094. doi:10.1212/WNL.0000000000010707

Extending Alzheimer disease biomarker studies into the Hispanic community

David A. Bennett, MD, and David S. Knopman, MD

Correspondence
Dr. Bennett
david_a_bennett@rush.edu

Neurology® 2020;95:665-666. doi:10.1212/WNL.0000000000010714

APOE 4 genotype strongly related to higher amyloid burden in vivo (amyloid PET), despite controversy on whether APOE genotype predicts AD in Hispanics

Neurobiology of Aging 103 (2021) 109–116

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

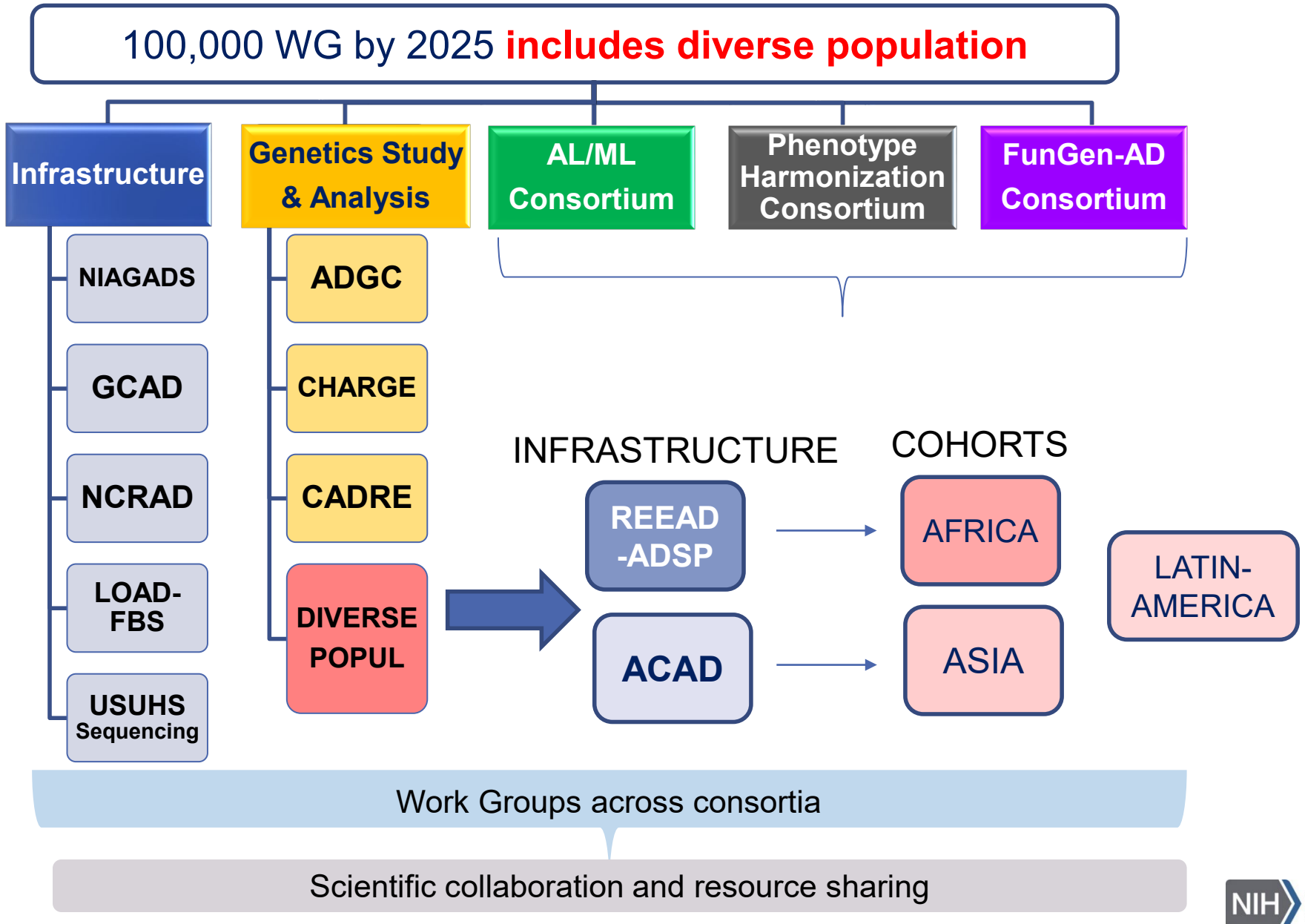
Sex differences in in vivo tau neuropathology in a multiethnic sample of late middle-aged adults

Priya Palta[a,b,*], Brady Rippon[a], Mouna Tahmi[a], Michelle Pardo[a], Aubrey Johnson[c], Zeljko Tomljanovic[c], Hengda He[c], Krystal K. Laing[c,h], Qolamreza R. Razlighi[f,h], Jeanne A. Teresi[g], Herman Moreno[g], Adam M. Brickman[c,d,e], William C. Kreisl[c,d,e,h], José A. Luchsinger[a,b]

- In a multiethnic urban cohort of 252 persons with a mean age of 64 years with MRI, amyloid PET, and Tau PET, females had higher amyloid and tau burden compared with men, despite better memory and thicker cortices.

