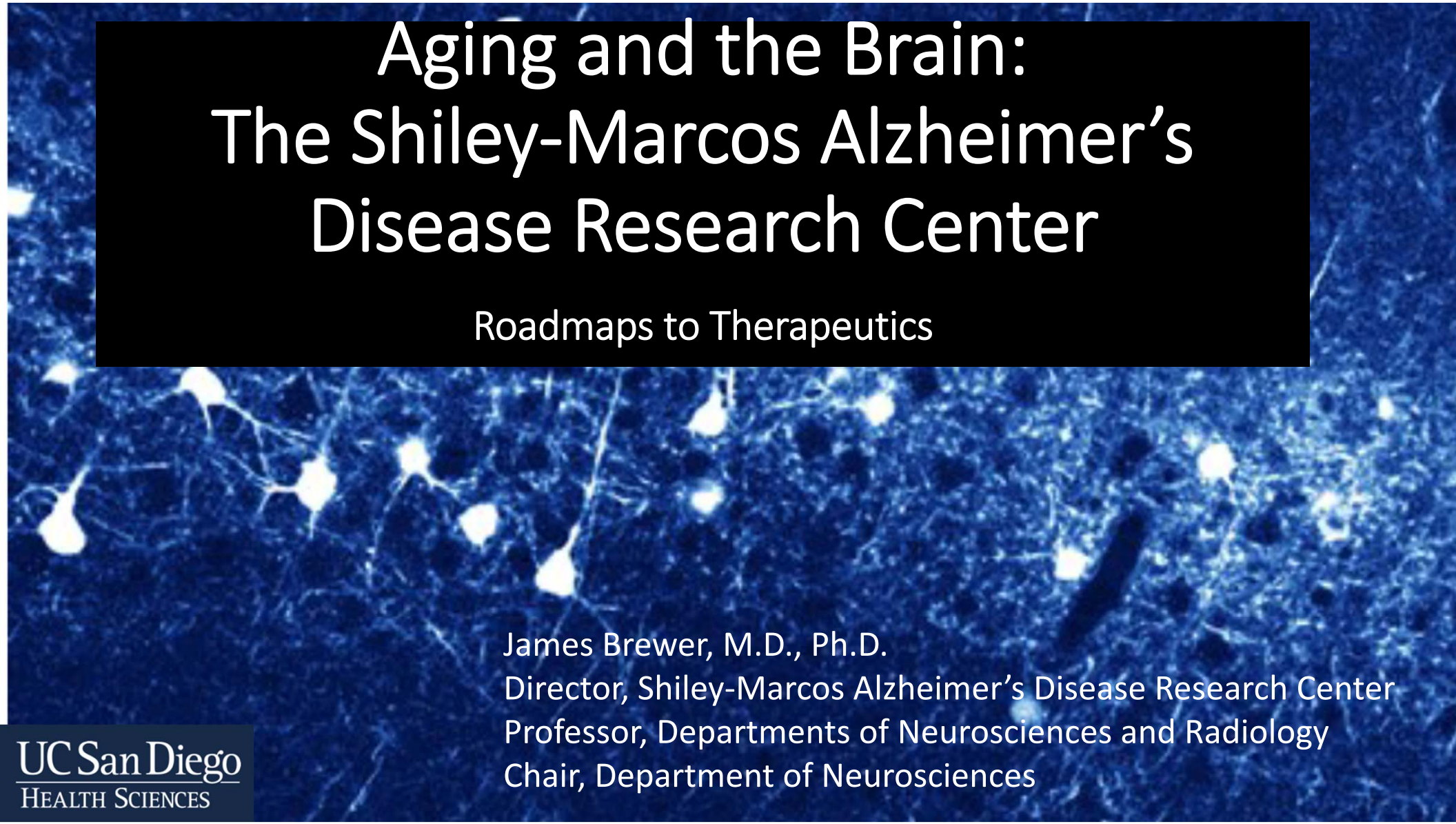

Aging and the Brain: The Shiley-Marcos Alzheimer's Disease Research Center

Roadmaps to Therapeutics

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

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Outline

- Background: Shiley-Marcos Alzheimer's Disease Research Center
- A Special Recognition
- The Changing Landscape of Aging
- New Tools of Discovery
- The Promise of the Future

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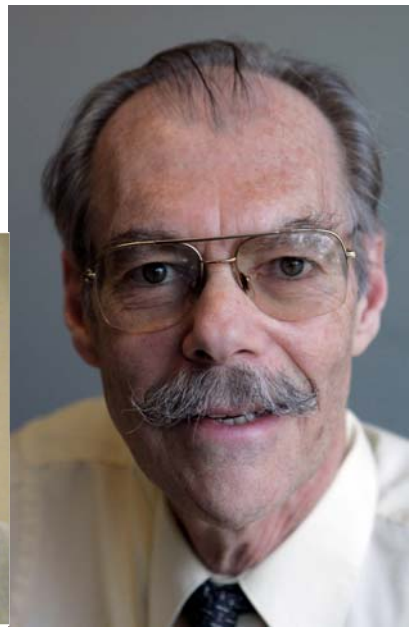
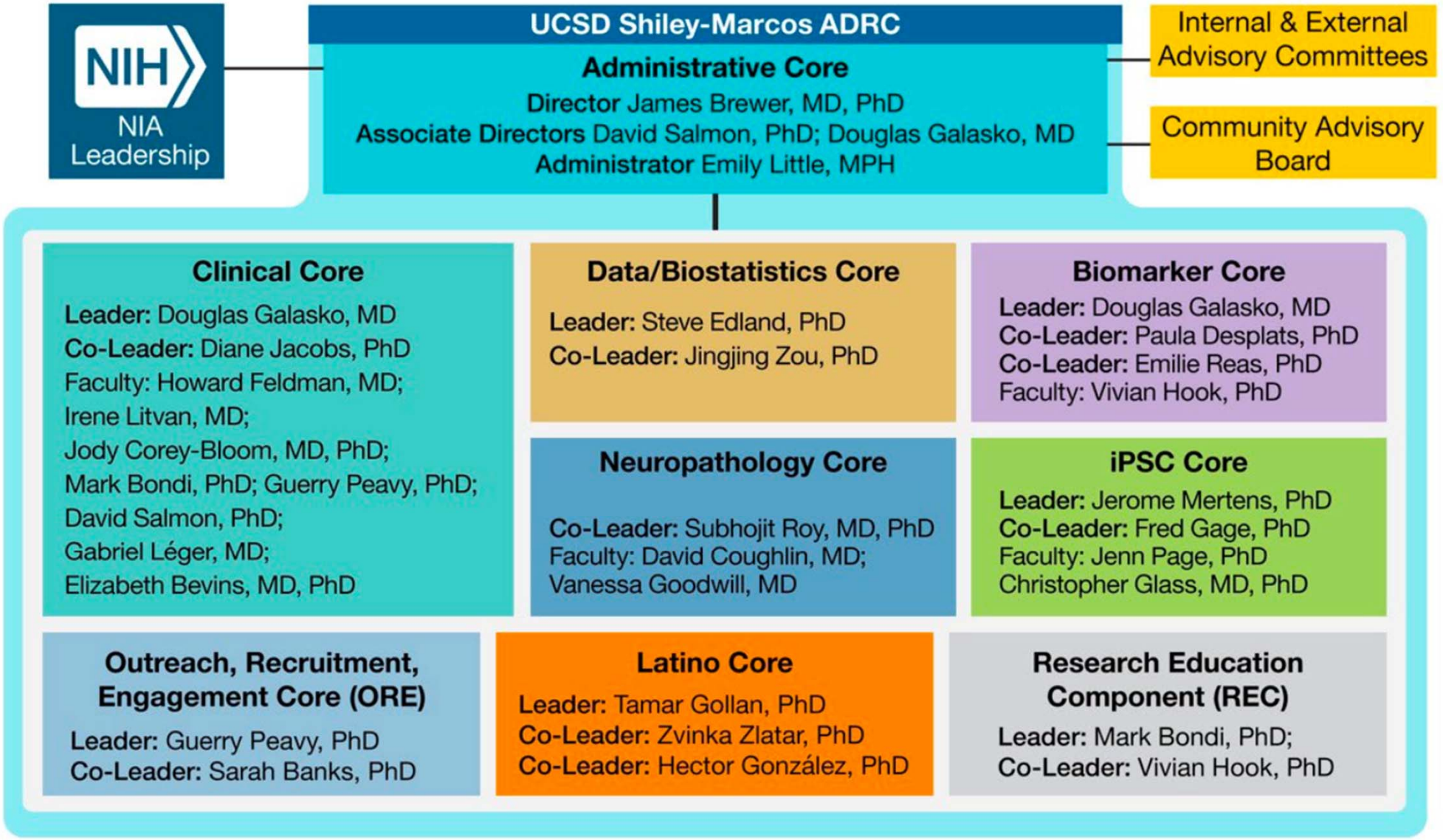
Shiley-Marcos ADRC History

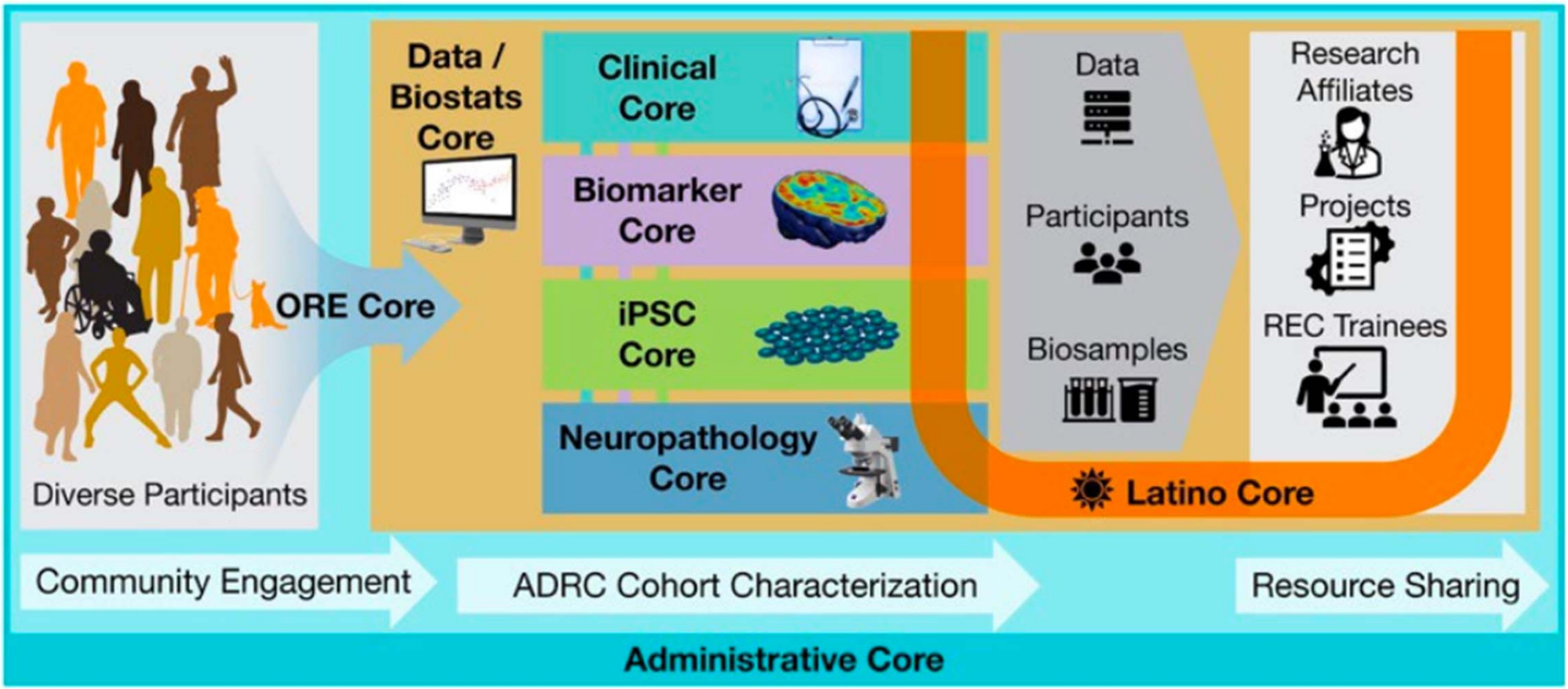
- Established in 1984 as one of first centers in the National Institute on Aging- Alzheimer's Disease Centers program
  - Bob Katzman, Leon Thal,
  - George Glenner, Bob Terry
  - Nelson Butters, Tsunao Saitoh



