Aging and the Brain:
Roadmaps to Therapeutics
The Shiley-Marcos Alzheimer's Disease Research Center and Center for Brain Health and Memory Disorders at UC San Diego

James Brewer, M.D., Ph.D.
Chair, Department of Neurosciences
Director, Shiley-Marcos Alzheimer's Disease Research Center
Professor, Departments of Neurosciences and Radiology
UC San Diego Health

UC San Diego
HEALTH SCIENCES

Outline

- Background:
  - UC San Diego Neurosciences
    - Research and Clinical Partnership for Advancing Knowledge and Care for Patients with Alzheimer's Disease and Related Disorders
      - The Shiley-Marcos Alzheimer's Disease Research Center
      - The Alzheimer's Disease Cooperative Study
      - The UC San Diego Center for Brain Health and Memory Disorders
- New Tools for Discovery
- New Tools for Care
- The Promise of the Future

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UC San Diego Neurosciences

A Nation-Leading Department with Bold Ideas and an Ambitious Vision for the Future

Fueled by creative and innovative concepts born from cross-fertilization

Engineers

Clinicians

Scientists

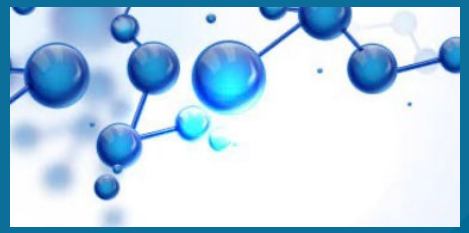





Educators

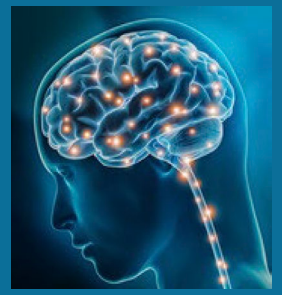
UC San Diego Neurosciences

Five Departmental Hubs of Innovation

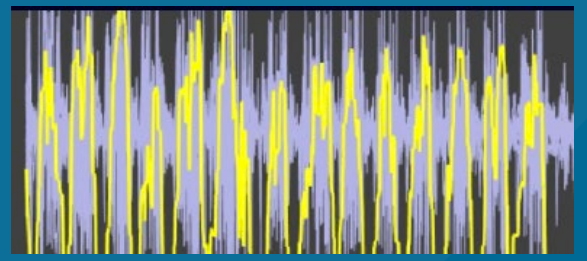


NeuroGenetics:
Unlocking the Power of the Genome toward New Neurodiagnostics and Neurotherapeutics

Metabolism, Aging, and Neurodegeneration



NeuroRecovery



Implantable Devices:
Decoding Brain Signals and Engineering New Brain-Machine Interfaces

Imaging the Brain and Nervous System-
In Vivo Probes and Reporters

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MEMORY DISORDERS RESEARCH

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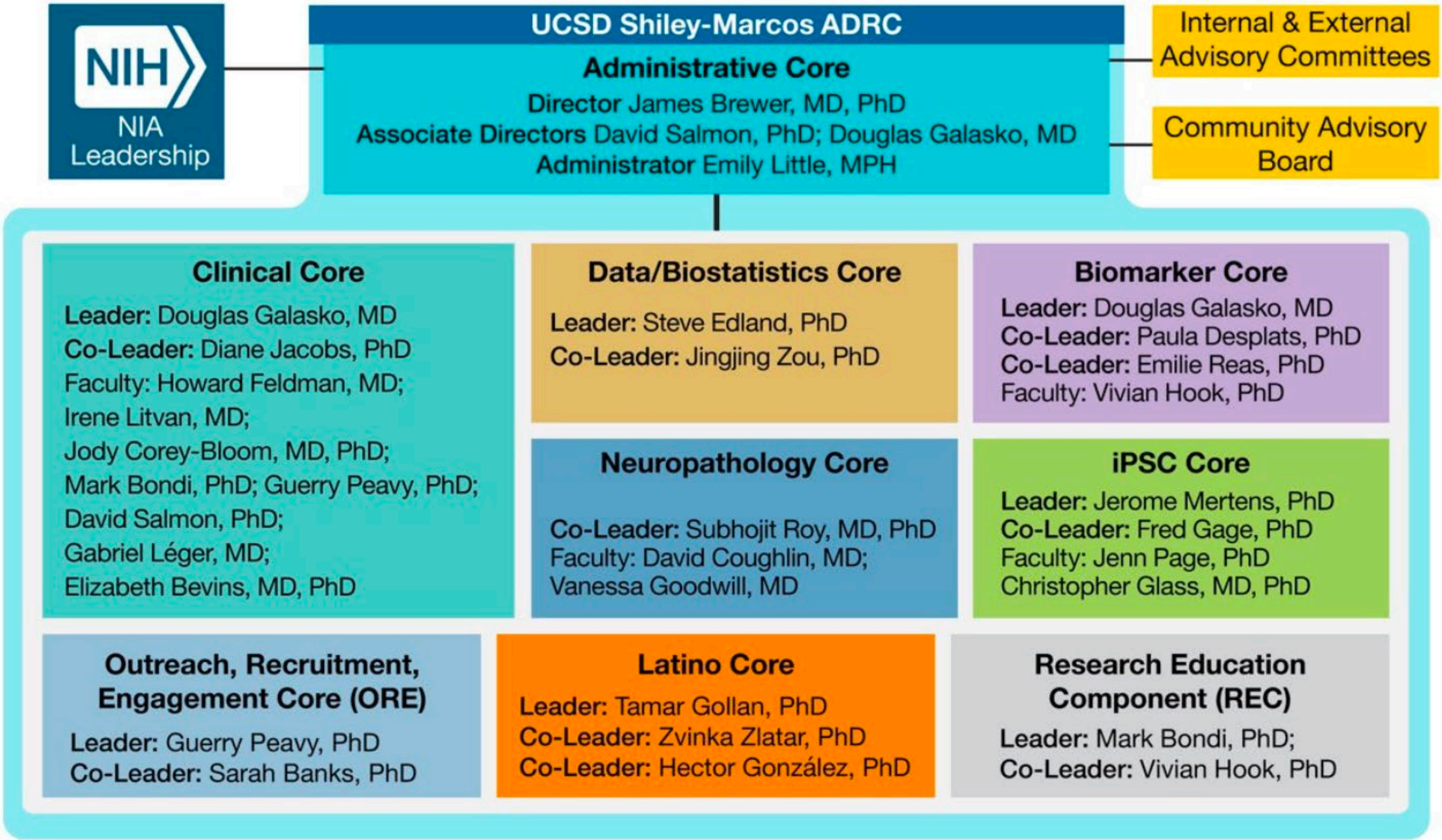
NIH
NIA Leadership
UCSD Shiley-Marcos ADRC
Administrative Core
Director James Brewer, MD, PhD
Associate Directors David Salmon, PhD; Douglas Galasko, MD
Administrator Emily Little, MPH
Internal & External Advisory Committees
Community Advisory Board
Clinical Core
Leader: Douglas Galasko, MD
Co-Leader: Diane Jacobs, PhD
Faculty: Howard Feldman, MD;
Irene Litvan, MD;
Jody Corey-Bloom, MD, PhD;
Mark Bondi, PhD; Guerry Peavy, PhD;
David Salmon, PhD;
Gabriel Léger, MD;
Elizabeth Bevins, MD, PhD
Data/Biostatistics Core
Leader: Steve Edland, PhD
Co-Leader: Jingjing Zou, PhD
Biomarker Core
Leader: Douglas Galasko, MD
Co-Leader: Paula Desplats, PhD
Co-Leader: Emilie Reas, PhD
Faculty: Vivian Hook, PhD
Neuropathology Core
Co-Leader: Subhojit Roy, MD, PhD
Faculty: David Coughlin, MD;
Vanessa Goodwill, MD
iPSC Core
Leader: Jerome Mertens, PhD
Co-Leader: Fred Gage, PhD
Faculty: Jenn Page, PhD
Christopher Glass, MD, PhD
Outreach, Recruitment, Engagement Core (ORE)
Leader: Guerry Peavy, PhD
Co-Leader: Sarah Banks, PhD
Latino Core
Leader: Tamar Gollan, PhD
Co-Leader: Zvinka Zlatar, PhD
Co-Leader: Hector González, PhD
Research Education Component (REC)
Leader: Mark Bondi, PhD;
Co-Leader: Vivian Hook, PhD

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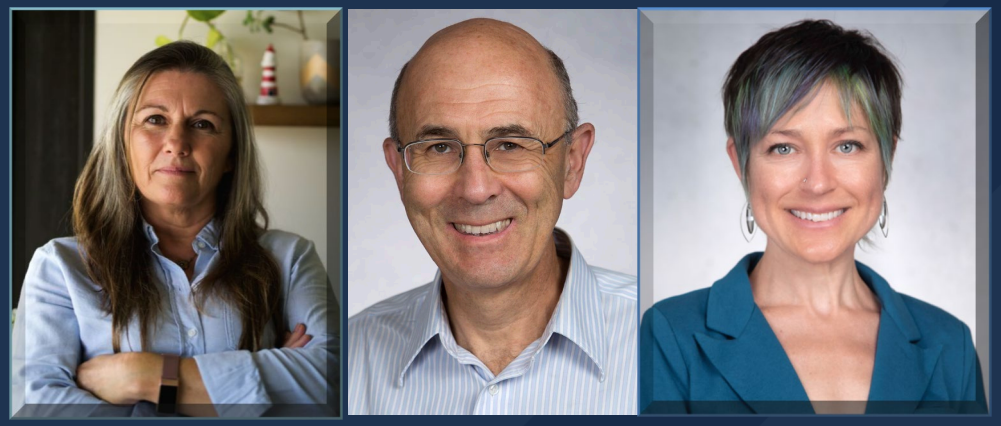
Biomarker