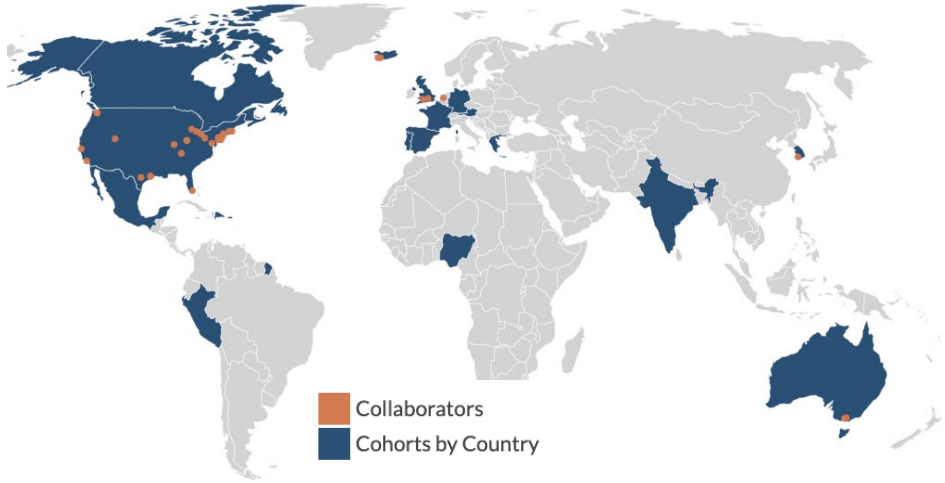
Alzheimer's Disease Sequencing Project

- *Over 75 risk loci and 20 genes (from the 75 loci) for AD identified*
- *Examples: BIN1, TREM2, CR1, PCALM, ADAM10, ABCD4, PLGC2, ANAX5, MEF2*
- *Involved in immune, neuronal/synaptic, endocytosis, lysosome* ***and*** *lipid metabolism*
- *Common polygenic variation increases risk prediction (APOE+others)*



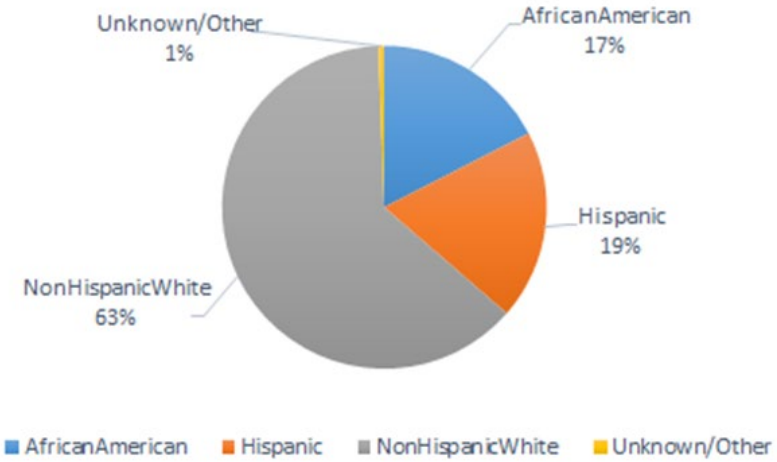
ADSP Follow-Up Study (FUS) 2.0: Diversity Initiative (PAR21-212) (FY2023-2028)

- **WGS 18,500 cases and 18,500 controls African, Hispanic, and Asian ancestry**
- Estimate assembling **130,000~150,000** genomes by 2027-2028
- Case control, epidemiologic, and family-based
- International collaborators: ***India, Africa, Mexico, Central and South America, Korea, Australia***