Shiley-Marcos ADRC
Housed in the Neurosciences Playground of La Jolla


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

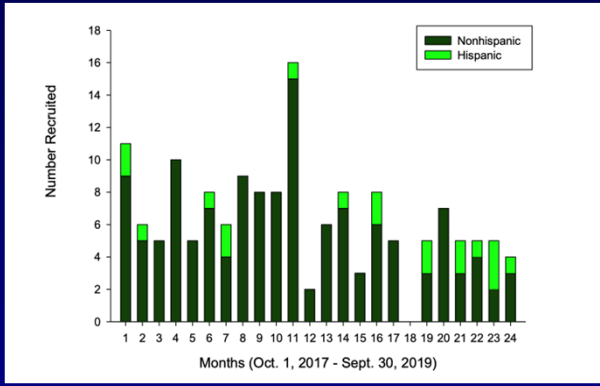
Overall Aims of the Center



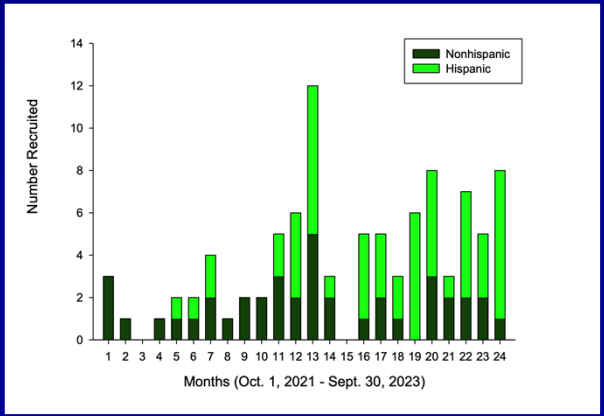
ADRC Team

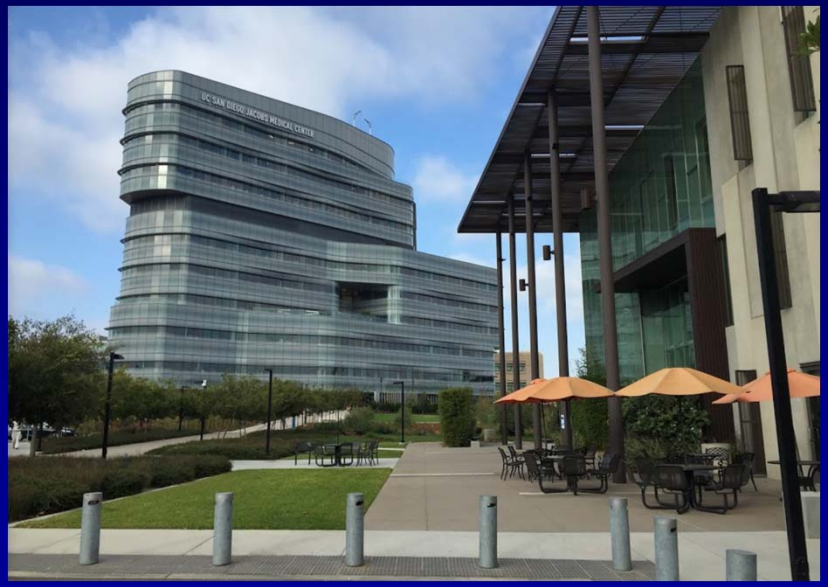
ADRC – Evolving our Culture

Latino Recruitment 2017-2019



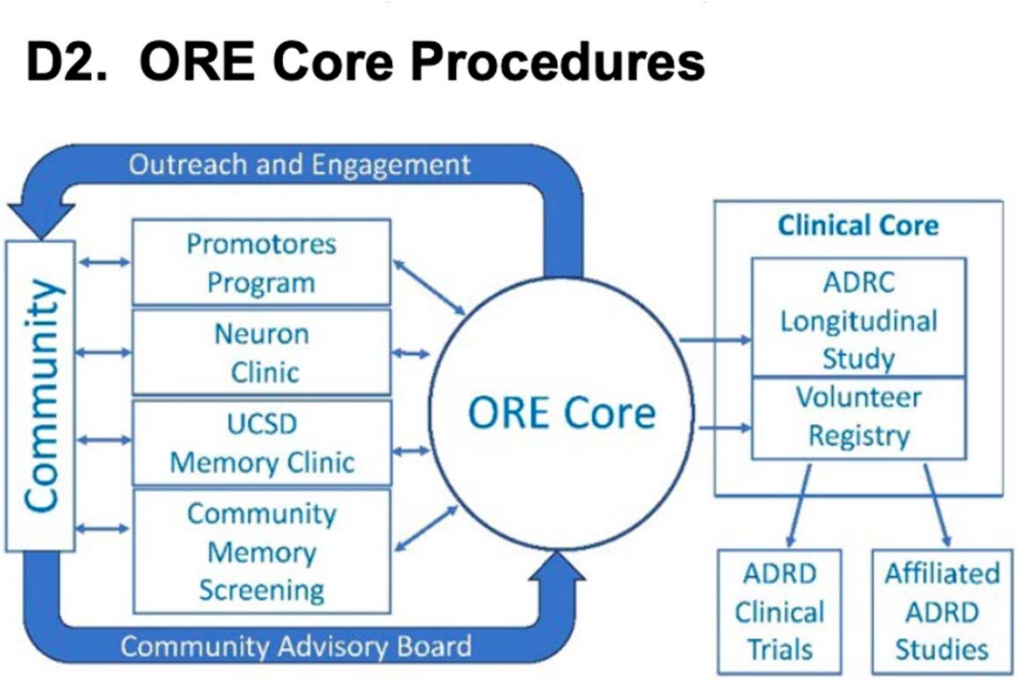
Latino Recruitment 2021-2023





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



Support and Quality of Life Programs
Outreach and Engagement Programs

- A huge thank you and special recognition to some of our most dedicated volunteer partners
  - The wonderful QOL trio of Joyce Camiel, Jayne Slade, and Genell Greenberg
  - Our outstanding outreach and engagement partner Phyllis Muñoz

Joyce Camiel

- Joyce and her husband Shimon were part of the UCSD ADRC support groups as participants since 2000. After Shimon's passing she began co-facilitating the caregiver support group. Joyce has been donating her time volunteering at least 3 hours weekly for over 15 years. The caregiver support group attendance is typically 25 people. Joyce also provides resources and support beyond the boundaries of the group to the caregivers that need it Joyce also participates in our Longitudinal Observation study.

Jayne Slade

- Jayne and her husband Hank were part of the UCSD ADRC support group as participants since 2000. Jayne continues to offer her time as a volunteer co facilitating the caregiver weekly support group with Joyce. After Jayne's husband Hank's passing Jayne continued her role as co-facilitator for the past 15 years and has become an integral part of the ADRC. Jayne also provides resources and support beyond the boundaries of the group to the caregivers that need it.

Genell Greenberg

- Our newest volunteer started with us during 2021. Having been a caregiver for her husband with Lewy Body Dementia she wanted to volunteer and offer support to others. Genell currently co facilitates the weekly Memory loss group with Tracey. Genell started a Monthly Lewy Body Caregiver Support Group once a month on zoom in 2022 . That group serves on average 16 caregivers. Genell also provides resources and support beyond the boundaries of the group to the caregivers that need it. She also helps out in the office making calls for the recruitment team and the Longitudinal study.

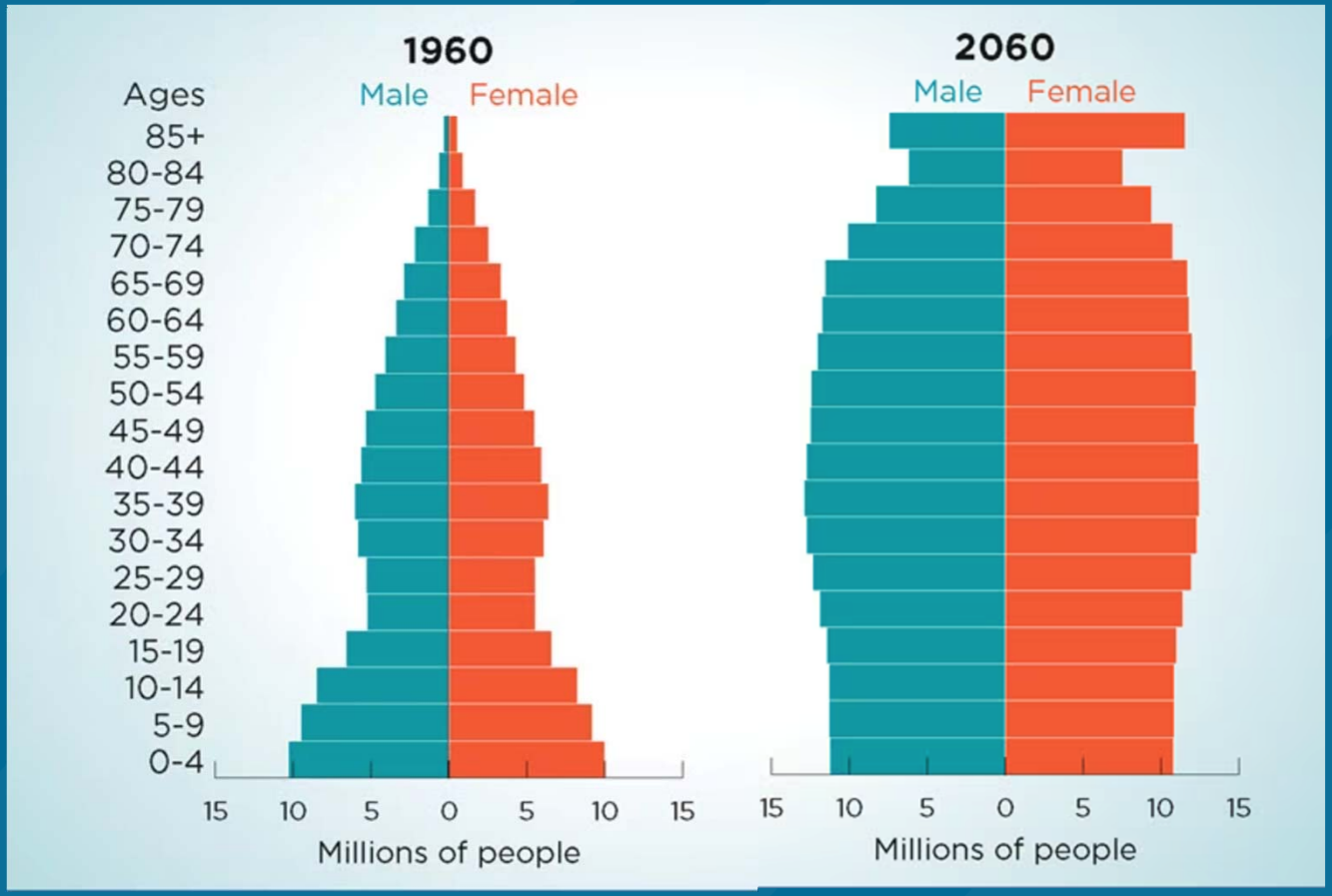
Phyllis Muñoz

- Phyllis has been volunteering at least 3 hours per week for the Latino and ORE Core's for the past 5 years. Phyllis completes outreach and engagement calls in Spanish for our Latino and ORE cores, enhancing the turnaround time for potential participants and minimizing phone tag for our staff saving us a great deal of time and money

THANK YOU!!!