Desplats-----Galasko-----Reas

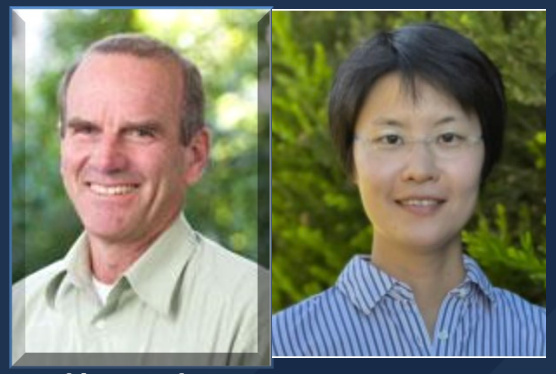
Neuropathology

Coughlin ----- Roy ------ Goodwill

Latino Core

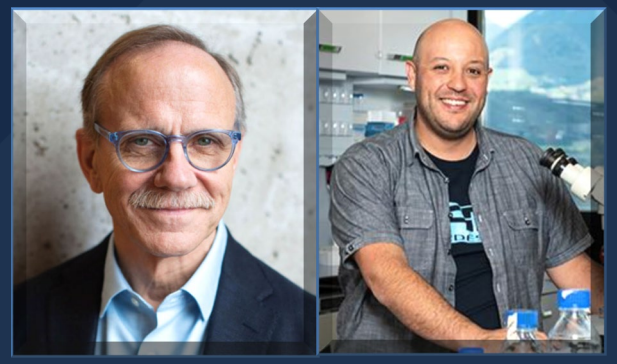
Gonzàlez-----Zlattar-----Gollan

Data Core



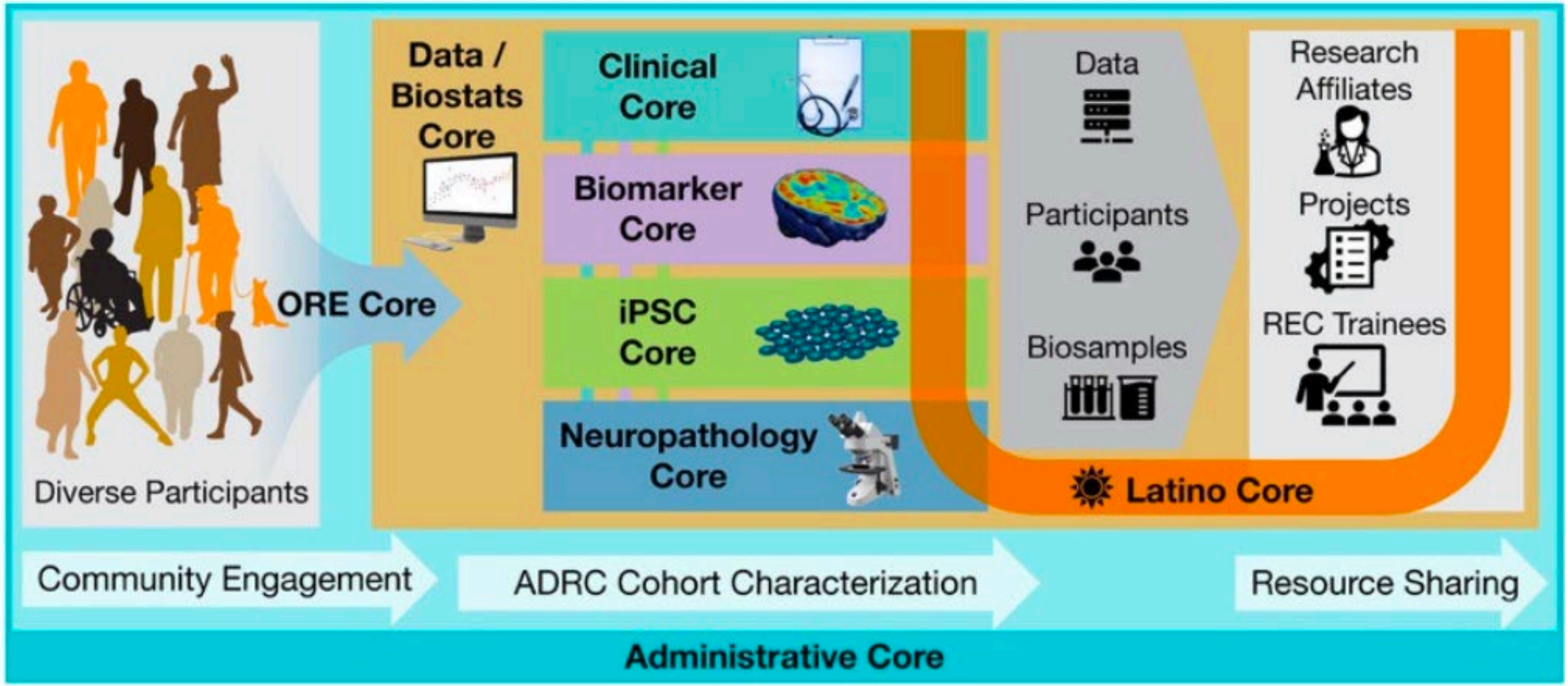
Edland ----- Zou

iPSC Core



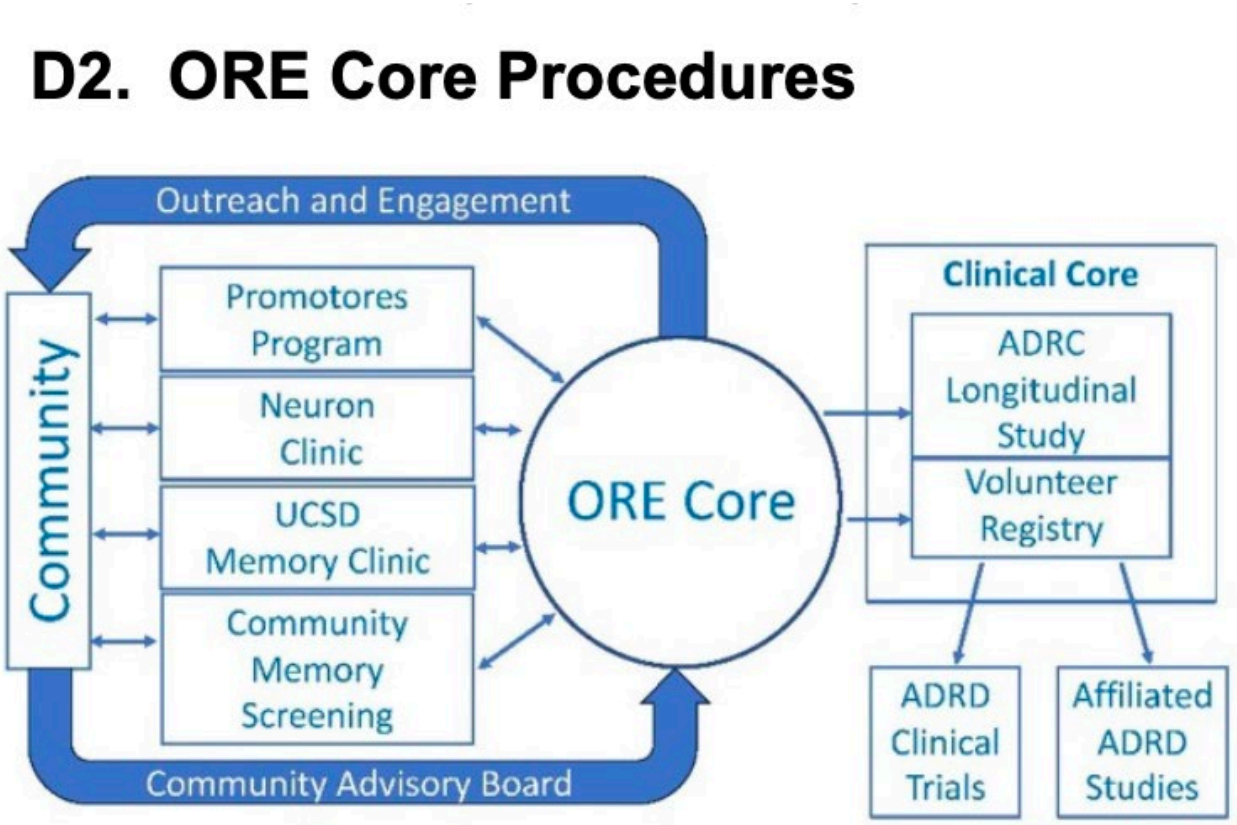
Gage ----- Mertens

Overall Aims of the Center



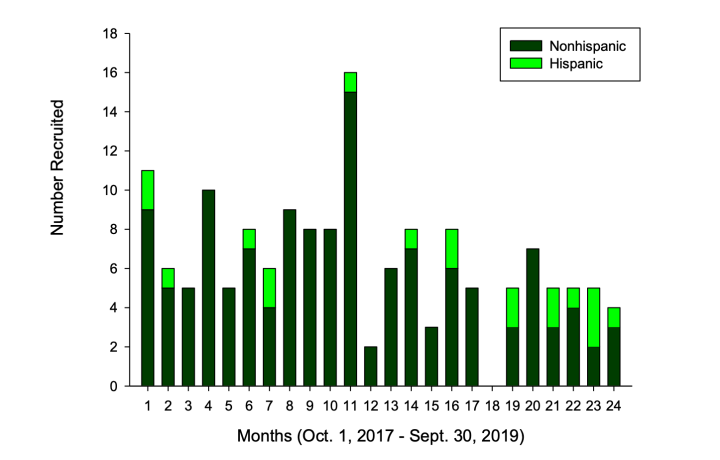
Outreach Recruitment and Engagement

- Recruitment Goals for Volunteer Registry
  - 200 new enrollees per year
- Seek to engage new partners to boost diversity of socioeconomic status (SES)
  - e.g. Serving Seniors