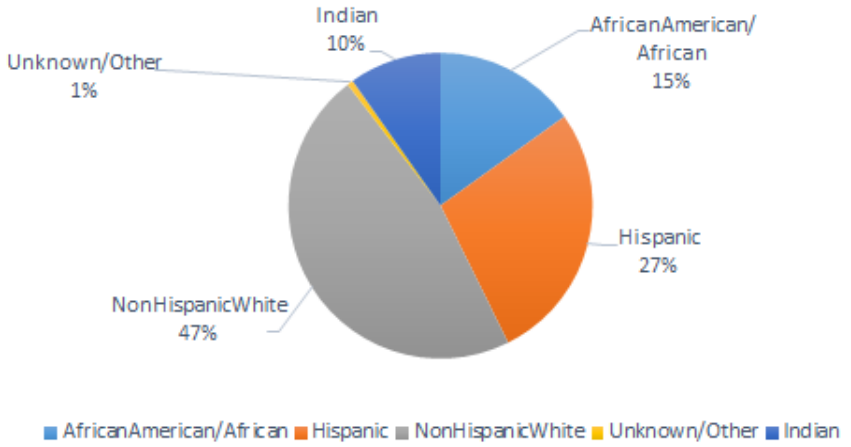


- ***Sample acquisition***
- ***Genotyping***
- ***Whole genome sequencing***
- ***Quality control***
- ***Variant calling***
- ***Data calling***
- ***Data sharing***
- ***Data harmonization***
- ***Analysis***
- ***Functional genomics***
- ***Machine Learning***

Release 3, 16,906 WGS, 2021



Release 4, 36,361 WGS, 2022



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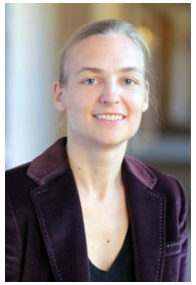
Recruitment and Retention for AD Diversity Genetic Cohorts in the ADSP (READ-ADSP)

University of Miami
Margaret Pericak-Vance
Brian Kunkle
Jeffery Vance



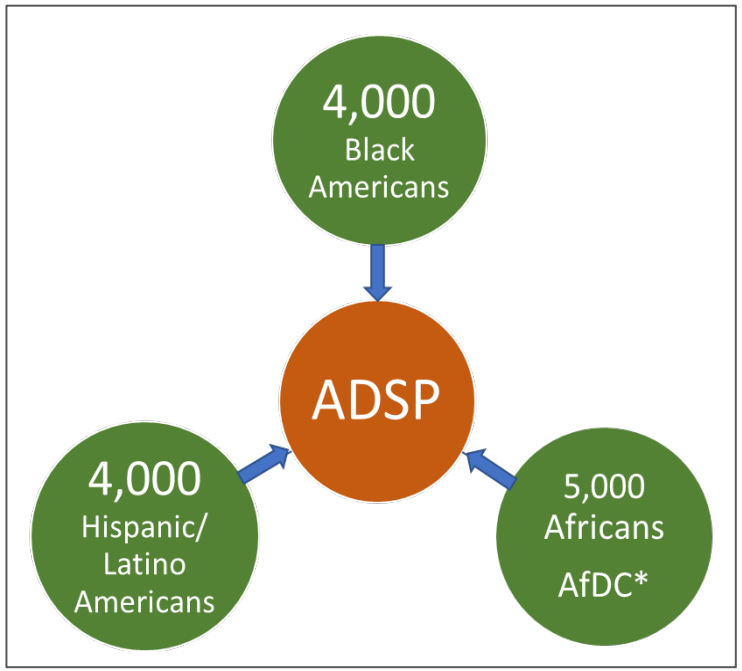
Wake Forest University
Goldie Byrd

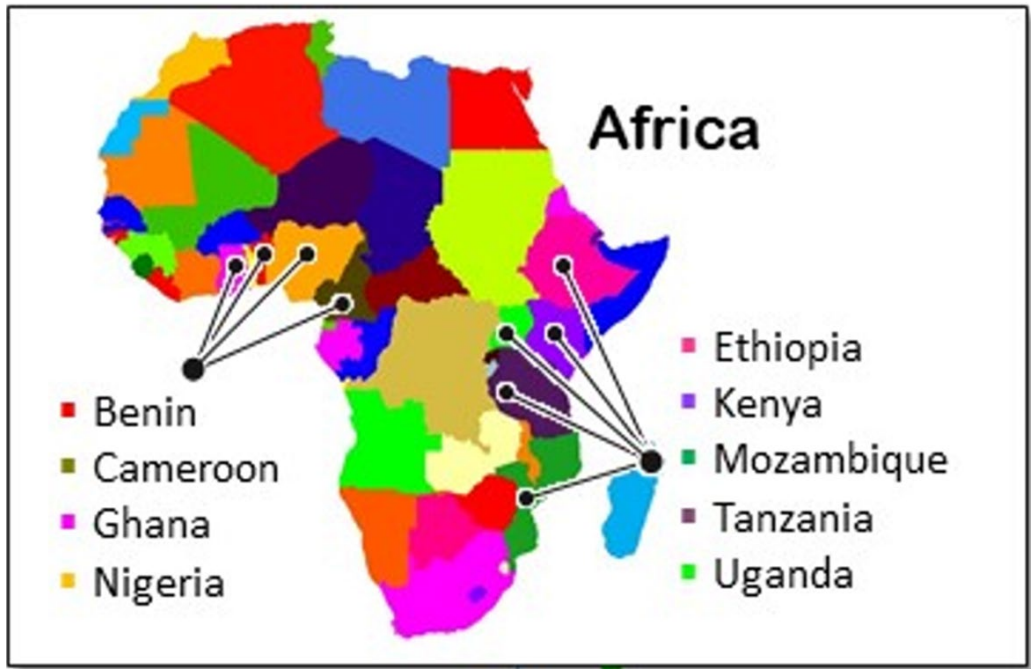
Columbia University
Giuseppe Tosto
Christiane Reitz