We all benefit greatly from your service

The Changing Landscape of Aging



Population Pyramid Population Pillar

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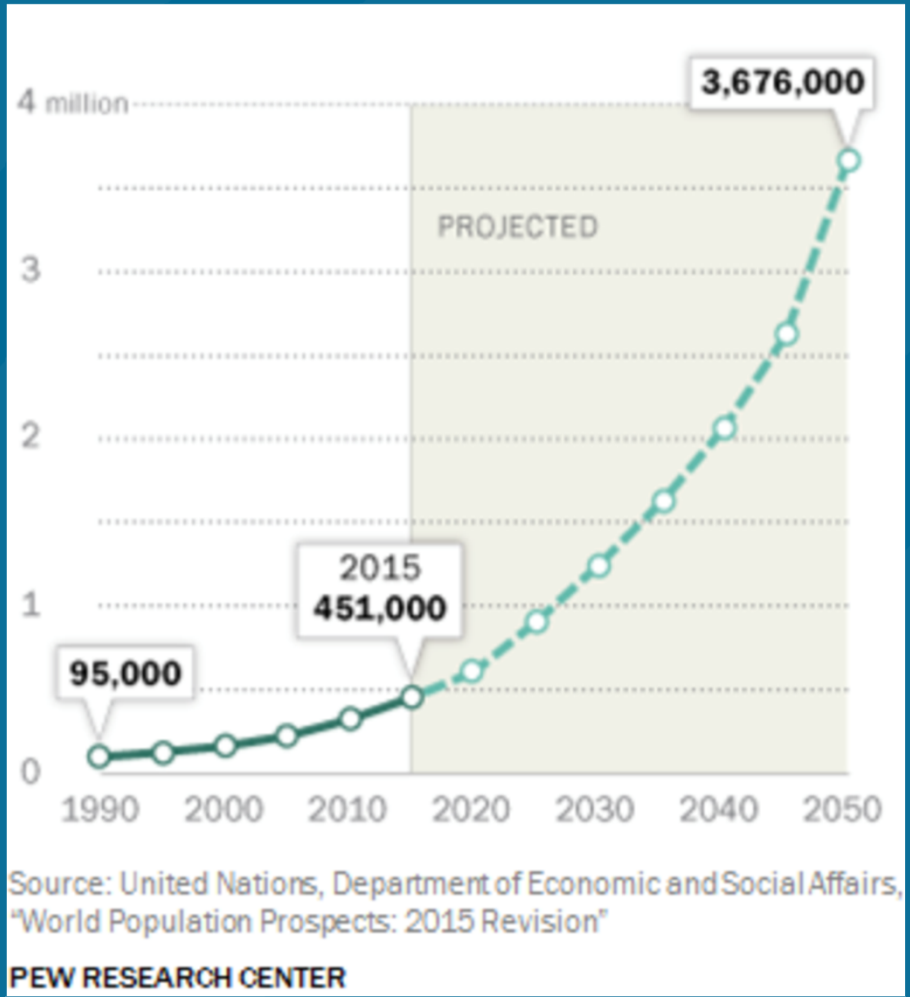
The Changing Landscape of Aging

Centenarians

1900- Rare
1950- 23,000
1990- 95,000
2021- 573,000



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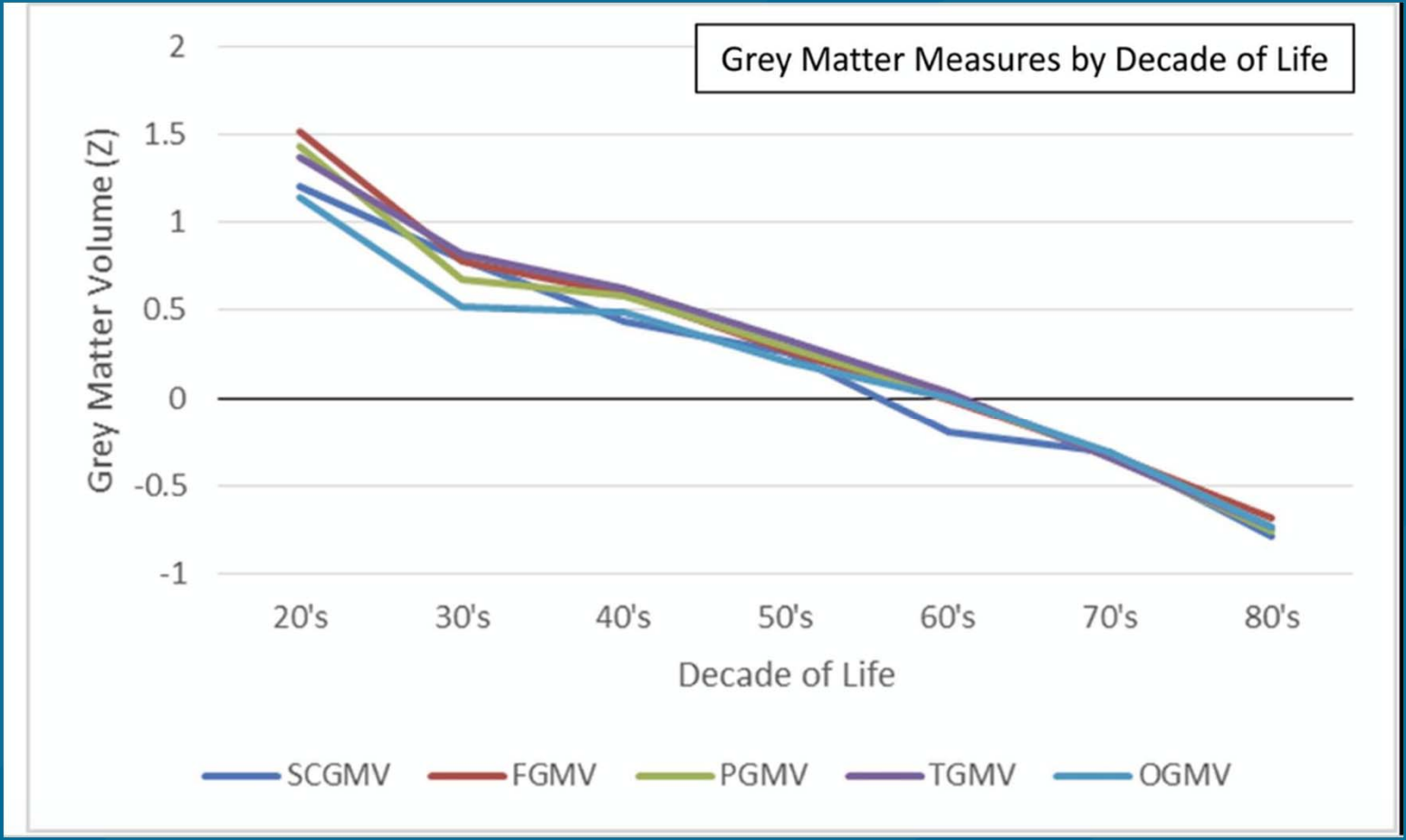
Brain Tissue Loss and Aging



Smith et al., 2023

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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)

  - Cross-genome assessment of protective and risk genes within an individual
    - Personalized Risk Scores/"Polygenic Hazard Score" for cognitive decline
- Advances in Quantitative Neuroimaging
  - Direct visualization of pathologic protein deposition and atrophy
- New Plasma and Biofluid Markers

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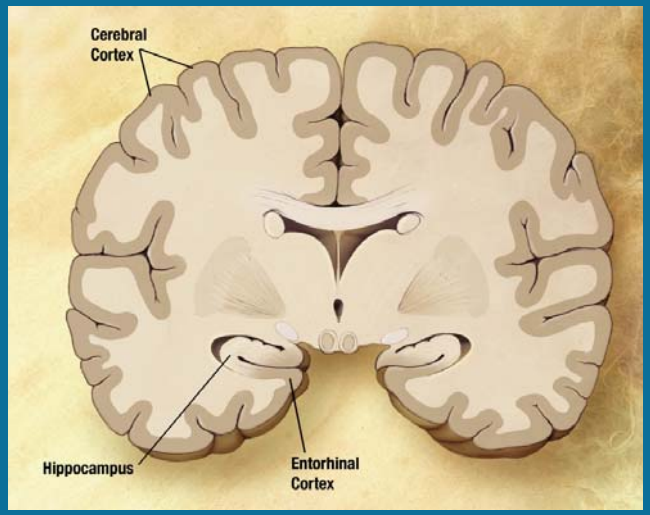
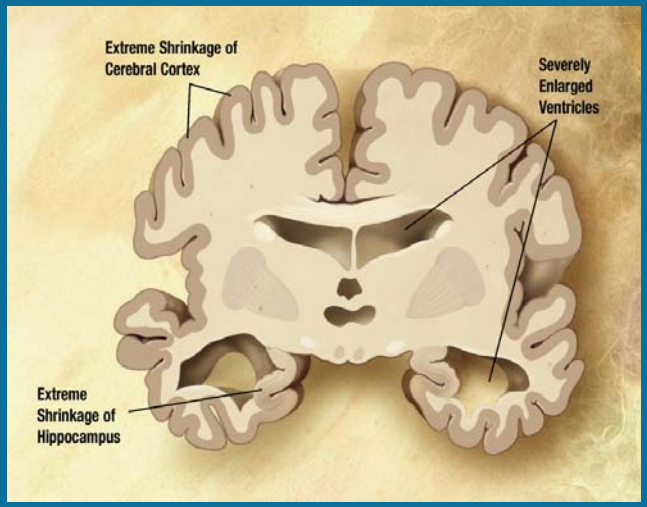
Healthy Brain

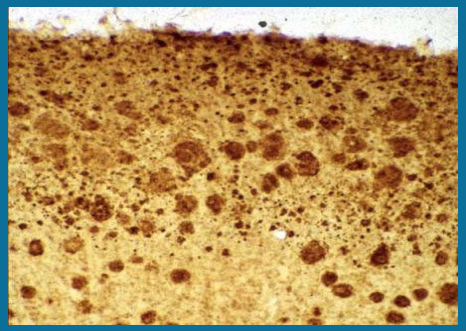


AD Brain



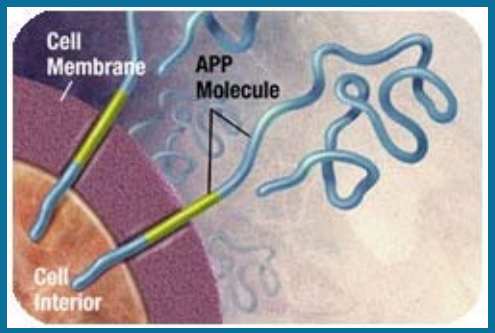
Minimal Amyloid Protein

Marked Amyloid Protein



AD and the Brain

1.