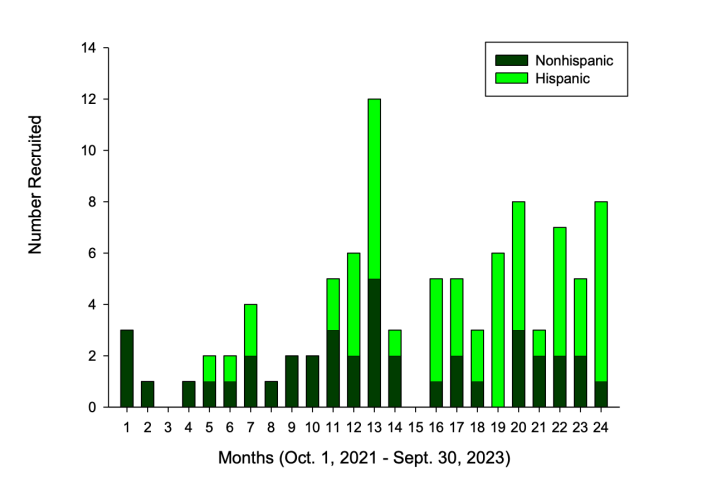


ADRC – Evolving our Culture

Latino Recruitment 2017-2019



Latino Recruitment 2021-2023



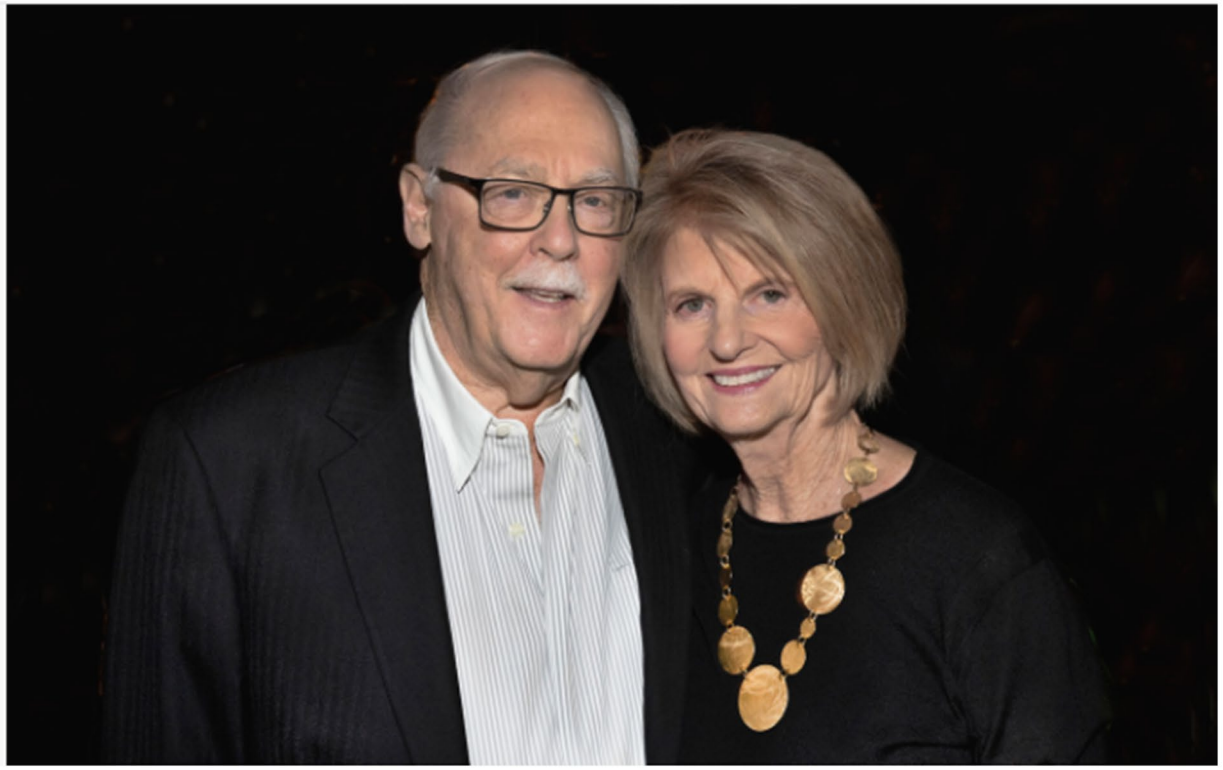
UC San Diego News Center

January 24, 2022

With a $50 Million Gift, USC and UC San Diego Join Forces in Alzheimer's Research

A transformative donation from the Epstein Family Foundation will accelerate Alzheimer's research at the two universities in a push to find better treatments and a cure

A joint gift to the University of Southern California (USC) and the University of California San Diego totaling $50 million from the Epstein Family Foundation will drive Alzheimer's research and accelerate the search for treatments and a cure.



Dan and Phyllis Epstein

THE ALZHEIMER'S DISEASE COOPERATIVE STUDY

Established 1991-

Serves as an academic-based Clinical Trial Network that advances the state of the art in ADRD trials

Pushes forward new ideas, often outside the standard dogma, yielding data collection for proof of concept
Advances innovative trial design and outcome measures
Open to trying new therapeutics without patentability or high profit potential
Guided only by the science… *To boldly go where pharma can't or won't*

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ADCS Current Portfolio (n=8)

☐ NIA ☐ Non-NIA

UC San Diego
SCHOOL OF MEDICINE

Active Projects

Study	Funding	Project Period and Amount
VIVA-MIND Phase 2A-B	**NIA R01, Vivoryon Therapeutics**	Apr2019-Jun2025 $21M
Benfotiamine Phase 2A-2B	**NIA R01**	Jul2022-Jun2028 $42.5M
NeuroRiderVR Phase 2	**NIA R01**	Mar2020-Feb2026 $6.9M
Sex/Gender Differences	**Alz Assoc**	Oct2023-Sep2026 $250K
Legacy RF1	**NIA RF1**	Sep2024-Aug2027 $3.3M
HALT-AD	**Mente Sana add-on to NIA R61/R33 AG077969 UCSD & Health System**	Jan2024-Dec208 $120K
CAN-THUMBS UP	**Canadian Institutes of Health Research**	Apr2019-Mar2029 $1.1M
Asian Cohort for Alzheimer's Disease (ACAD)	**NIA (U19)**	Jul2023-Jun2028 $2.8M

Upcoming Clinical Trials: Grants Submitted

Study	Funding/Partner	Submission Date and Amount	Phase
ALX-001 Allyx: Tim Siegert Yale: Steve Strittmatter **Contact PI: H Feldman**	NIA/Allyx R01	Oct 2024 $37.9M	Phase 1B and 2A n=150
Atomoxetine (P4P) Emory: Alan Levey, David Weinshenker **Contact PI: H Feldman**	Epstein, NIA R01	Oct 2024 $17.6M	Phase 2A-B Ph 2A n=40 Ph 2B TBC
POSIT Stanford: Vankee Lin **Contact PI: J Pa**	NIA R01	Oct 2024 $31.4M	Phase 3 n=788
SMARRTER UCSF: Kristine Yaffe **Contact PI: J Pa**	NIA R01	Feb 2025 $44.5M	Phase 2 n=1032

Upcoming Clinical Trials in Development

Study	Funding/Partner	Submission Date	Phase
HER-CARE	Wellcome LEAP	Pending submission Apr 2025	Target trial emulation
P4P Platform Trial	Epstein, NIA R01	~ 2025	Phase 2A Multiple arms n=250

DISCOVER

Alzheimer's Research & Therapy BMC

Posiphen to lower amyloid precursor protein
Phase 1B trial---------onto Phase 3
Galasko *et al. Alzheimer's Research & Therapy* (2024) 16:151
https://doi.org/10.1186/s13195-024-01490-z

UC Cures Initiative NEAT Trial in Mild Cognitive Impairment

Neurology®

Nicotinamide to lower phosphorylated tau
Phase 2A trial-----problems with bioavailability
Grill J et al Neurology 2025 Jan 14;104(1):e210152.
Ketron G et al Alz Res &Therapy 2025

peace AD
prazosin for disruptive agitation in Alzheimer's Disease

Phase 2 trial of Prazosin in preparation for submission
Drs. Elaine Peskind & Dr. Murray Raskind

Benefits on levels of agitation
Preliminary data

T2 PROTECT AD
The Troriluzole Trial (T2) for Alzheimer's Disease

Feldman HH et al Under revision
Ph 2 trial--------negative clinical and biomarker results

Primary and Usual Care papers in press
Phase 2-3 trial on Aerobic training vs Stretching and balance
Lead authors: Dr. Laura Baker (primary) & Dr. Aladdin Shadyab (usual care)

EXERT

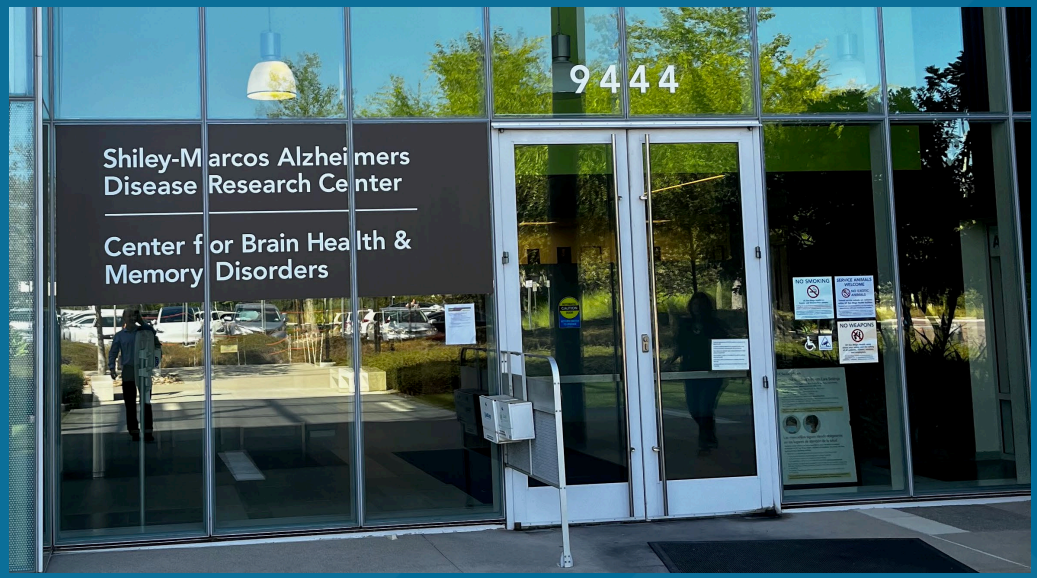
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

MEMORY DISORDERS CLINICAL CARE

UC San Diego
Health Sciences

The UC San Diego Center for Brain Health and Memory Disorders

- Established to Provide State-of-the-Art Brain Health Care and Support
  - Considering both the Aging Patient and Families/Caregivers
- Access to Clinical Trials and Research Advances
- Safe Delivery of New Therapeutics