University of Ibadan
Rufus Akinyemi
Adesola Ogunniyi


Case Western Reserve University
Jonathan Haines
Will Bush



- DNA, RNA, Plasma Biomarkers and CVD markers
- Whole Genome Sequencing
- Social Determinants of Health (SDOH)
- *Provide the basis for integrated studies of biological and social risks of AD.*

*AfDC; African Dementia Consortium

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Examples of ADSP Foreign Cohorts in Asia

Gwangju Alzheimer's & Related Dementias (GARD) Study – Korea	PI: Lindsay Farrer (Boston University) Korea site PI: Kunho Lee (Chosun University)
KBASE2: Korean Brain Aging Study, Longitudinal Endophenotypes and Systems Biology	PI: Andrew Saykin (Indiana University) Korea site PI: Don Young Lee (Seoul National University)
Aspirin in Reducing Events in the Elderly (ASPREE) Trial cohort – Australia	PI: Paul Lacaze (Monash University)
Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD) – India	PI: Jinkook Li (University of Southern California)

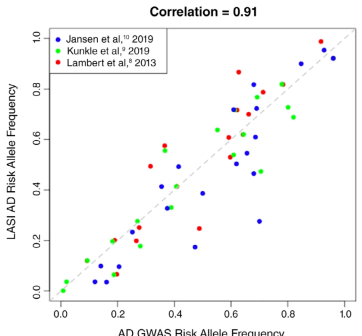







Association Between Episodic Memory and Genetic Risk Factors for Alzheimer's Disease in South Asians from the Longitudinal Aging Study in India–Diagnostic Assessment of Dementia (LASI-DAD)

Jennifer A. Smith, PhD,† Wei Zhao, PhD,* Miao Yu, MS,* Kalee E. Rumfelt, BS,* Priya Moorjani, PhD,‡§ Andrea Ganna, PhD,¶ Aparajit B. Dey, MD,‖ Jinkook Lee, PhD,** and Sharon L.R. Kardia, PhD**



SNP	Gene	β	*P* value
rs2830500	*ADAMTS1*	−.38	.003
rs10948363	*CD2AP*	.35	.004
rs9473117	*CD2AP*	.36	.009
rs4147929	*ABCA7*	.29	.03

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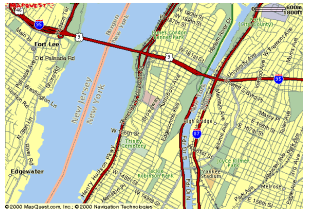
Examples of Latin American and Hispanic Cohorts

WHICAP-Washington Heights, Hamilton Heights and Inwood

PI: Richard Mayeux et al (Columbia U)



EFIGA- Estudio Familiar de Influencia Genetica en Alzheimer

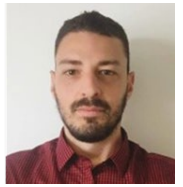
PI: Richard Mayeux et al (Columbia U)

Only *PINX1* and *TREM2* survived replication rom IGAP and EFIGA

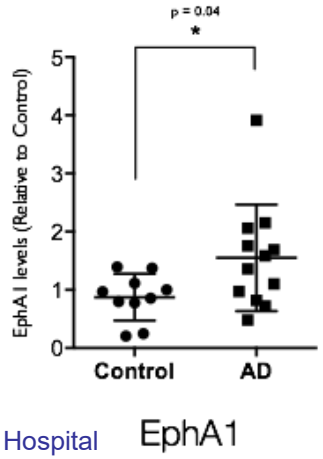
Studies of Amerindian populations in South America – Peru and Bolivia