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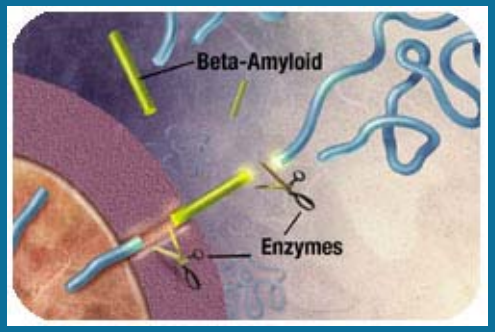
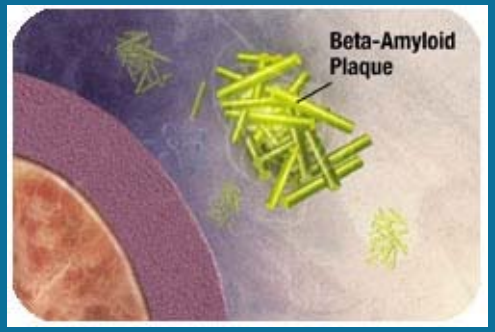


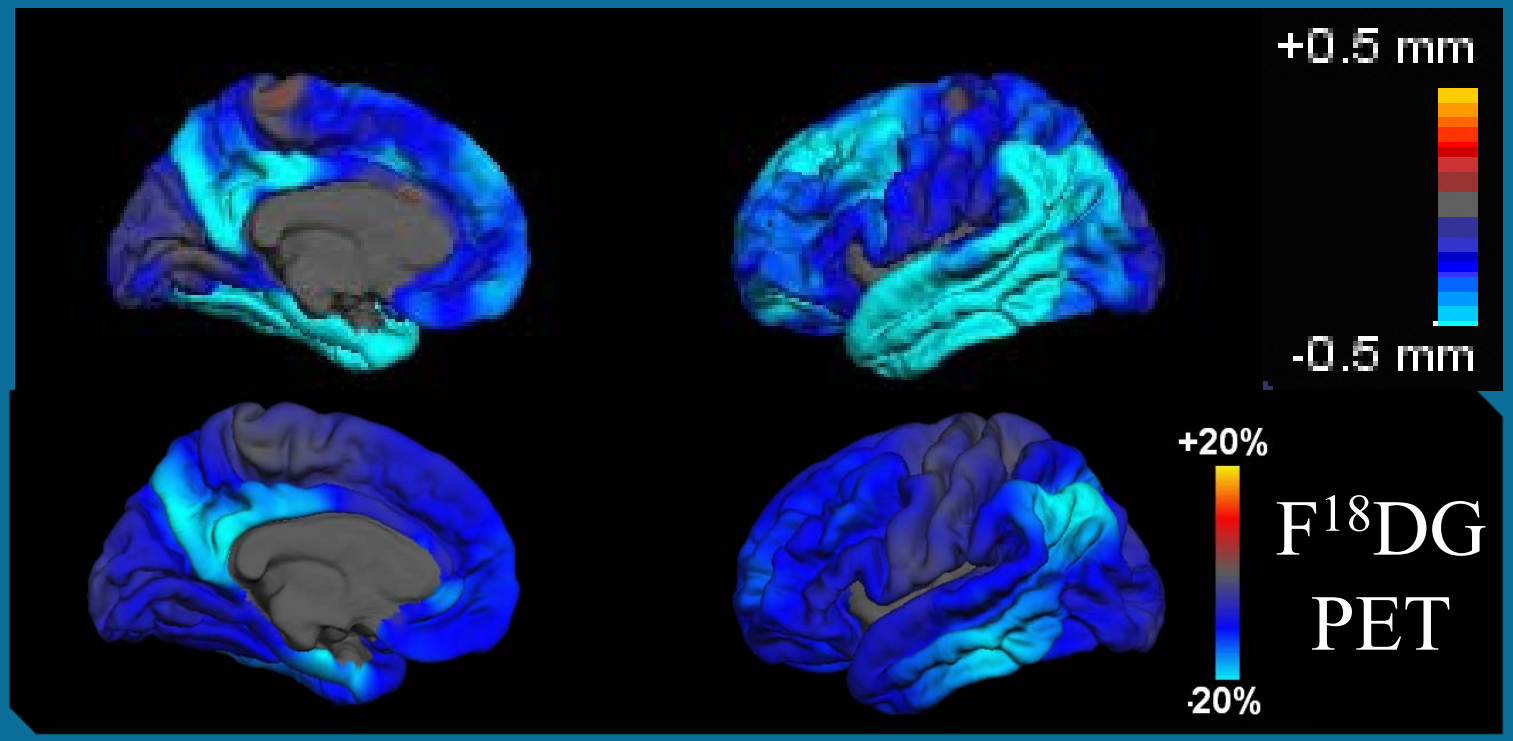
3.



Volumetric MRI

Cortical Thickness

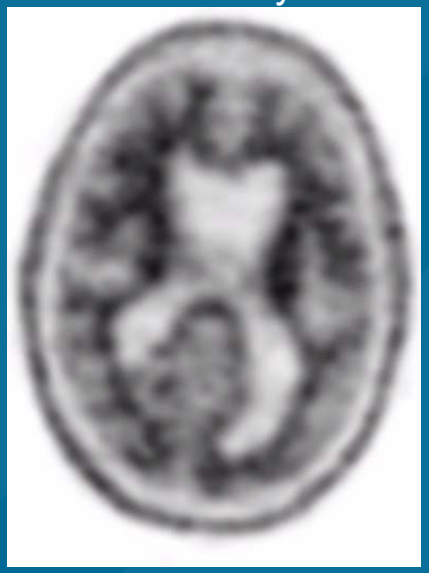
AD versus Controls
n=139 NC, 84 AD



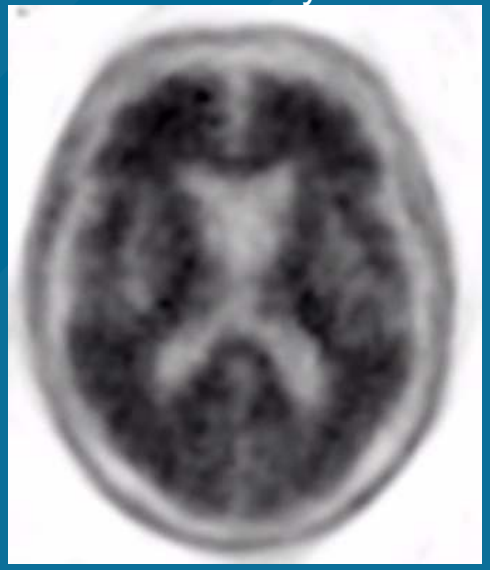
New Tools for Investigation and Discovery

- Advances in Quantitative Neuroimaging
  - Direct visualization of pathologic protein deposition