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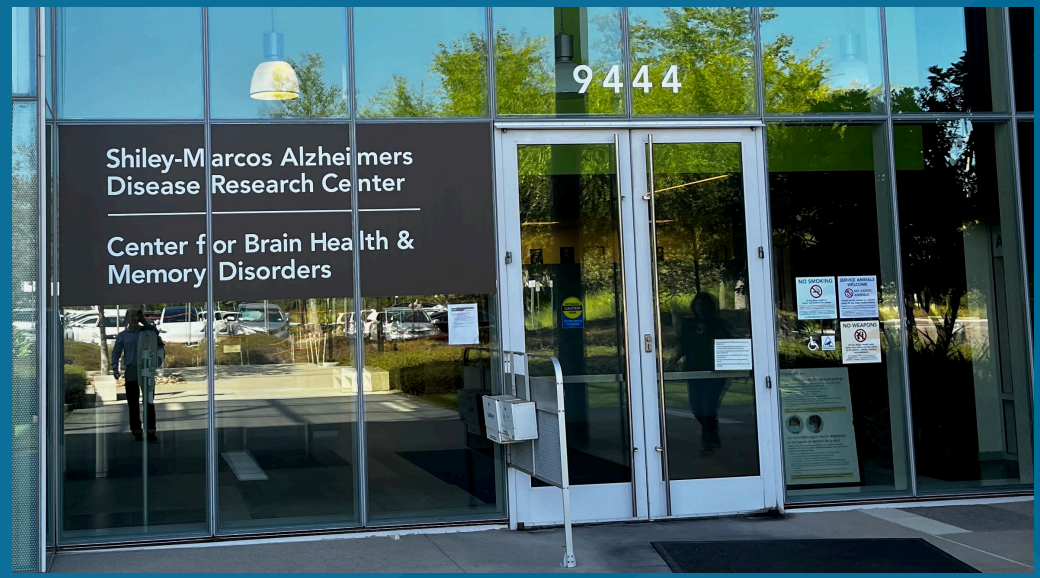
The UC San Diego Center for Brain Health and Memory Disorders

- Multidisciplinary Team with Renowned Specialist Expertise
  - Neurologists
  - Neuropsychologists
  - Geriatric Psychiatrist
  - Geriatrician
  - Nurse Practitioner
  - Social Worker
  - Nursing and Medical Assistant Staff



- <u>Fully Dedicated to Care of Aging Patients with Memory Disorders</u>

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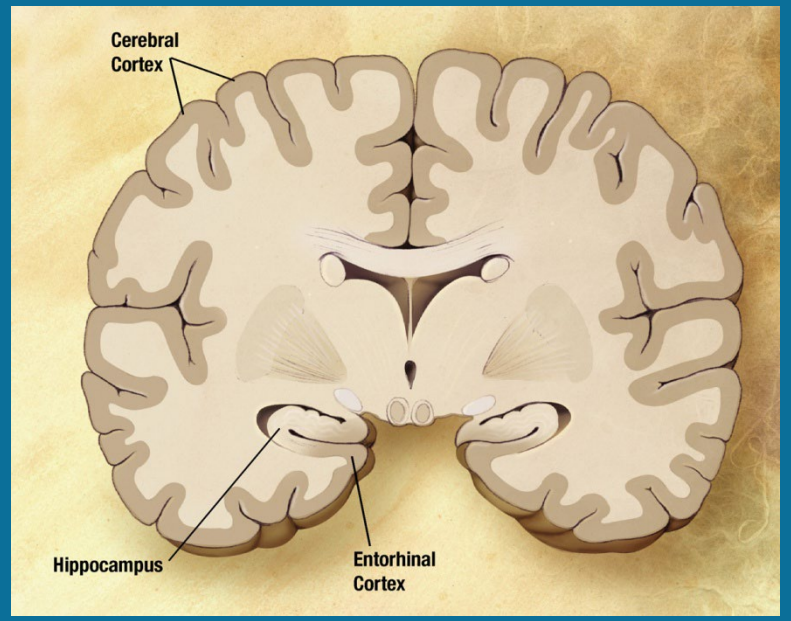
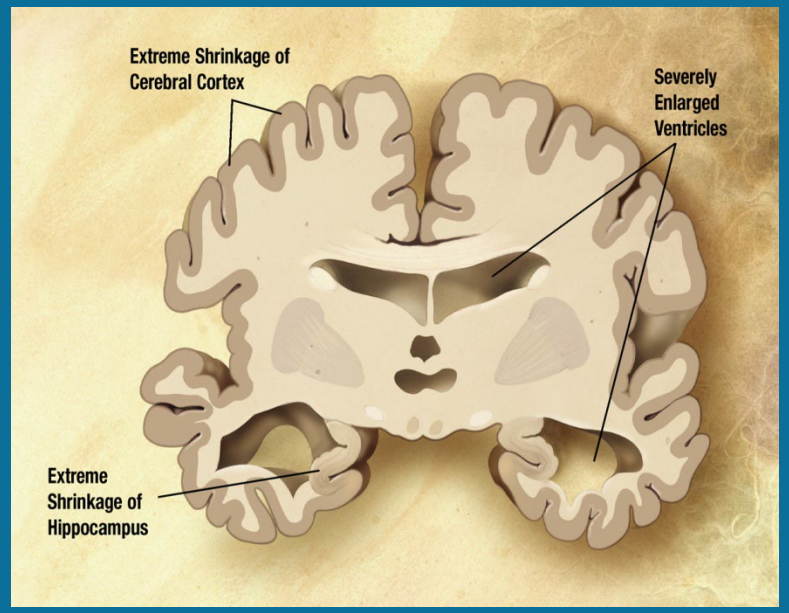
Health Sciences

Healthy Brain

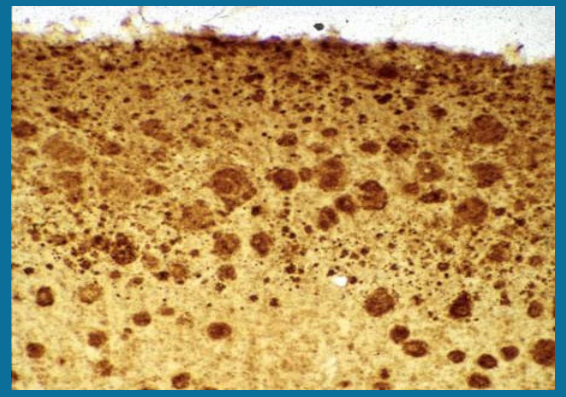


AD Brain



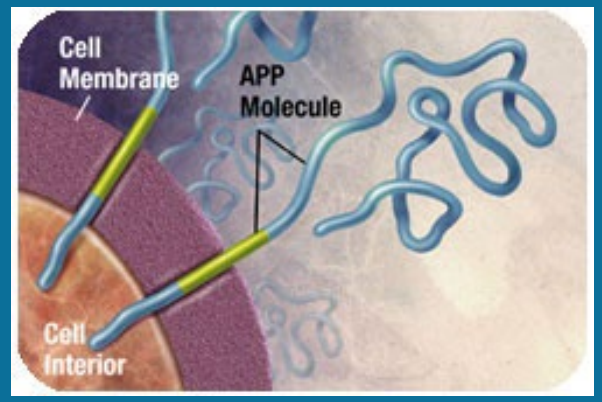
Minimal Amyloid Protein

Marked Amyloid Protein

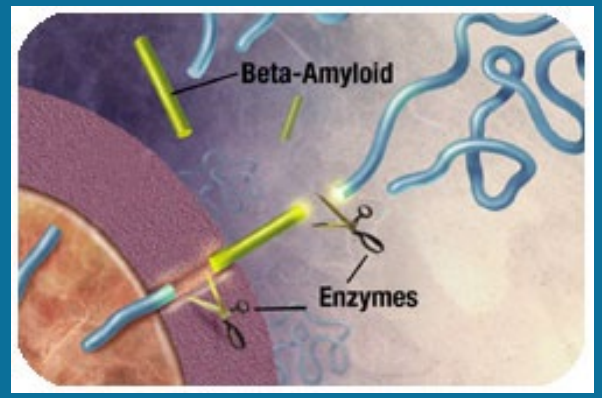


AD and the Brain

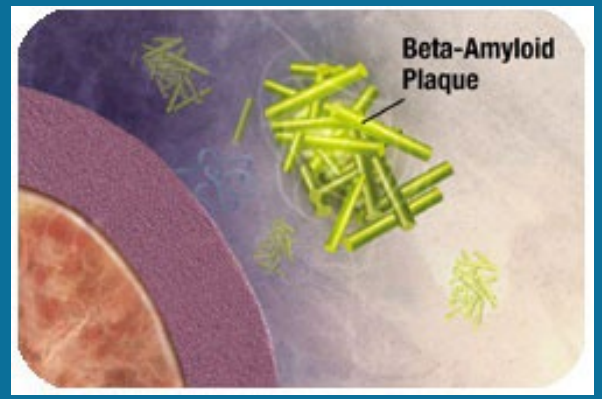
1.



2.