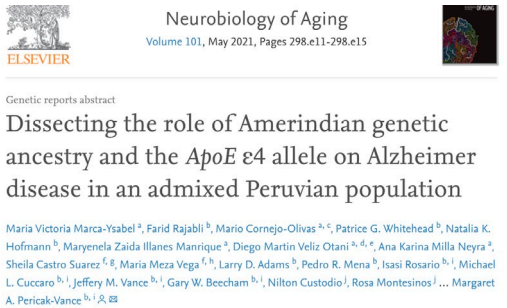
1,700 dementia cases and 1,850 healthy controls

PI: Giuseppe Tosto (Columbia U), Margaret Pericak-Vance, Eden R (U. Miami). Martin, Mario Cornejo-Olivas (Bolivia), Nilton Custodio (Peru)

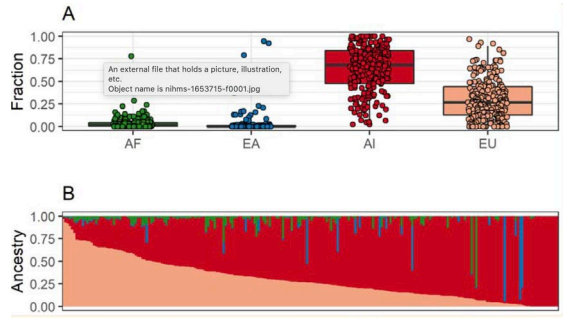


CHR	Function	Gene	AA change
2	nonsynonymous	BIN1	K358R
6	nonsynonymous	CD2AP	T374A
6	nonsynonymous	CD2AP	K633R
7	nonsynonymous	EPHA1	P460L
8	nonsynonymous	CLU	T203I
11	exonic/splicing	MS4A6A	V218M
11	nonsynonymous	PICALM	P495A
11	nonsynonymous	PICALM	H458R
19	nonsynonymous	ABCA7	L101R
19	nonsynonymous	ABCA7	R880Q
19	nonsynonymous	ABCA7	V1599M
19	stopgain	ABCA7	E1679X





Risk for AD from *ApoE ε4* in Peruvians is higher than we have observed in NHW populations



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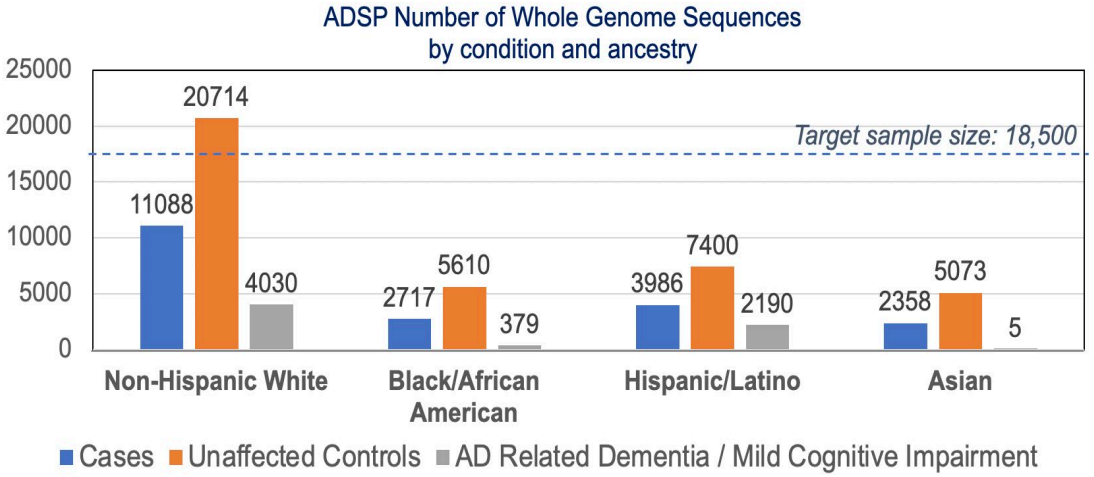
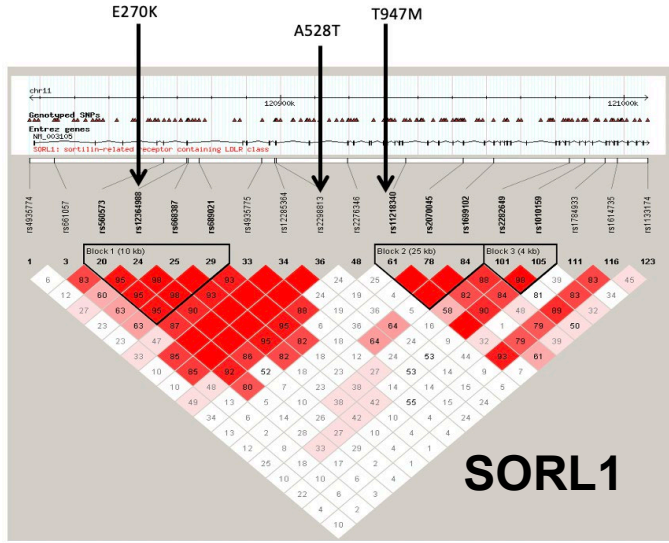
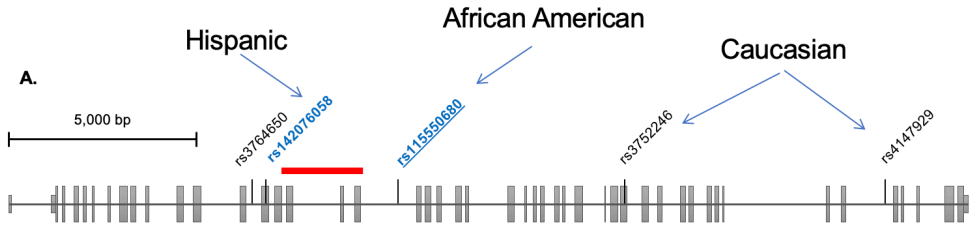
ADSP Follow-Up Sequencing (FUS) 2.0: Diversity Initiative