Normal Amyloid

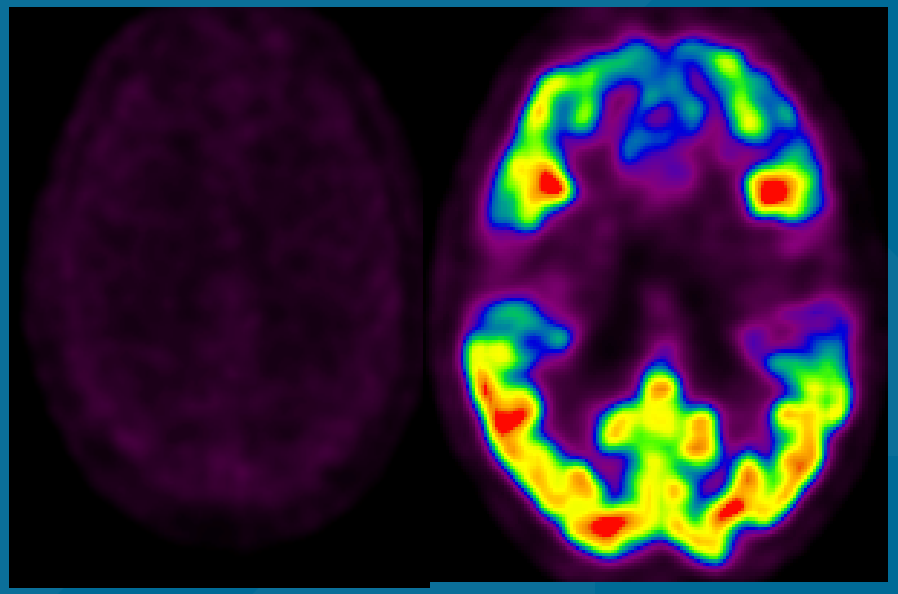


Elevated Amyloid



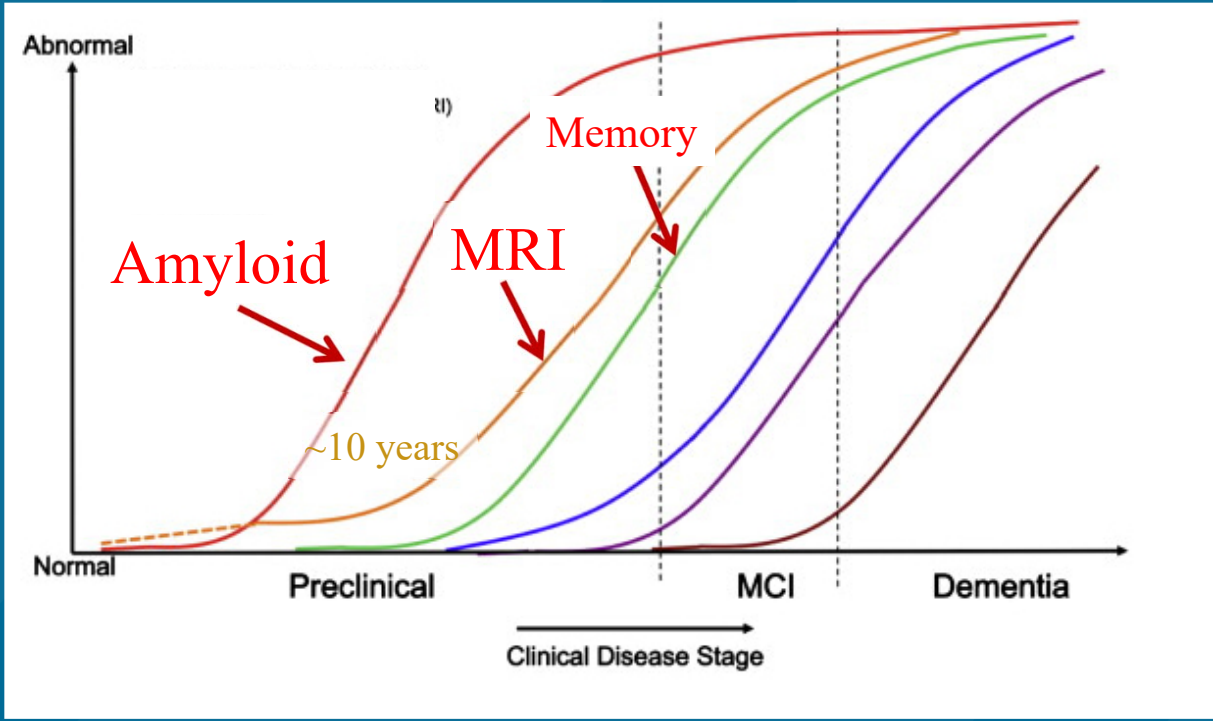
Normal Tau

Elevated Tau



New Tools for Investigation and Discovery

- New Markers



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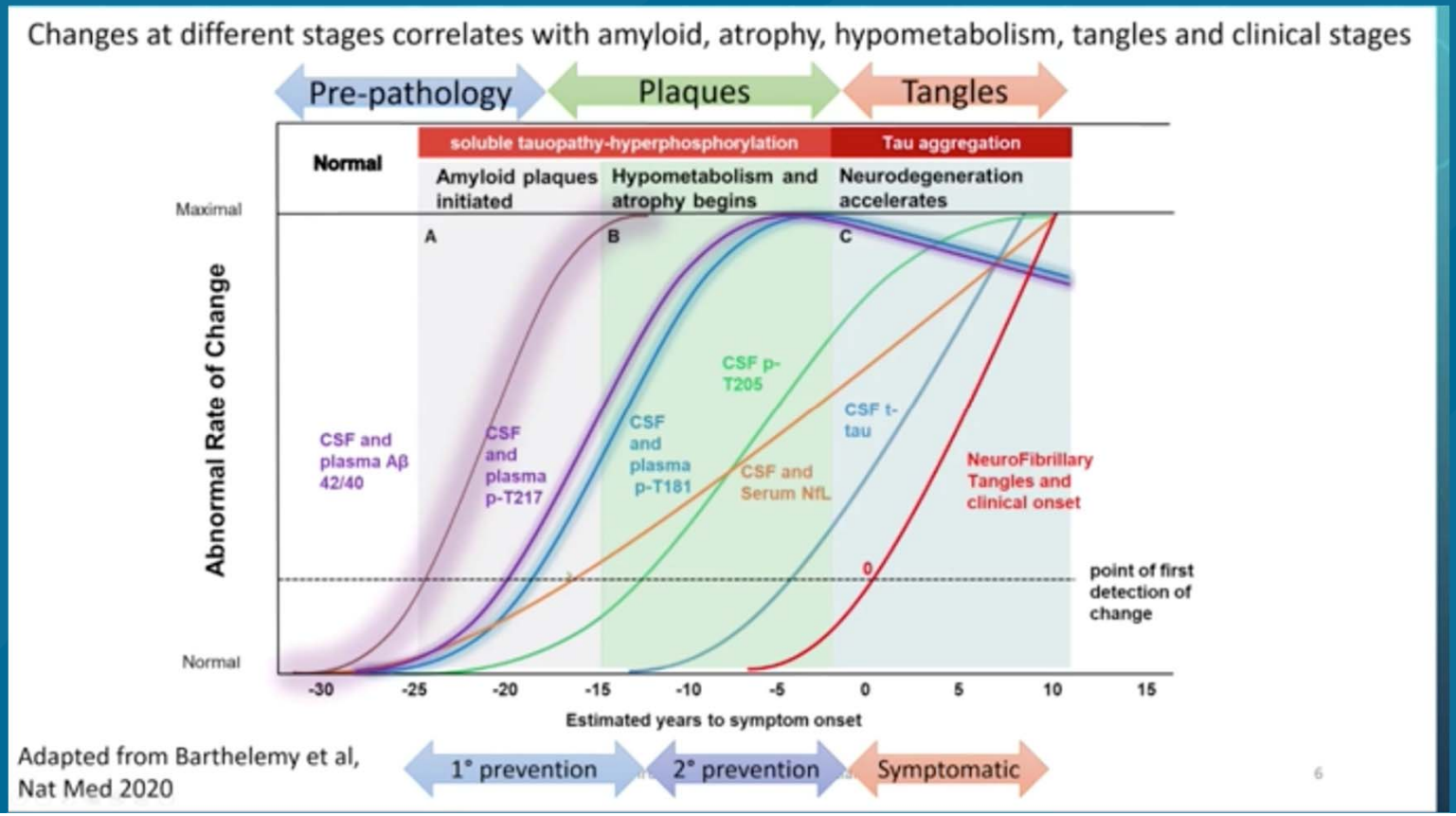
New Tools for Investigation and Discovery

- New Plasma and Biofluid Markers



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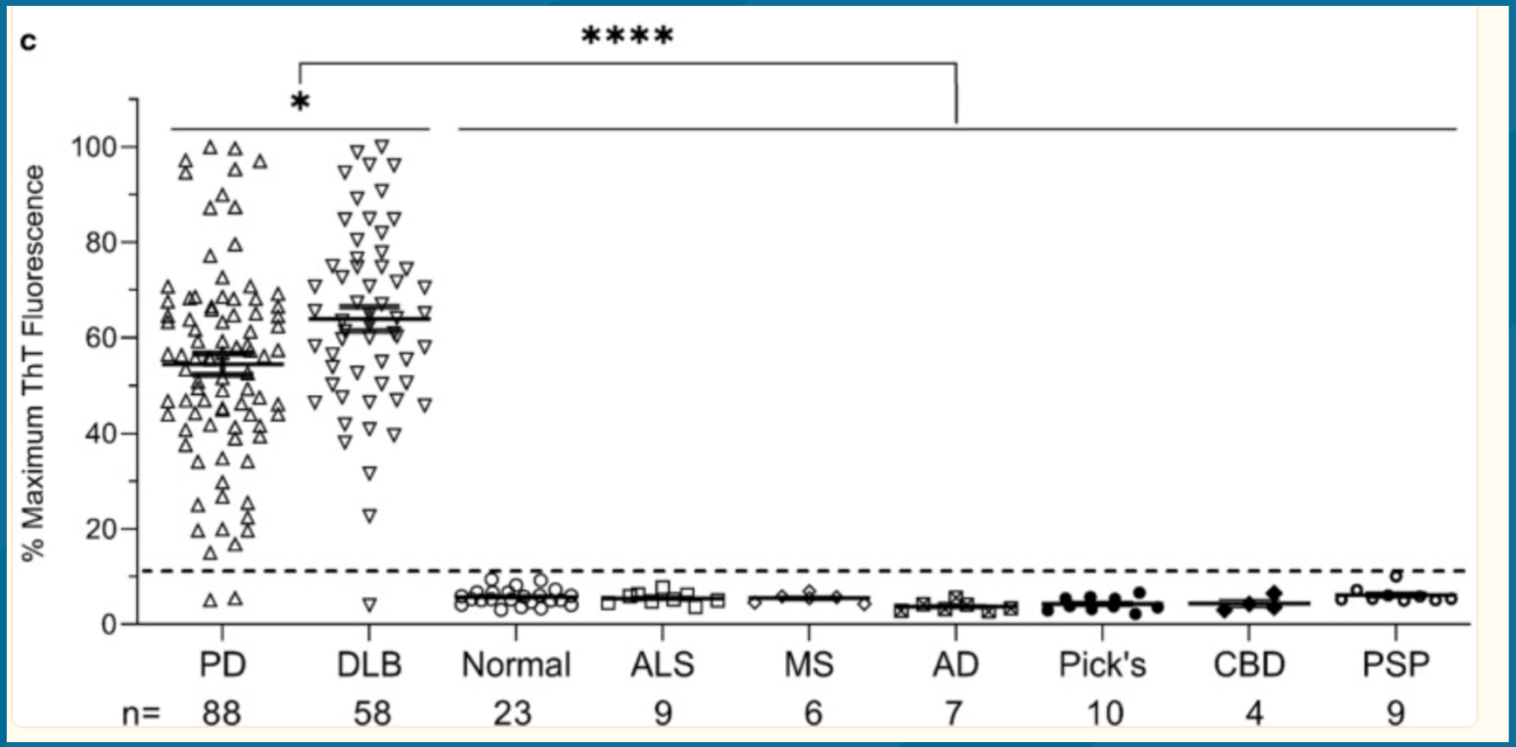
New Tools for Investigation and Discovery

- New Plasma and Biofluid Markers

CSF- RT-QuIC Synuclein Seeding Assay



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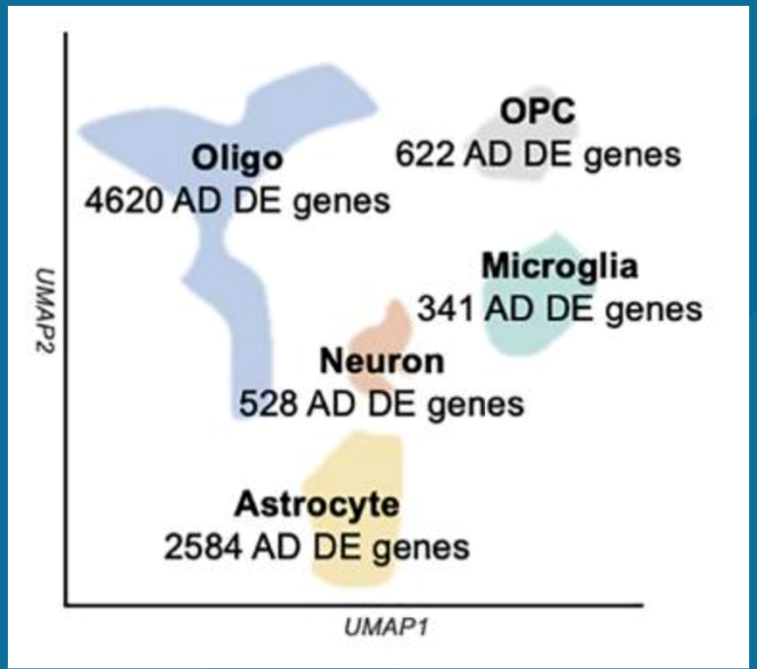
New Tools for Investigation and Discovery

- 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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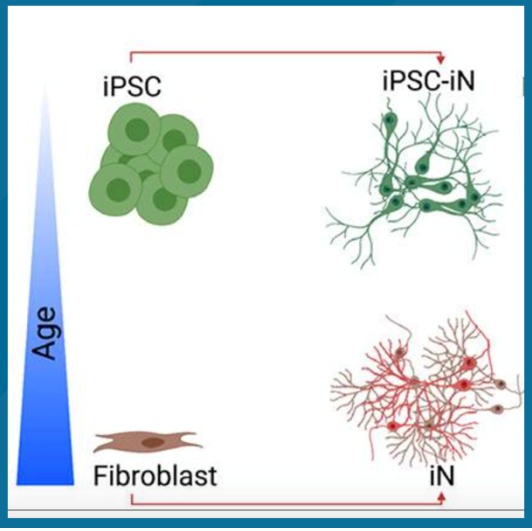
New Tools for Investigation and Discovery

- ”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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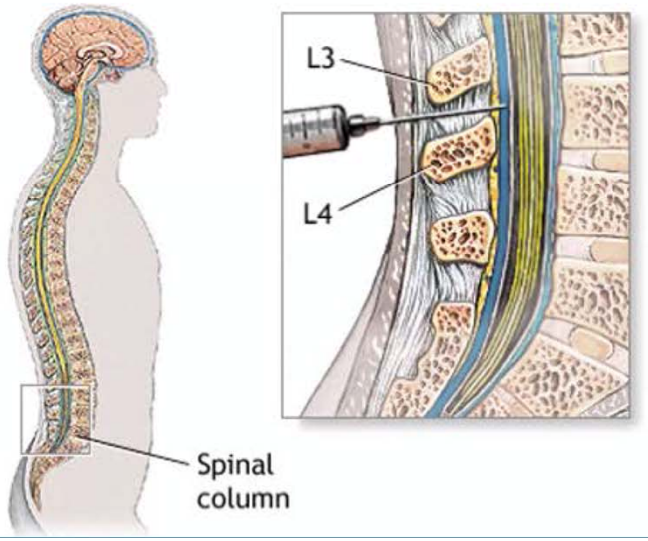
The Promise of the Future