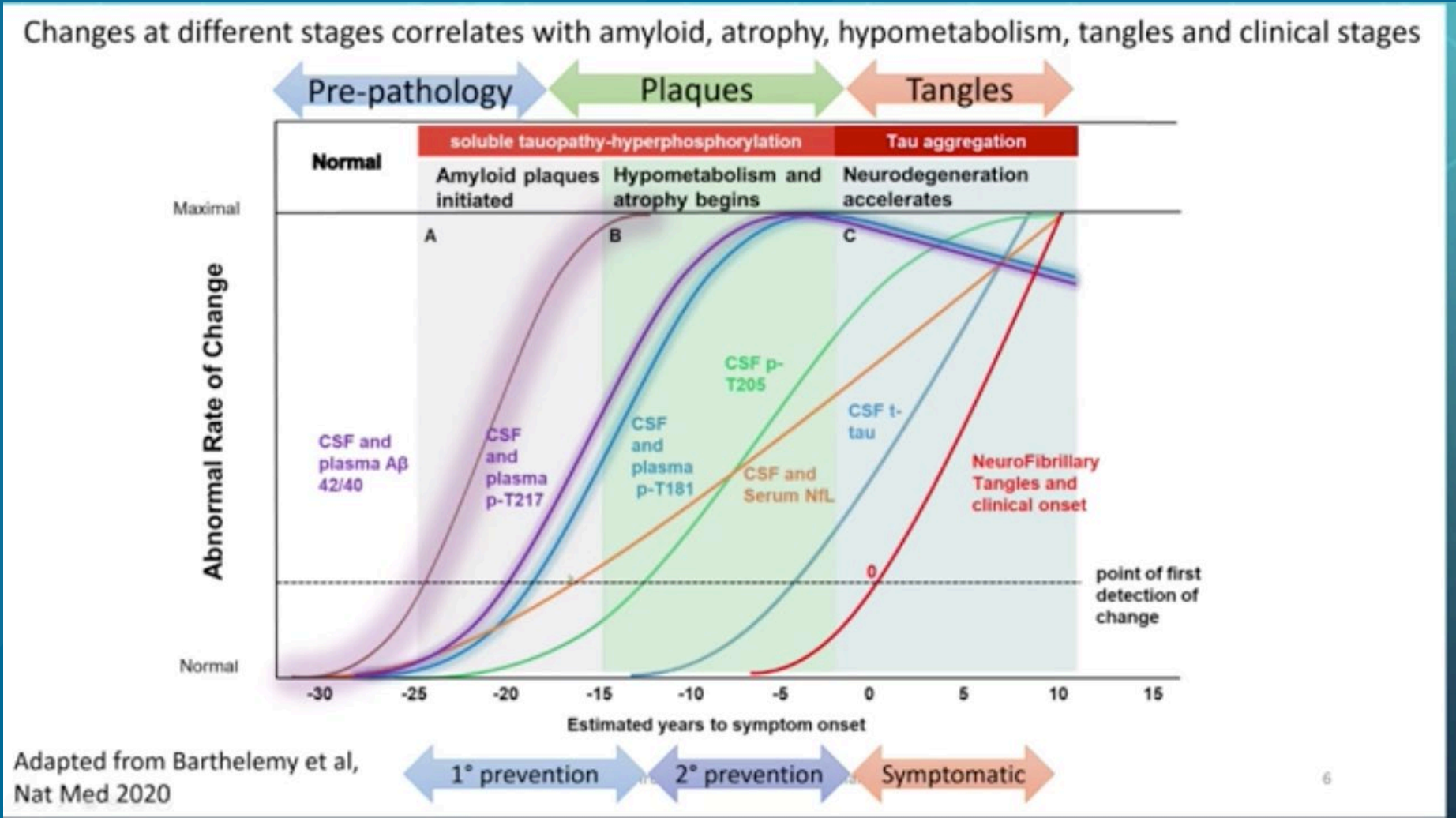


3.



New Tools for Investigation and Discovery

- New Plasma and Biofluid Markers



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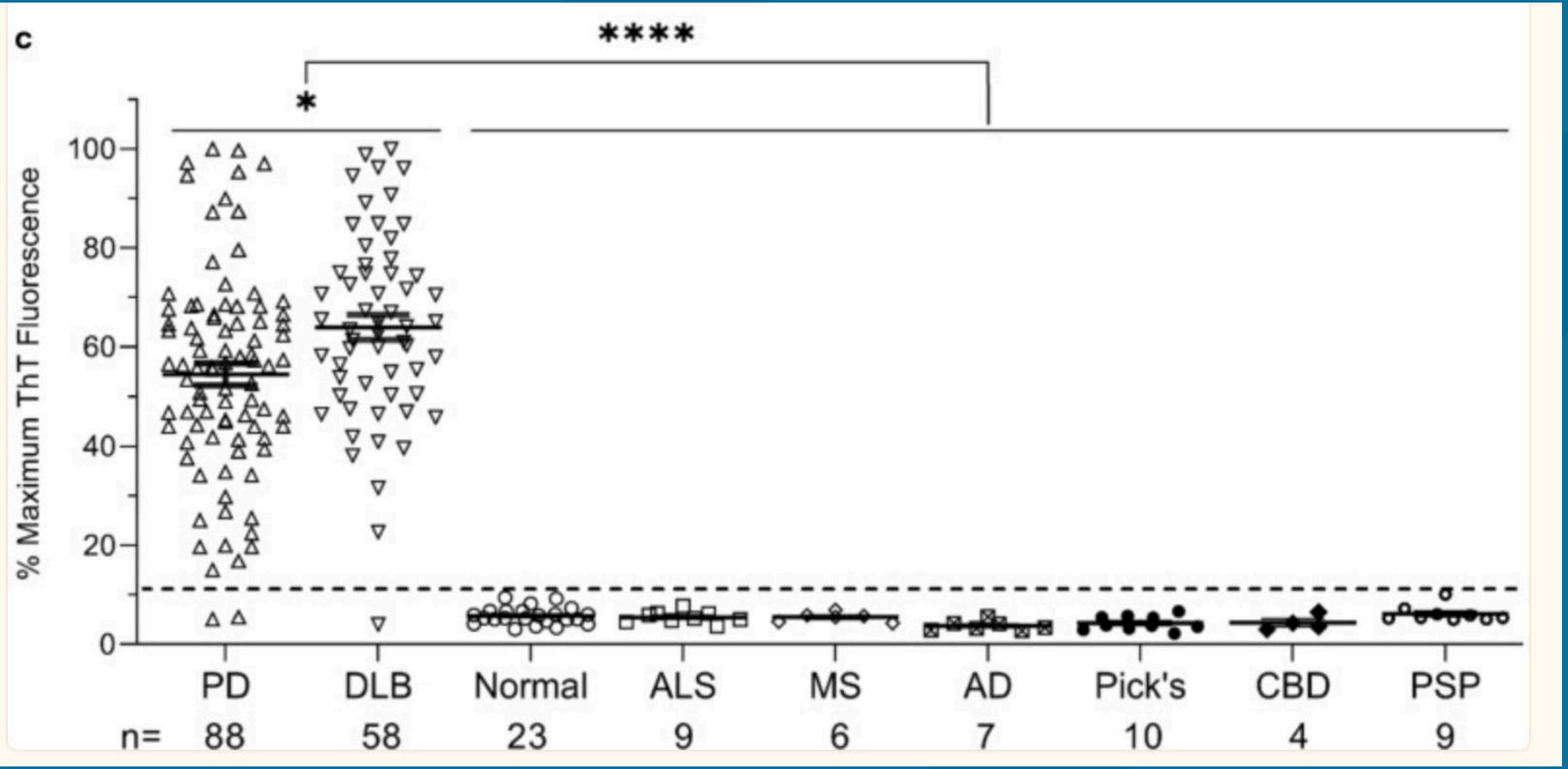
New Tools for Investigation and Discovery

- New Plasma and Biofluid Markers to investigate the Heterogeneity of AD

CSF- RT-QuIC Synuclein Seeding Assay



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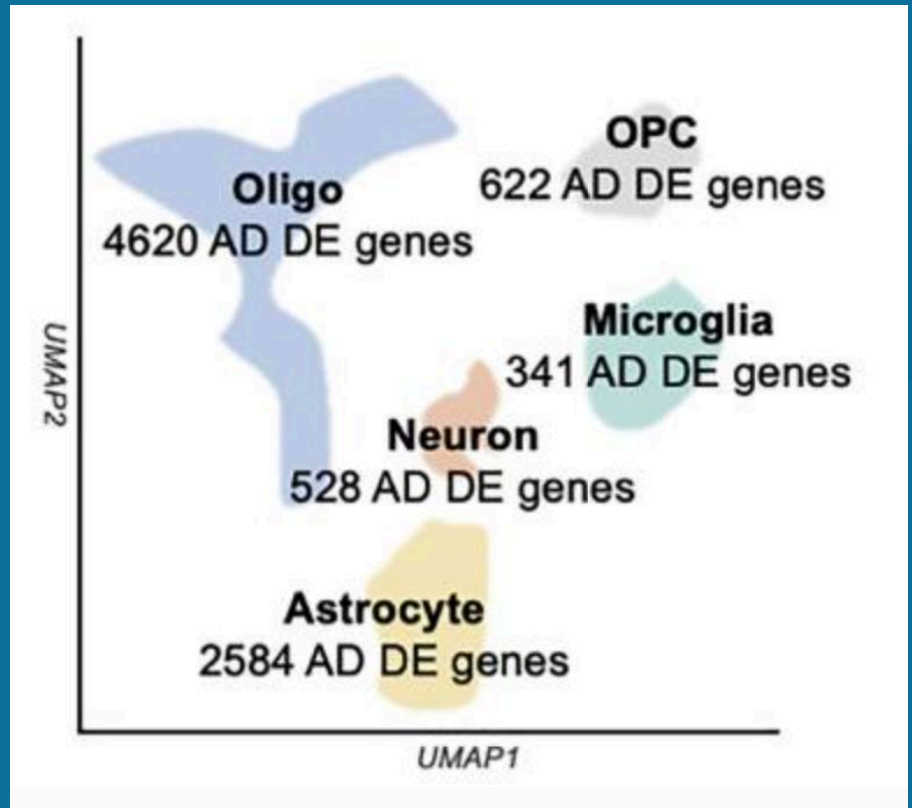
New Tools for Investigation and Discovery

- Rapid Increase in Availability of Genetic Tools

  (and the Computational Power to Process the Data)

  - Ability to assess gene expression across cell types and impact of disease
    - ”The Transcriptome”



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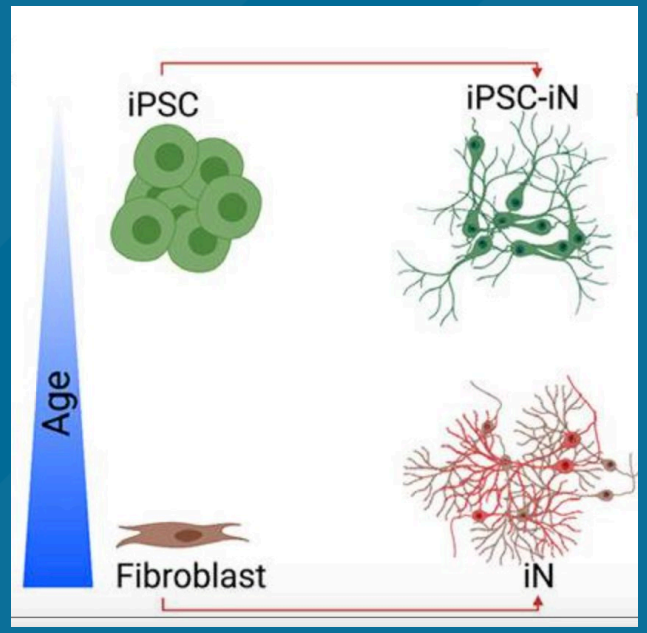
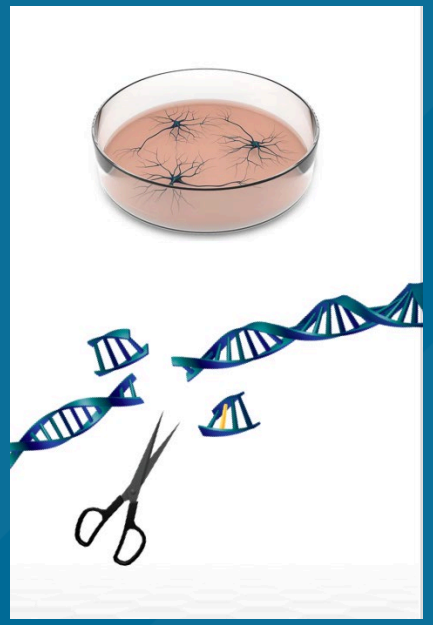
New Tools for Investigation and Discovery