Position of rare coding mutations identified in ***SORL1*** in relation to common SNPs *(Vardarajan, Annals of Neurology, Feb 2015)*



ABCA7 Deletions and Mutations



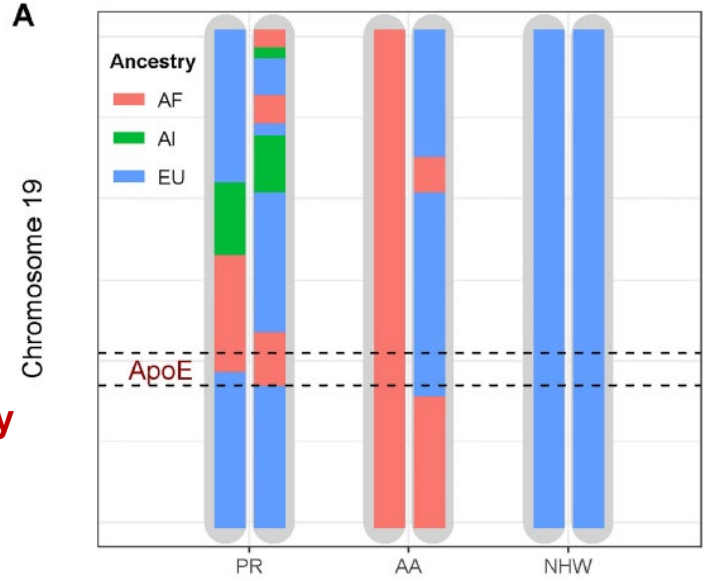
- **Twice as frequent in AA as in Non-Hispanic Whites (NHW)**
- ABCA7 protein is involved in APP processing (endosomal compartment)
- Frame shift deletion was found in AA, but was absent in NHW
- This deletion is **a common ethnic specific variant**

Ancestral origin of *ApoE ε4* Alzheimer disease risk in Puerto Rican and African American populations

Farid Rajabli[1✉], Briseida E. Feliciano[2], Katrina Celis[1], Kara L. Hamilton-Nelson[1], Patrice L. Whitehead[1], Larry D. Adams[1], Parker L. Bussies[1], Clara P. Manrique[1], Alejandra Rodriguez[2], Vanessa Rodriguez[1], Takiyah Starks[3], Grace E. Byfield[3], Carolina B. Sierra Lopez[2], Jacob L. McCauley[1], Heriberto Acosta[4], Angel Chinea[2], Brian W. Kunkle[1], Christiane Reitz[5], Lindsay A. Farrer[6], Gerard D. Schellenberg[7], Badri N. Vardarajan[5], Jeffery M. Vance[1,8], Michael L. Cuccaro[1,8], Eden R. Martin[1,8], Jonathan L. Haines[9], Goldie S. Byrd[3], Gary W. Beecham[1,8✉], Margaret A. Pericak-Vance[1,8✉*]

Compared with individuals with European ***APOE-ε4*** local ancestry

- those with **African local ancestry have lower risk of AD**
- those with **Amerindian local ancestry have higher risk**