- **Rapid Increase in Availability of Genetic Tools**
- 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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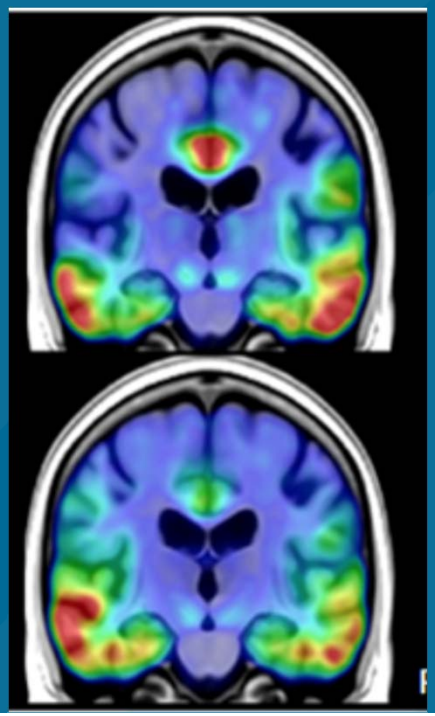
The Promise of the Future

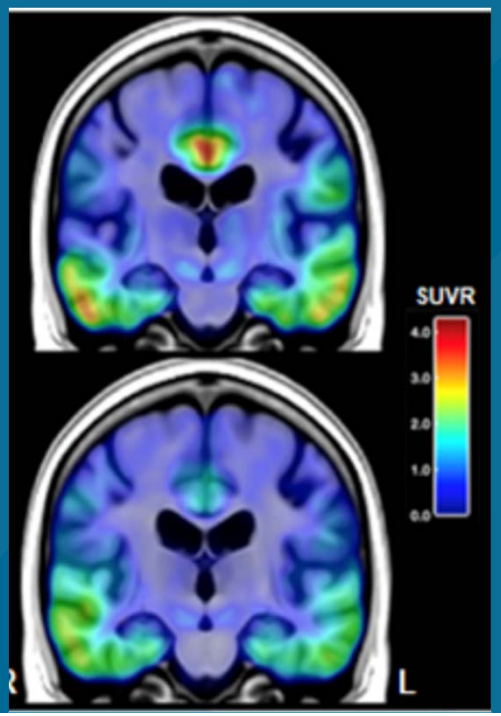
- **Rapid Increase in Availability of Genetic Tools**
- Anti-sense Oligonucleotides (ASO)
  - Gene-Therapy delivery to the central nervous system

Pt 1

Pt 2



12 Months
On Anti-Tau
ASO Dosed
Every 3 Months



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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 aim to increase feedback between Participant ←→ Center

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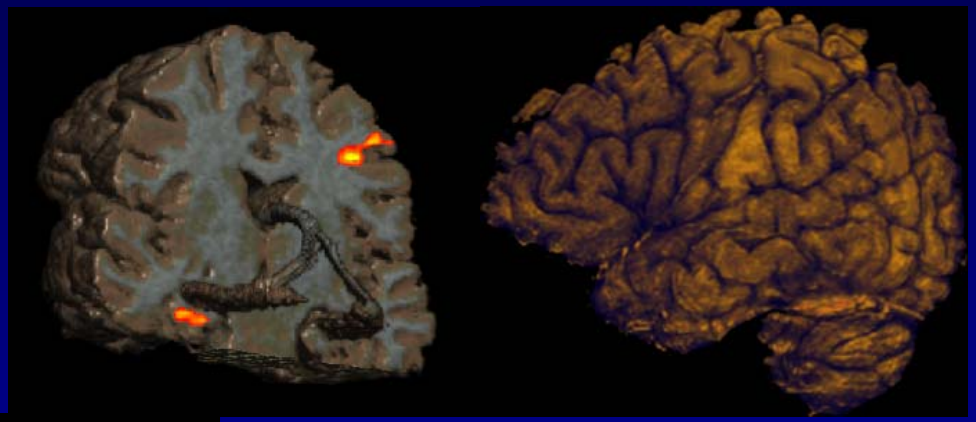
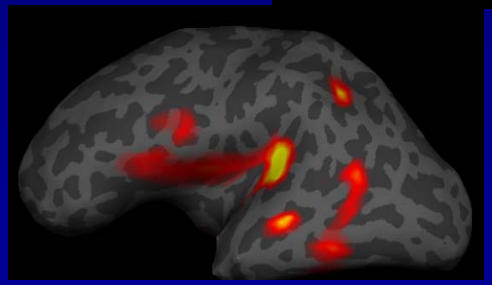
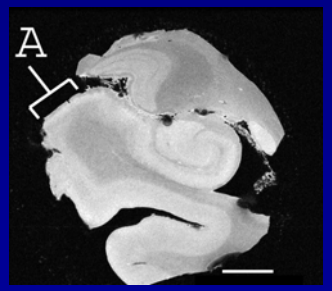
Thank You





James Brewer, M.D., Ph.D.
UCSD Shiley Marcos ADRC
The UCSD Human Memory Laboratory



New treatments and clinical trials for Alzheimer's Disease

Douglas Galasko, MD
Professor, Dept. of Neurosciences
University of California, San Diego
and VA Medical Center, San Diego

UC San Diego
SCHOOL OF MEDICINE

University of California, San Diego
Shiley-Marcos
Alzheimer's Disease
Research Center

New treatment and diagnostic testing

U.S. FOOD & DRUG ADMINISTRATION

← Home / News & Events / FDA Newsroom / Press Announcements / FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval

FDA NEWS RELEASE

FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval

Action Follows Confirmatory Trial to Verify Clinical Benefit

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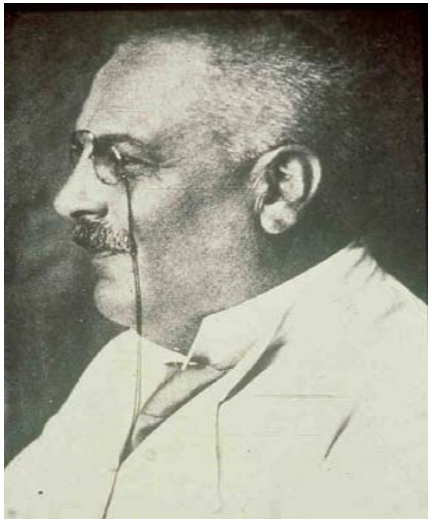
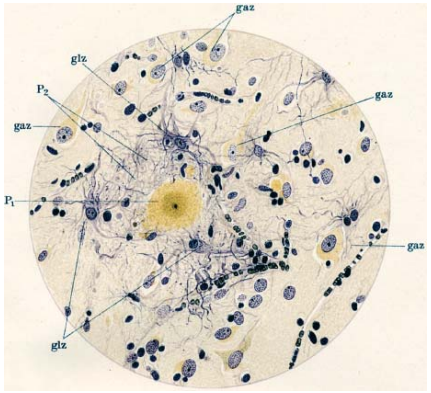
More Press Announcements **For Immediate Release:** July 06, 2023

Biomarker tests bring Alzheimer's disease to life



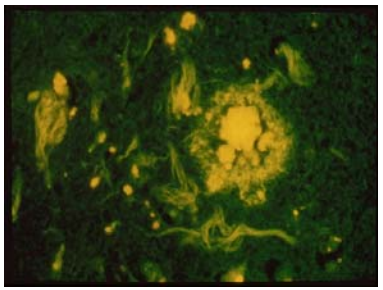


- Alzheimer's can only be diagnosed at autopsy

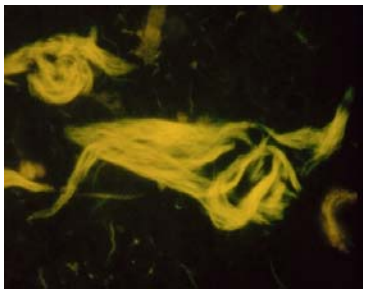
  FALSE!

- Biomarkers measured by brain imaging or in CSF or plasma can identify the key pathological lesions, **plaques** and **tangles**, during life.