- ”Disease in a Dish” Human Cell Models
  - Skin biopsy→Induced pluripotent stem cells→Variety of human cells
  - Direct transformation of skin fibroblasts into neurons
  - Ability to recapitulate the brain environment
    - Organoids (“Minibrains”) with various cell types and vessels





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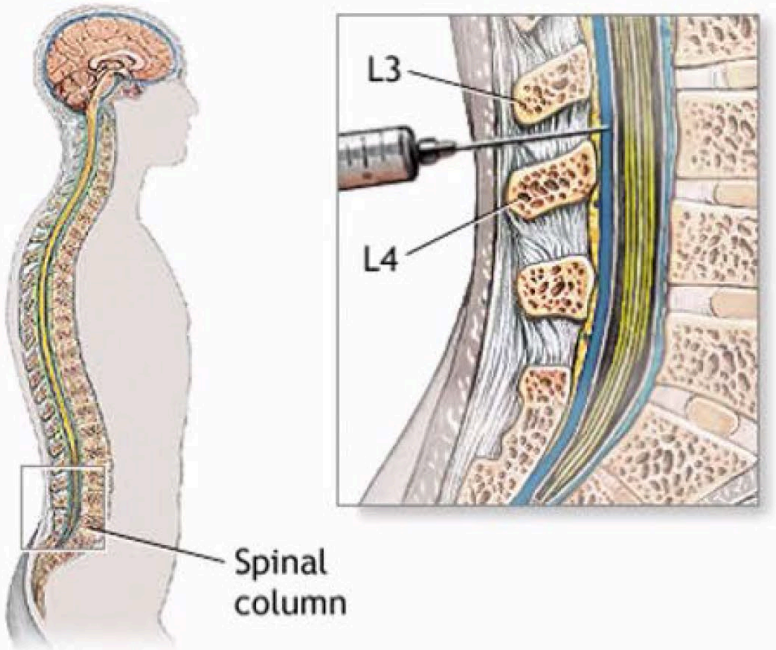
The Promise of the Future

- **<u>Rapid Increase in Availability of Genetic Tools</u>**
- Anti-sense Oligonucleotides (ASO)
  - Gene-Therapy delivery to the central nervous system

Antisense Drugs can teach us about disease reversibility



- Do not modify DNA directly
- Reversible and dose-dependent
- 'Plastic-like' stability
- Q3 month dosing
- Can permeate entire CNS
- Can be conjugated to 'homing' probes

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The Promise of the Future

- **<u>Rapid Increase in Availability of Genetic Tools</u>**
- Anti-sense Oligonucleotides (ASO)
  - Gene-Therapy delivery to the central nervous system

Pt 1

Pt 2

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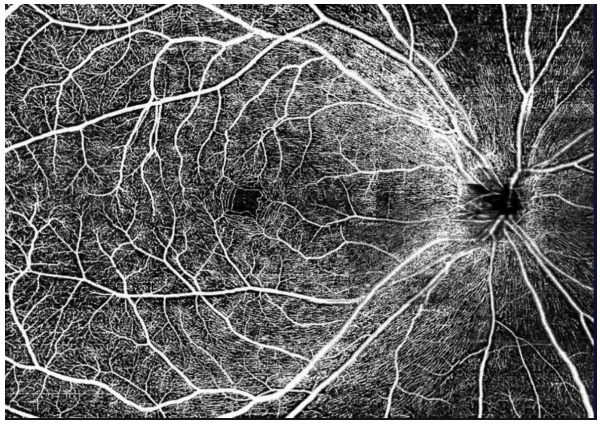
Health Sciences

Phenotyping Goals

At the Shiley-Marcos Alzheimer's Disease Research Center

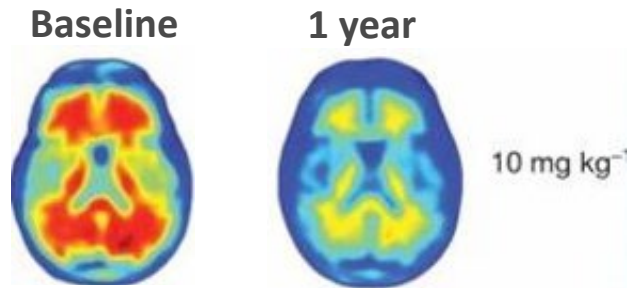
- C, A, T, N, V, G Characterization
  - C- Cognitive (Neuropsych testing, Clinical Eval)
  - A- Amyloid (CSF Amyloid)
  - T- Tau (CSF Tau; Imaging Tau)
  - N- Neurodegeneration (MRI)
  - V- Vascular (MRI, OCTA?)
  - G- Genetics (PHS)
  - S- Synuclein Seeding Assay



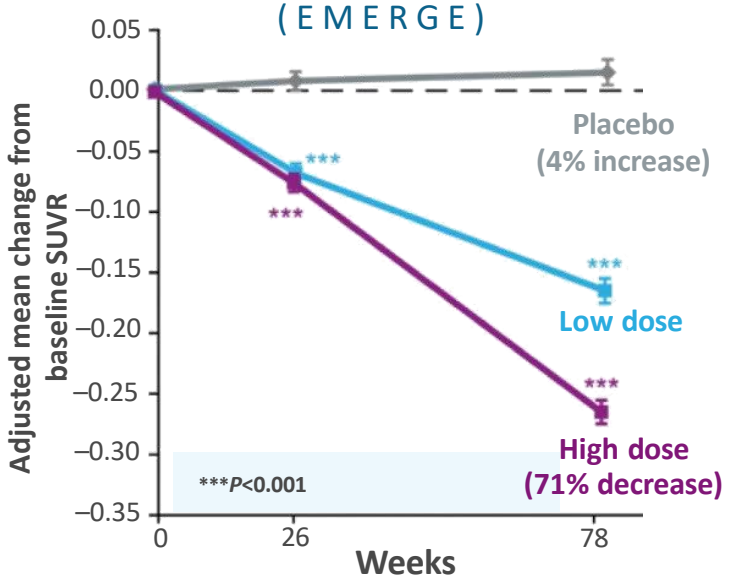
- Plus CSF, Plasma, and iPSC (capable) Banking for future discovery
- Autopsy for confirmation and brain-tissue-based scientific discovery

AMYLOID-B–TARGETING DMT

EVIDENCE IN AD PATHOLOGY

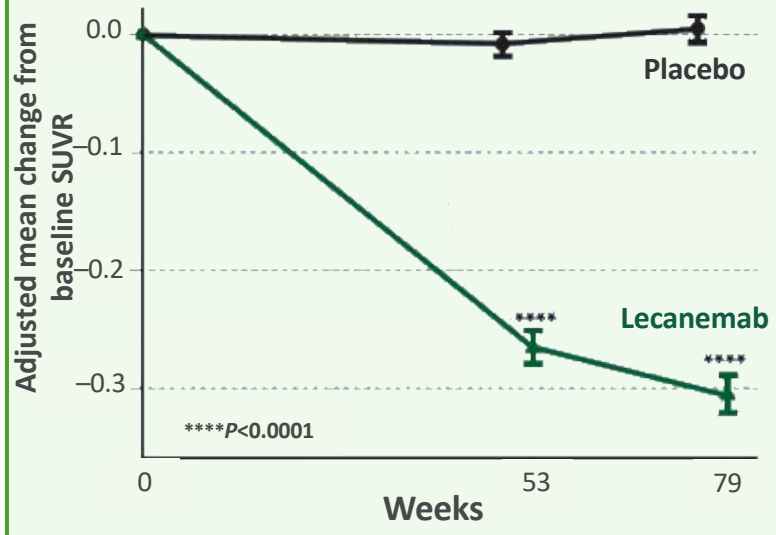


CHANGE IN AMYLOID PET (EMERGE)



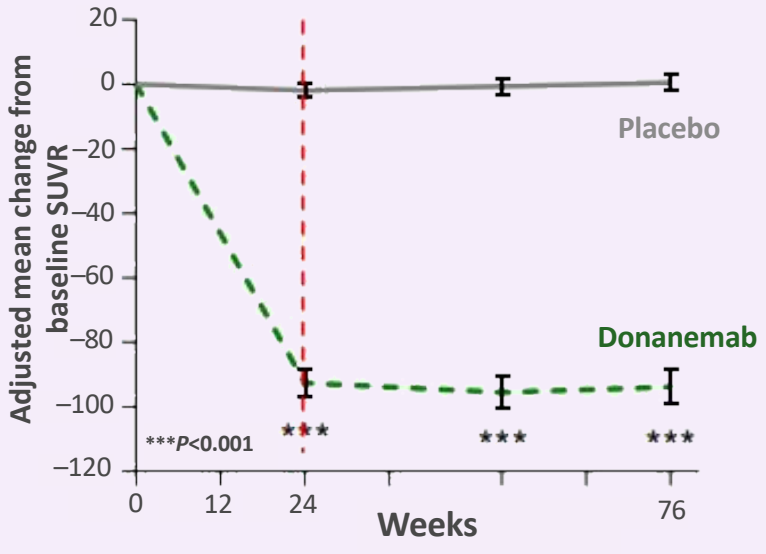
LECANEMAB

CHANGE IN AMYLOID PET



DONANEMAB

CHANGE IN AMYLOID PET

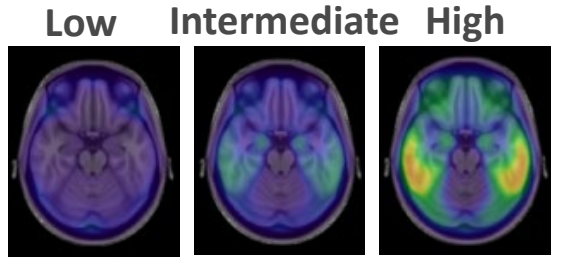


*Significant amyloid clearance demonstrated by **all approved and late-stage ATTs***

Haeberlein B et al. Two randomized phase 3 studies of aducanumab in early AD. *J Prev Alzheimers Dis.* 2022;9(2):197-210. • Sabbagh M. Key trial design aspects and clinical outcomes of the lecanemab phase 2b (Study 201) trial and open-label extension (OLE) in early AD. *Proc AD/PD* 2022. • Mintun MA et al. Donanemab in early AD. *N Engl J Med.* 2021;384(18):1691-1704. Sevigny J, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016;537(7618):50-56.