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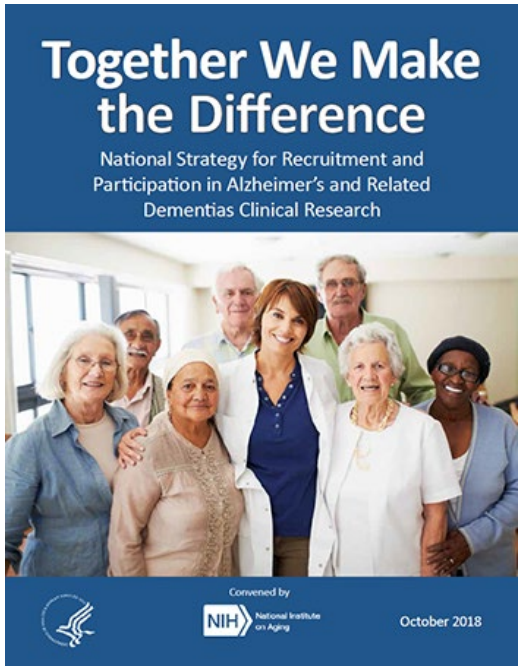
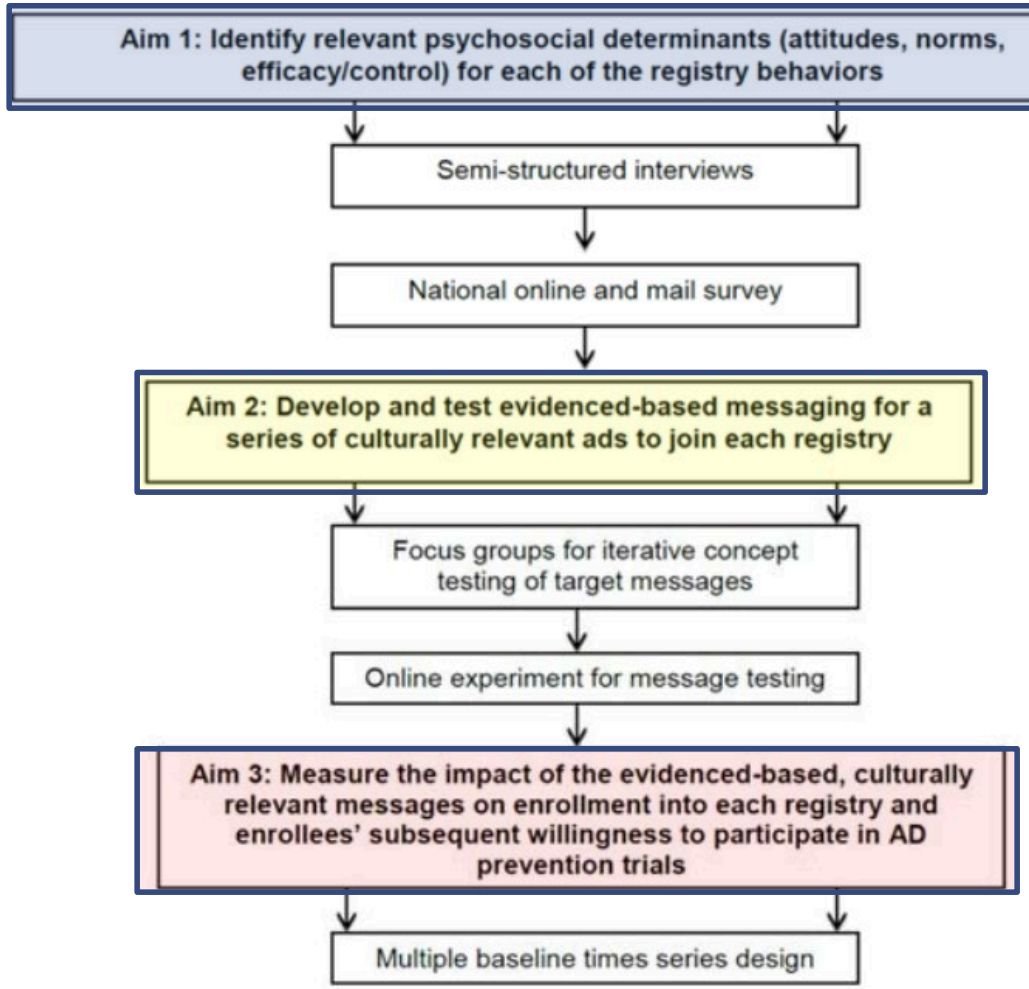
Study to Expand Registry Participation of Underrepresented Populations (STEP-UP)

Banner Health

MPIs: Jessica Langbaum, (Banner Alzheimer's Institute) & Amy Bleakley, (University of Delaware)
Co-Investigators: Rachel Nosheny, (UCSF) and Jason Karlawish, (Univ Pennsylvania)
NIA program director: Cerise Elliott





COVID-19 Supplement

Aim 1: COVID-19 news coverage and willingness to participate in AD-related research