Biomarkers can map A,T and N

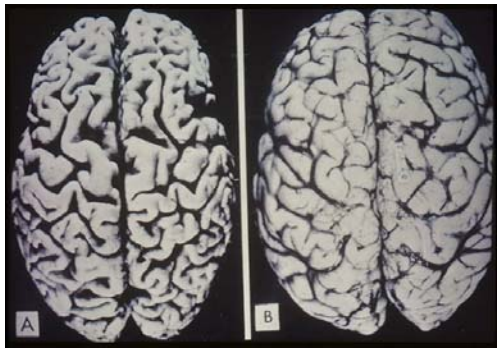


Amyloid plaques



Neurofibrillary tangles

A: Amyloid PET
CSF or plasma Aβ42/40
T: Tau PET,
CSF or plasma: P-tau

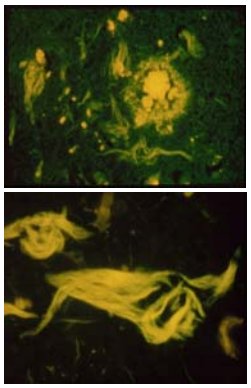


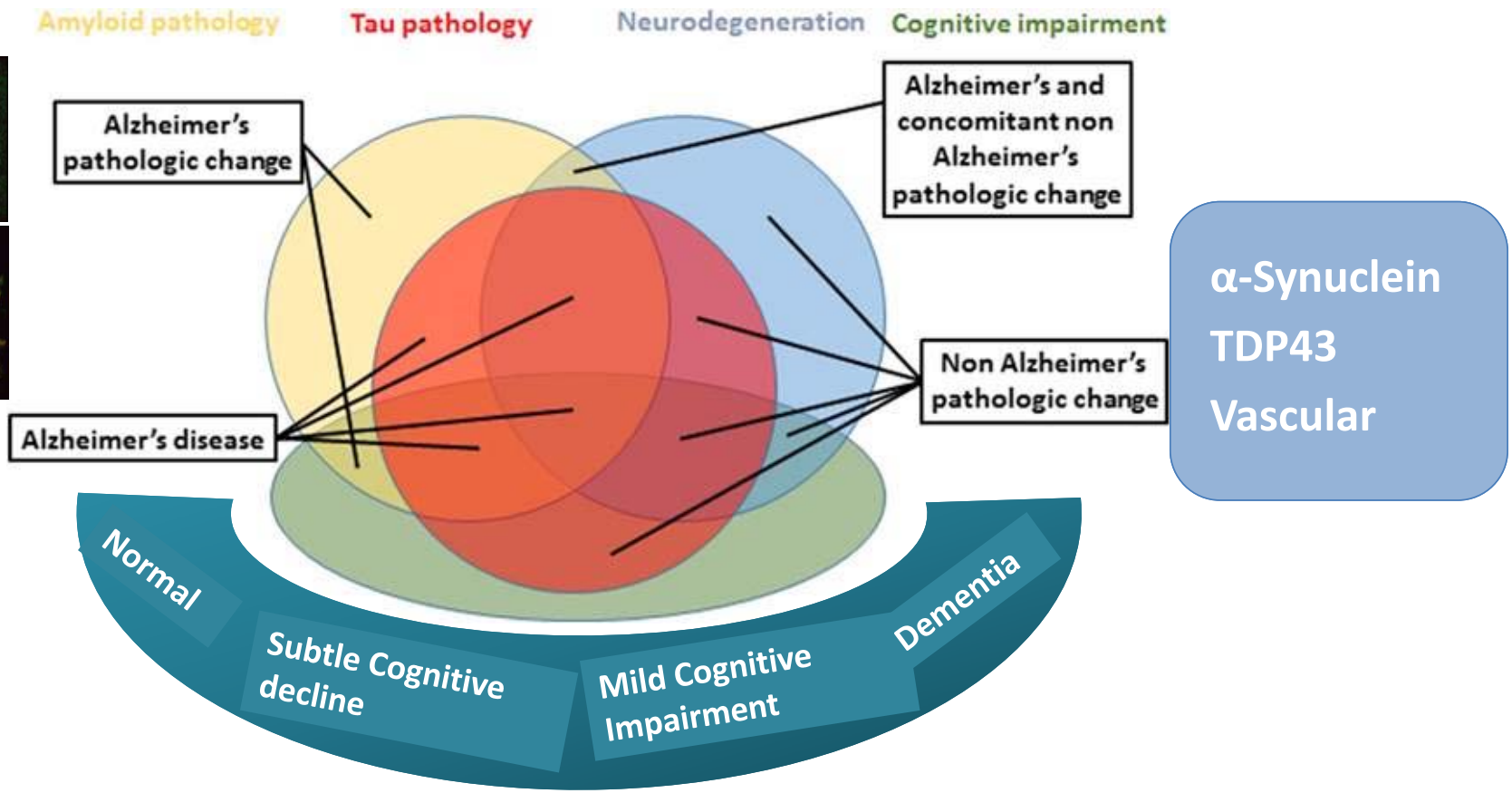
Brain atrophy and neuron loss

N: **Anatomy:**
MRI: atrophy, pathways
PET: glucose use
Biochemistry:
CSF or plasma: tau, NfL, etc

NIA-AA Research Framework: Towards a biological definition of Alzheimer's disease – A, T, N

Jack et al, Alzheimer's and Dementia, 2018

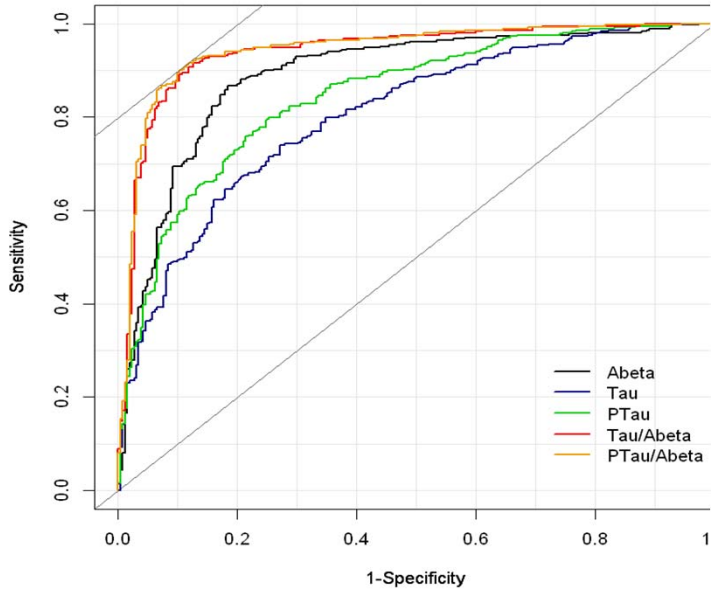




Two FDA-approved CSF biomarker tests

Elecsys and Lumipulse assays use fully automated devices to measure CSF Aβ42, t-Tau and p-Tau181

Ratios of CSF biomarkers perform better than single biomarkers



AUC values:

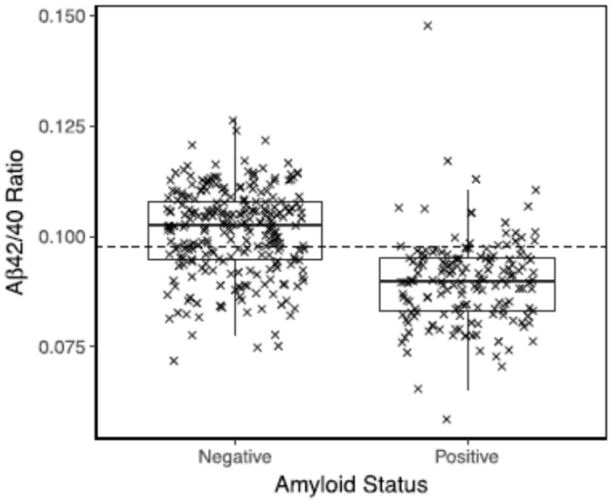
p-tau/$A\beta_{1-42}$	**0.944**
t-tau/$A\beta_{1-42}$	**0.940**
$A\beta_{1-42}$	0.889
p-tau_{181}	0.845
t-tau	0.803

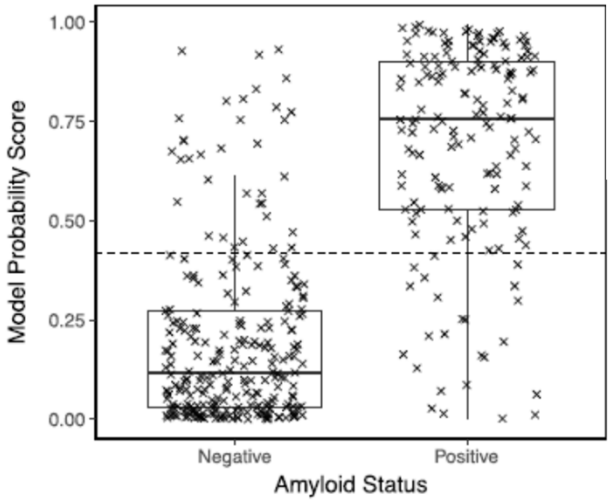
Emerging diagnostic blood tests

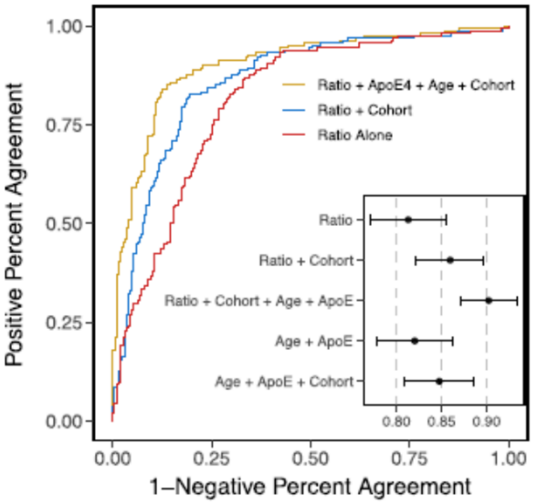
- Plasma **Aβ42/Aβ40** ratio

- An IP-mass spect assay is marketed by a Company - C2N
- Correlates well with brain amyloid measured by PET or CSF
- Improved accuracy if age and APOE e4 genotype are also measured - called “Precivity”

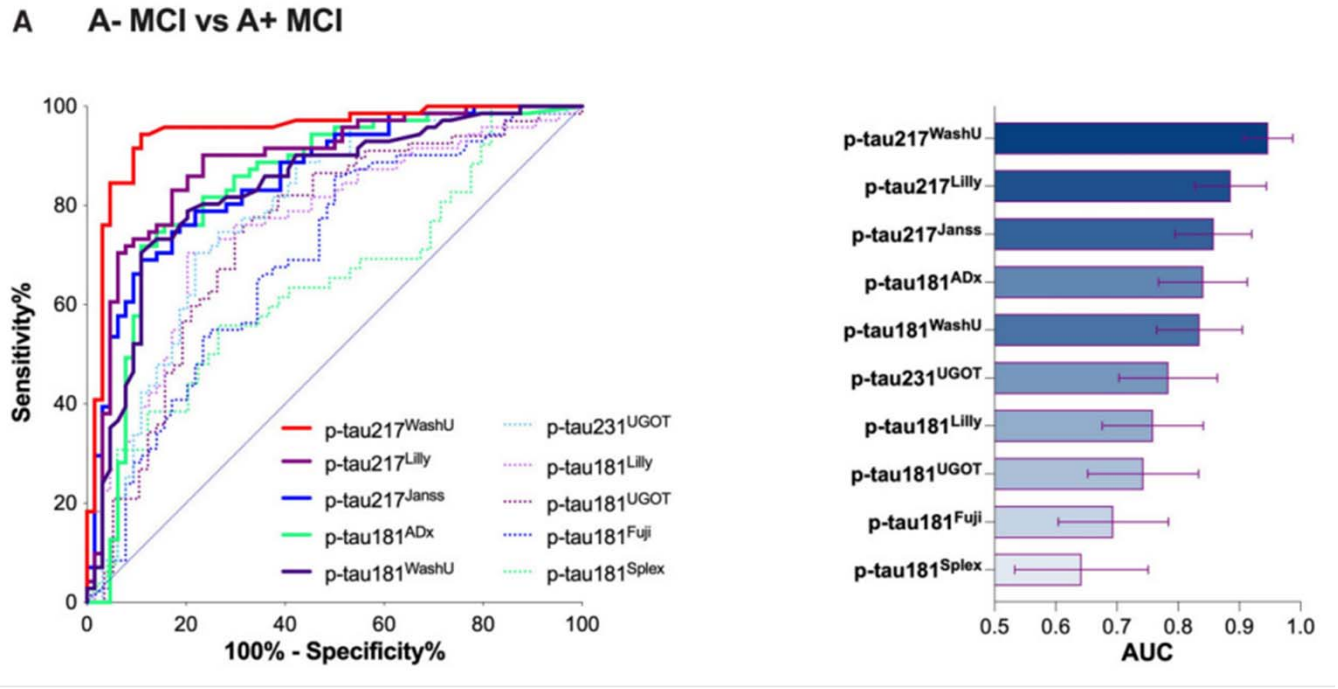
West et al, 2021







Plasma Tau biomarkers



Janelidze 2023

pTau217 performed best in a head to head comparison, at predicting or ruling out people with MCI with a positive amyloid PET scan

pTau blood tests are starting to be offered by freestanding labs

Anti-amyloid immunotherapy

Lecanemab: binds to soluble protofibrils of amyloid and clears amyloid from plaques.

Positive phase 2 and phase 3 trials.