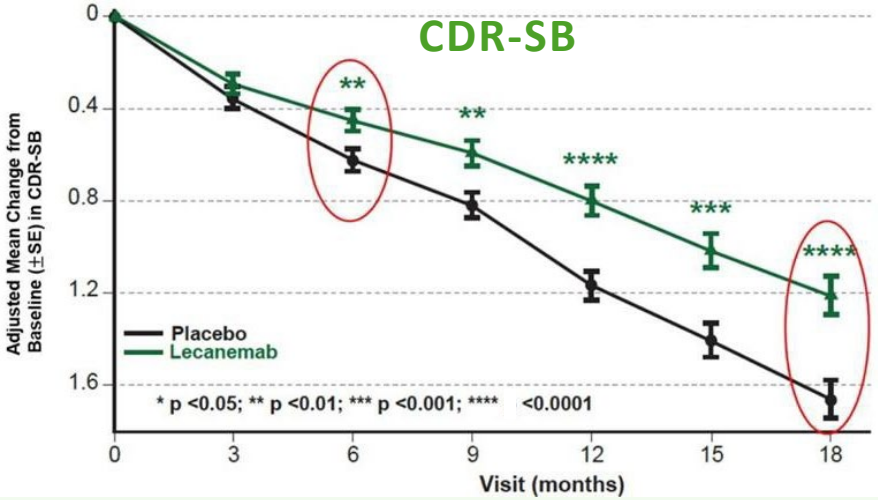
SUVR: standardized uptake value ratio

CLINICAL OUTCOMES



LECANEMAB (IV BIWEEKLY)

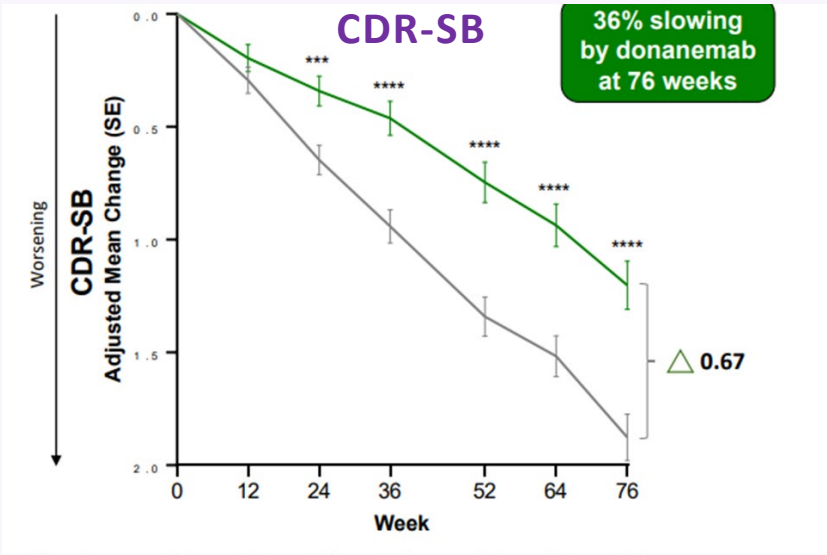
- **27% slowed cognitive decline on CDR-SB at 18 months (*P*<0.0001)**
- Low tau sub-study: 76% no cognitive decline & 60% improved at 18 mo



TRADITIONAL FDA APPROVAL

DONANEMAB (IV MONTHLY)

- **36% slowed cognitive decline on CDR-SB at 18 months (low/medium tau)**
- 47% had no progression at 1 year



UNDER REGULATORY REVIEW

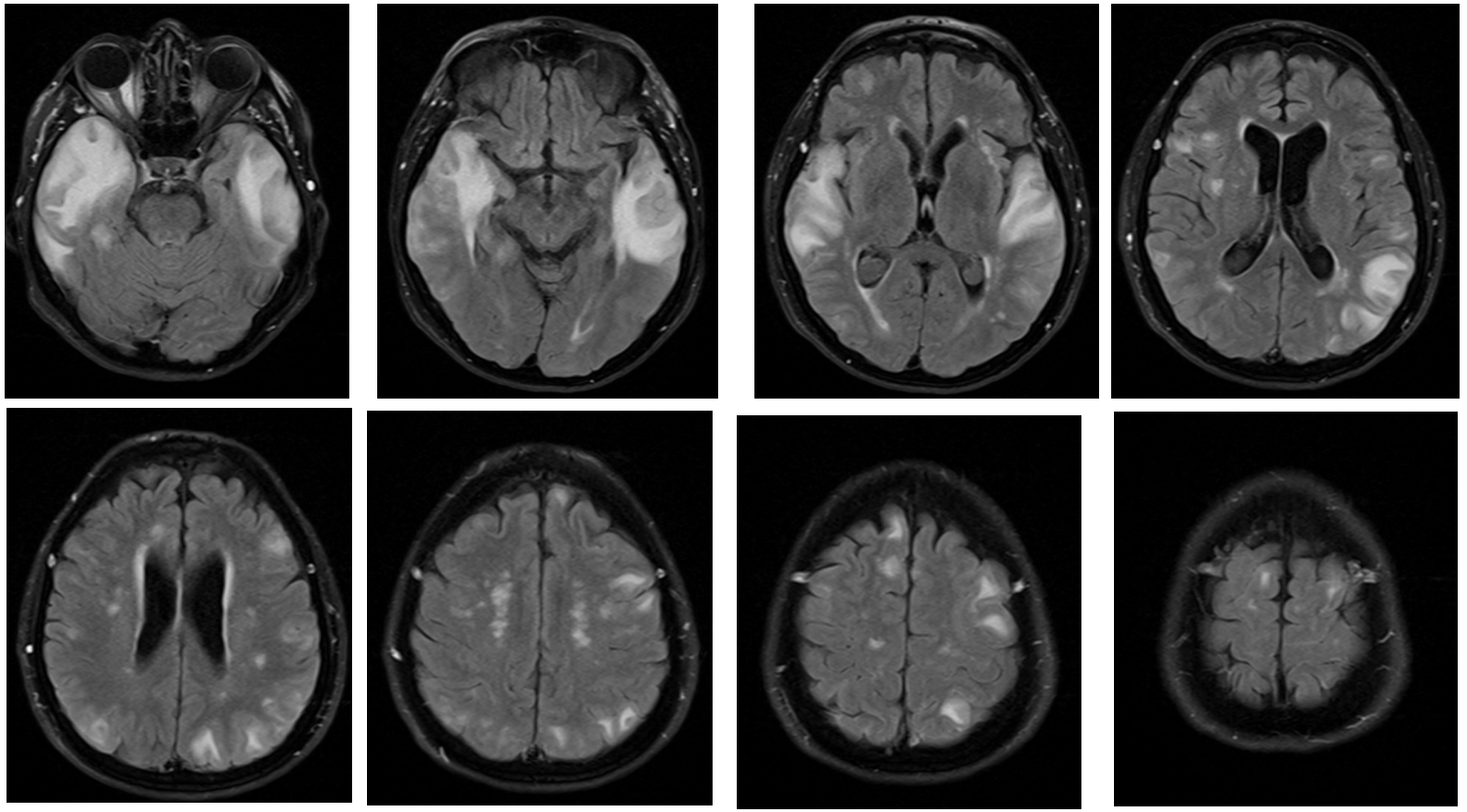
Haeberlein B, et al. Two Randomized Phase 3 Studies of Aducanumab in Early AD. J Prev Alzheimers Dis. 2022;9(2):197-210. van Dyck C. A study to confirm safety and efficacy of lecanemab in participants with early AD (Clarity AD). Presented at CTAD 2022, San Francisco, CA. Sims JR, et al. Donanemab in Early Symptomatic AD: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512–527. Eisia Inc. Lecanemab for Early AD: Long-Term Outcomes, Predictive Biomarkers and Novel Subcutaneous Administration. Late Breaking Symposium 4; Presented at CTAD 2023, Stockholm, Sweden.

Imaging in the Era of AD Disease-Modifying Therapeutics

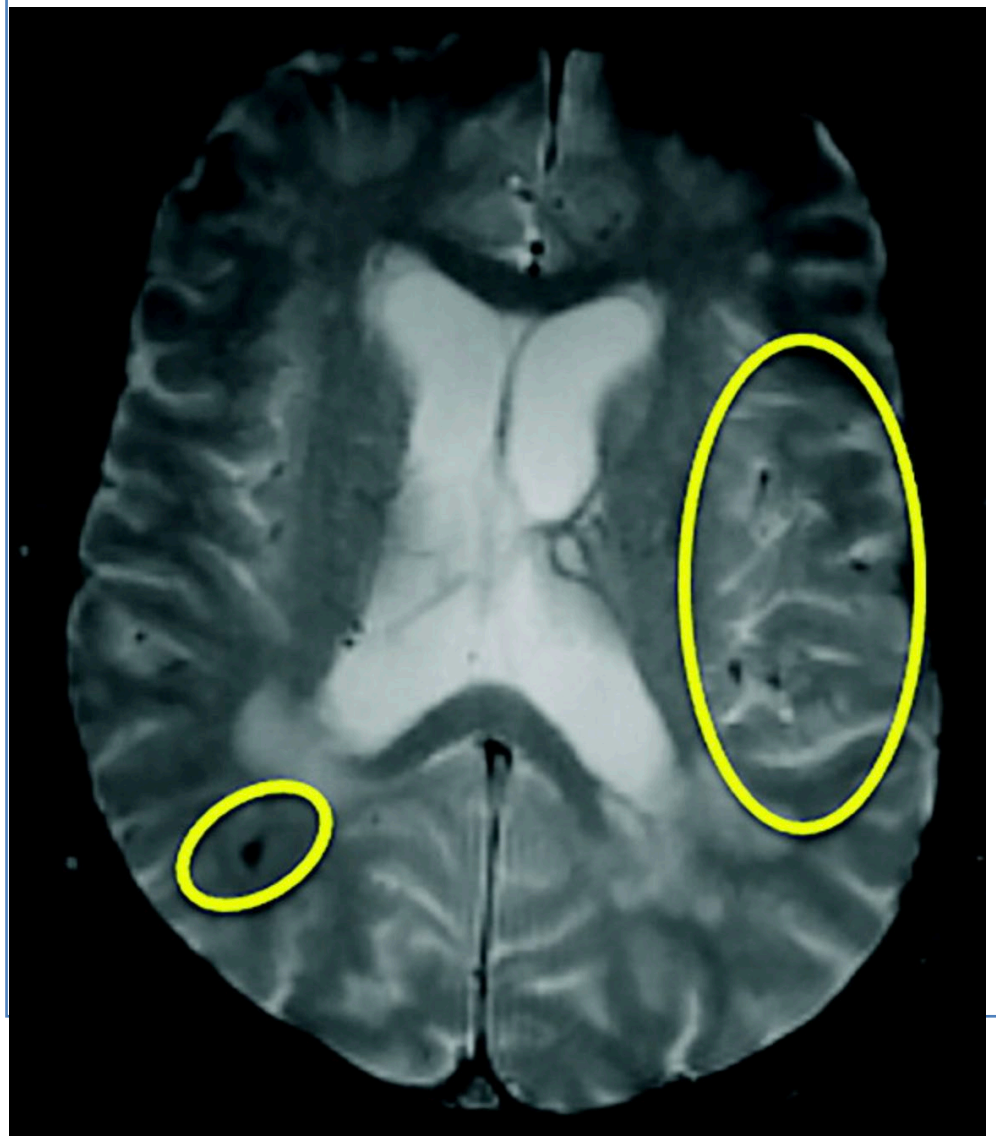
- New Anti-Amyloid Monoclonal Antibodies
  - "Up to 40%" slowing of disease progression
  - Brain amyloid levels normalized
  - Significant risk of brain swelling and bleeding
  - Requires frequent MRI-based monitoring
    - Especially during first 6 months of treatment initiation