Conducted cross-sectional national surveys stratified by racial and ethnic groups over 12mo to monitor how changes in the pandemic and news coverage may be related to attitude shifts

Aim 2: Identify determinants of COVID-19 related health behaviors

Bleakley et al., *Ann Behav Med,* 2022

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Study to understand Black, Hispanic and older adults willingness to participate in AD Registries

Interviews in 60 adults (20 White, 20 Hispanic, 20 Black; equal numbers of men and women) (*Bleakley et al JAD 2022)*

- Few differences between racial, ethnic or sex groups some differences in behavioral beliefs

National survey in 1500 adults ages 50-80, oversampling for Black & Hispanic respondents
(in preparation for submission to Alz & Dementia)

- No differences in intention to join a registry by race, ethnicity or sex

- White women were more likely than White men to take memory & thinking tests every 6mo;

- White women were more likely than Hispanic men to provide family member contact info;

Table 3
Prevalence of elicited beliefs by racial/ethnic group

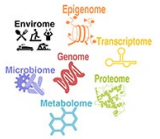
Belief	Total	Black ($n = 20$)	White ($n = 20$)	Hispanic ($n = 20$)
Behavioral beliefs	%	%	%	%
"*Bad things that would happen*"				
Concern for privacy	15.0	10.0	10.0	25.0
Being asked to participate in study with experimental drug or other treatment	40.0	45.0	30.0	45.0
Lack of transparency	3.3	10.0	0	0.0
Misuse or mismanagement of data	11.7	10.0	10.0	15.0
Confronting personal cognitive decline	10.0	10.0	10.0	10.0
Pressure to join study	8.3	5.0	15.0	5.0
Nothing or don't know	20.0	20.0	25.0	15.0
"*Good things that would happen*"				
Advance science or find a new discovery	60	65.0	60.0	55.0
Help others	36.7	45.0	20.0	45.0
Improve personal health or memory	21.7	20.0	30.0	15.0
Personal interest or novelty	21.7	15.0	40.0	10.0
Track personal progress or brain health over time	10.0	10.0	10.0	10.0
Important normative referents				
Spouse or partner	23.3	15.0	15.0	40.0
Children	36.7	40.0	20.0	50.0
Siblings	23.3	30.0	20.0	20.0
Friends or neighbors	28.39	30.0	25.0	30.0
Extended family	21.7	25.0	15.0	25.0
Healthcare provider	5.0	0	5.0	10.0
Facilitators				
Convenience	26.7	25.0	25.0	30.0
Modality	35.0	50.0	25.0	30.0
Providing written information	36.7	40.0	45.0	25.0
Results transparency	1.67	0	5.0	0
Barriers				
Enrolling would be demanding or difficult	10.0	15.0	5.0	10.0
Health problems	3.33	10.0	0	0
Inconvenient	23.3	25.0	25.0	20.0
Technology or computer	16.7	15.0	25.0	10.0
Transportation	6.7	5.0	5.0	10.0
Having to travel to a physical location	10.0	10.0	15.0	5.0
Lack of information	10.0	5.0	20.0	5.0
Medication side effects	5.0	0	5.0	10.0
Nothing or don't know	18.3	25.0	25.0	5.0

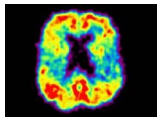
Bleakley et al JAD 2022

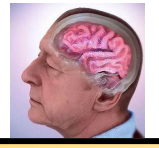
NIH National Institute on Aging

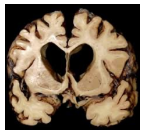
Translating AD/ADRD studies in diverse populations to personalized medicine

NIA Program Directors: N. Silverberg, C. Elliot, M. Miller, A. Yao, J. Larkin, D. Martin, D. Anderson, S. Petanceska, L. Ryan, N. Arunkumar









Genetic and Genomic Data

Multi-OMICS Data

Clinical Data

Biomarkers Data

Neuropath Data

Data Harmonization*

ADSP/NEW COHORTS

NIAGADS

ADRC's, DIVERSE DPPOS, COHORTS

NACC

AMP-AD DIVERSITY

AD Knowledge Portal

ADNI4, HABS-HD, ACTC

LONI Laboratory of Neuro Imaging

Personalized Medicine

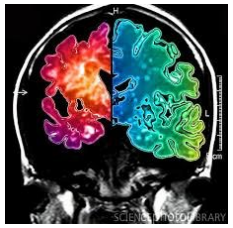
NIH National Institute on Aging

THANKS

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

General FOAs:
https://www.nia.nih.gov/research/funding

Alzheimer's Disease and Related Dementias FOAs:
http://www.nia.nih.gov/AD-FOAs



NIA- Division of Neuroscience
https://www.nia.nih.gov/research/dn

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