Week	0	4	12	24	52	76
MRI	★	★	★	★	★	★
Amyloid PET scan	★			★	★	★
Tau PET scan	★					★

Amyloid Related Imaging Abnormality – Edema/Effusion



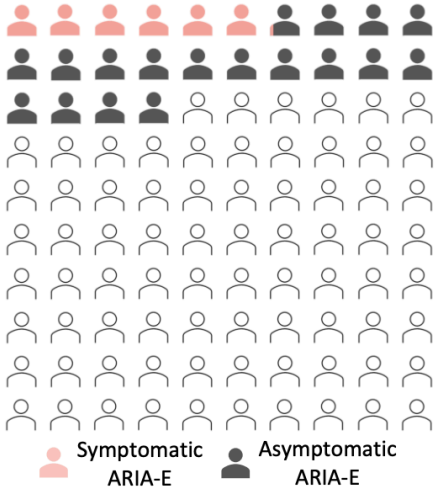
Amyloid Related Imaging Abnormality – Hemosiderin/Blood Products



Higher Risk in APOE4 Carriers

ARIA by APOE Status %[a,b]	Placebo	Donanemab
ARIA-E		
Non-carrier	**0.8%**	**15.7%**
Heterozygous carrier	**1.9%**	**22.8%**
Homozygous carrier	**3.4%**	**40.6%**
ARIA-H[c]		
Non-carrier	**11.2%**	**18.8%**
Heterozygous carrier	**12.0%**	**32.3%**
Homozygous carrier	**20.5%**	**50.3%**

24% of donanemab-treated participants experienced ARIA-E



INITIAL REFERRAL: PRE-THERAPY

WHAT THE NEUROLOGIST IS LOOKING FOR

INCLUSION FACTORS

- ✓ Evidence of amyloid (imaging or fluid)
- ✓ MRI within 12 months of treatment initiation
- ✓ **Patient is eligible and willing to receive multiple MRIs**

EXCLUSION FACTORS

- X Acute or subacute hemorrhage or infarction
- X Extensive existing cerebrovascular disease
- X Excessive ARIA-H risk
- X Intraparenchymal mass or inflammatory lesion

Helpful to have bidirectional communication about likelihood/evidence the patient is or will be uncomfortable or uncooperative during MRIs

ARIA severity: Influence on Clinical Management

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E (edema)	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity measuring >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.
ARIA-H: Micro hemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhage	10 or more microhemorrhages
ARIA-H Superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	>2 focal areas of superficial siderosis
ARIA-H:			
Macro hemorrhage			≥ 1 macro hemorrhage(s)

ARIA severity: Influence on Clinical Management

<table>
<tr><td rowspan="2">Clinical Symptom Severity</td><td colspan="4">Radiographic Severity</td></tr>
<tr><td>Mild</td><td>Moderate</td><td colspan="2">Severe</td></tr>
<tr><td></td><td>ARIA-E & H</td><td>ARIA-E & H</td><td>ARIA-E</td><td>ARIA-H
or Macrohemorrhage</td></tr>
<tr><td>Asymptomatic</td><td><u>Continue Dosing</u> with increased surveillance</td><td colspan="2" rowspan="2"><u>Suspend Dosing</u> with increased surveillance. Once ARIA-E is resolved <u>AND</u> ARIA-H is stable, the patient may resume dosing at the same dose.</td><td rowspan="2"><u>Permanently Discontinue Dosing</u> with increased surveillance</td></tr>
<tr><td>Mild to Moderate</td><td></td></tr>
<tr><td>Severe†</td><td colspan="4"><u>Note:</u> In the most severe symptomatic ARIA, high-dose corticosteroid therapy should be considered</td></tr>
</table>

† “Severe” ARIA symptoms will be defined as symptoms that are attributable to radiographically confirmed ARIA and involve seizure, require hospitalization, cause incapacitation, increase risk of permanent deficits, and/or significantly impact a patient’s activities of daily living.

Cross-Specialty Coordination in Safety Monitoring

- Across patients and timepoints
  - Seek imaging protocol consistency, trained radiologists, standardization of reporting
- Avoid switching across scanners and sequences
- Automation tools may increase standardization and extend a base level of quality across rural, urban, academic, and underserved practices

Cross-Specialty Assessment of Amyloid Removal and Disease Progression

- Cessation of Therapy
  - Confirmed removal of amyloid may guide decision
  - Measurement of disease progression
    - clinical and imaging assessment
    - potential to unmask other disease processes in the absence of amyloid
  - Repeated imaging may lend opportunity for quantitative longitudinal tracking of atrophy rate and lesion resolution
    - Motion and positioning resilient cross-study registration

Ambulatory and Emergency Department Workflow

- Emergency Care Impacts
  - Challenge posed by increased need for urgent MRI for otherwise benign complaint
    - Headache in a long-term headache sufferer
    - Confusion in a patient with diagnosed cognitive impairment
    - Dizziness
  - Alteration of risk-benefit of anticoagulants and thrombolytics across a range of thromboembolic diseases
    - Radical change for acute stroke emergency care pathway

Ambulatory and Emergency Department Workflow

- Ambulatory Care Impacts
  - Patient flow increase
  - Practices need to accommodate demand for regular and timely scheduled MRI
  - Opportunity to track trajectory
  - Improved understanding of ARIA risk across populations
- New trials may reveal improved safety profile in earliest phases of disease and mitigate ARIA concerns.

The Promise of the Future

- We are on the Road to Neurotherapeutics in Brain Aging
  - Biomarker-based improvements in diagnosis and predictive prognosis
    - Reveals heterogeneity and personalized impacts of aging
    - Individualized therapies and approaches will clearly be needed
  - Progress enabled through tremendous advances in neurosciences research
    - Bolstered by creative use of genetic tools and big data science
    - Highlights the value of bridging clinicians and researchers
  - Modular gene- and RNA-based therapies show particular new promise
    - Administrative infrastructure for safety/ethics/regulatory navigation is needed

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THANK YOU FOR YOUR PARTICIPATION

- We couldn't do this without you
  - Tell your friends
  - Stay involved
    - Join research studies as possible
    - Help us understand new markers and models (which may involve our collection of skin and/or blood samples)
  - We are NOW increasing biomarker result feedback between

Participant ←→ Center

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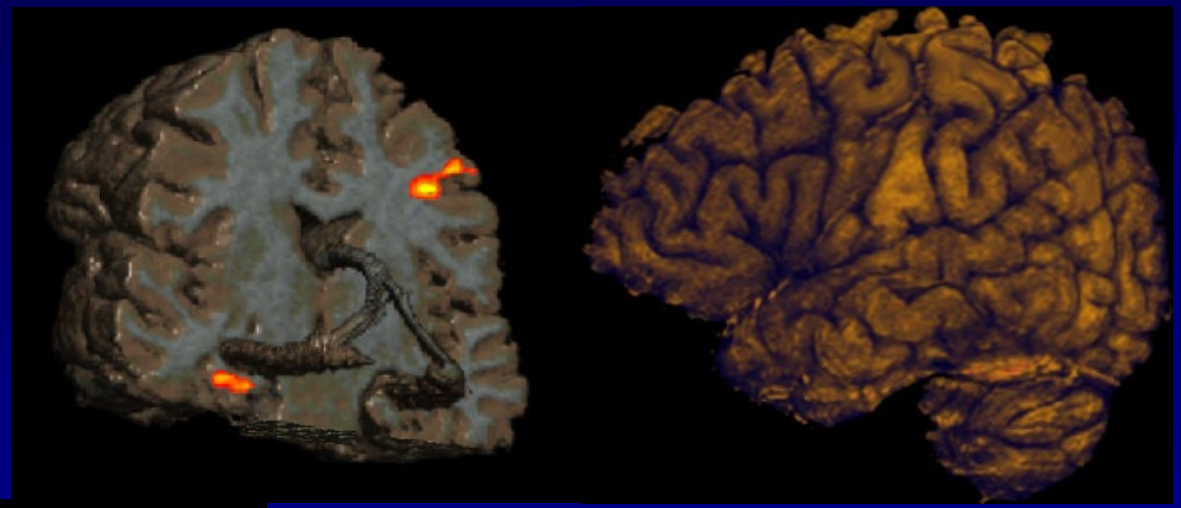
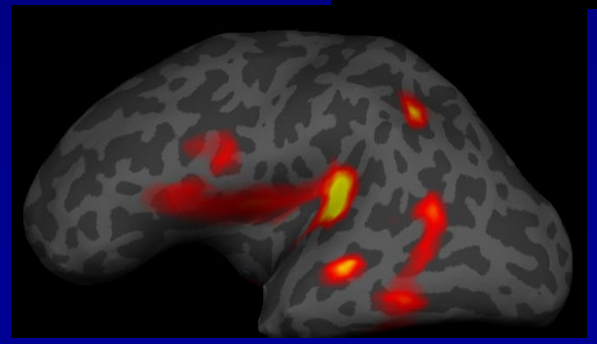
Thank You





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