FDA approval in July 2023; covered by CMS

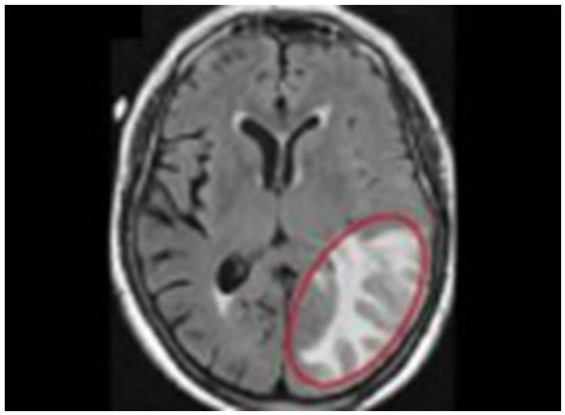
Donanemab: binds to insoluble amyloid and clears plaques

Positive phase 2 and phase 3 trials

Both antibodies slowed clinical progression
Both were associated with an adverse event called ARIA. This resulted in a **boxed warning** from the FDA

ARIA – Amyloid Related Imaging Abnormality

- Most ARIA events are asymptomatic and can be seen on MRI
- However, symptoms may occur:
  - headache, nausea, confusion, dizziness
  - rarely stroke or seizures



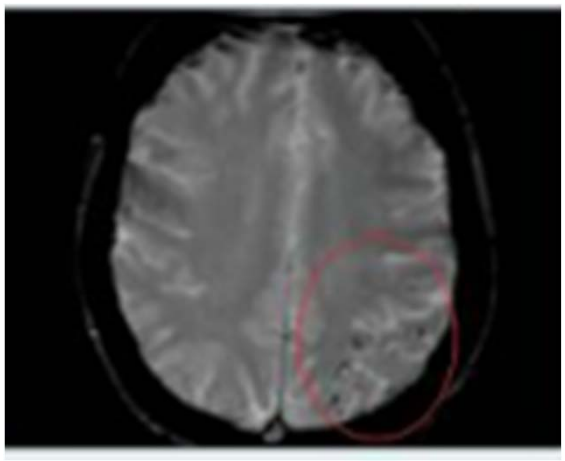
ARIA-E

Mitigate

Baseline MRI: exclude people with > 4 microhemorrhages

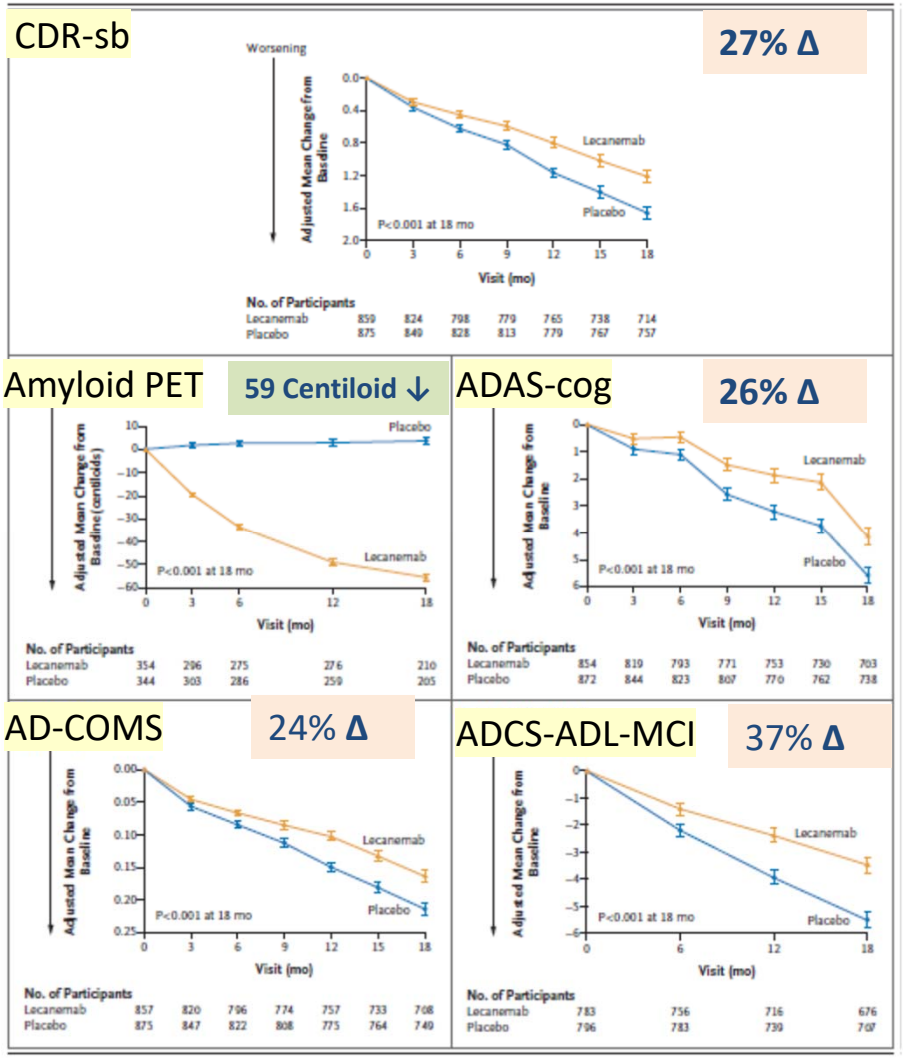
Monitor

Safety MRI at 2, 3 and 6 months and if symptoms emerge esp. early in treatment



ARIA-H

Lecanemab lowers amyloid and slows progression



Lecanemab 10 mg/kg vs placebo

- IV 2 weekly x 18 months
- N =1795 (898 Lecanemab; 897 placebo)
- Slowed clinical progression

ARIA-E

12.6% of Lecanemab, 2.8% symptomatic

ARIA-H

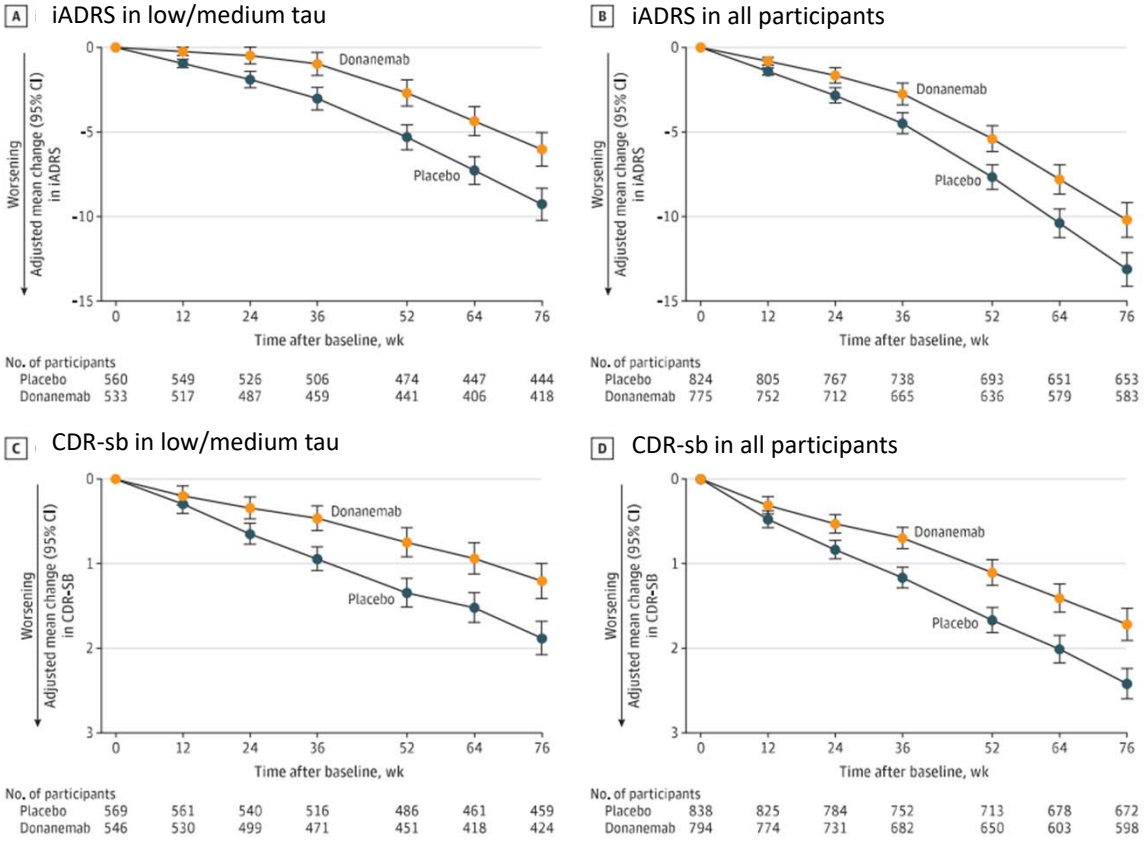
8.9% of Lecanemab, 7.8% of placebo

ARIA risk higher in people who are APOE e4 carriers

(ε2-3/2-3 5.4%, ε2-3/**4 10.9%, ε4/4 32.6%)**

Van Dyck, C. H. van *et al.*. *New Engl J Med* **388**, 9–21 (2022).

Donanemab clears amyloid and has clinical benefit



- Phase 3 trial x 18 months
- Donanemab I-V every 4 weeks
- MCI/mild AD
- slowing of a composite scale (IADRS-AD) by **37%**
- slowing of ADCS-ADL by **37%**

- Cleared amyloid in 80% by 76 weeks -> treatment was stopped
- Clinical benefits were stronger in people with low tau PET burden

1.6% rate of serious ARIA

Lecanemab (‘Leqembi) enters clinical practice

Leqembi is FDA-approved and covered by MediCare

- Referring MDs need to:
  - detect MCI or mild dementia
  - Have some knowledge of anti-amyloid immunotherapy

- Subspecialty clinics need to:
  - handle referrals of appropriate patients for consideration of therapy in a timely manner
  - use biomarker tests to confirm the diagnosis
  - Discuss treatment and manage it for appropriate patients

UCSD Memory Disorders Clinic: discussion with patients

Diagnosis: MCI or Mild AD requires biomarker confirmation of Alzheimer's
e.g., CSF or amyloid PET
- blood tests are emerging but are not yet FDA approved

Best if the specialty memory clinic carries out this testing

Treatment requires IV infusions every 2 weeks

Costs: Lecanemab costs $26,000 per year. While covered by Medicare, there may be significant copayments for drug, infusions, diagnostic tests and the 3 safety MRIs.

Potential risks: ARIA and infusion reactions

If a patient is interested and appropriate

- Review the workup for MCI/mild dementia
- Repeat components as needed
- Review inclusion/exclusion criteria
- Obtain Alzheimer biomarker (CSF or amyloid PET or plasma)
- Obtain MRI with GRE or SWI sequences to assess microbleeds
- Obtain APOE genotyping to evaluate ARIA risk
- Discuss treatment plan with patient and family

Monitoring while on Lecanemab/Leqembi

- General health and cognition
- Infusion Center manages infusion reactions
- Symptoms that might be ARIA -> may need to go to ER
- Safety MRIs: weeks 8, 12 and 26
- - if significant or symptomatic ARIA –> hold or stop treatment
- New initiation of anticoagulation and IV TPA treatment may carry major risk of intracranial hemorrhage – if these are necessary, probably should stop Leqembi

RESEARCH ARTICLE

Cost-Effectiveness of Lecanemab for Individuals With Early-Stage Alzheimer Disease

Hai V. Nguyen, PhD, Shweta Mital, PhD, David S. Knopman, MD, and G. Caleb Alexander, MD

Neurology® 2024;102:e209218. doi:10.1212/WNL.0000000000209218

Correspondence
Dr. Nguyen
hvnguyen@mun.ca

Discussion

Neither targeted lecanemab treatment nor treatment unrestricted by *APOE* ε4 genotype is cost-effective vs SoC alone for patients with MCI or mild dementia due to AD. Lecanemab would be cost-effective in some settings if priced below $5,100 per year.

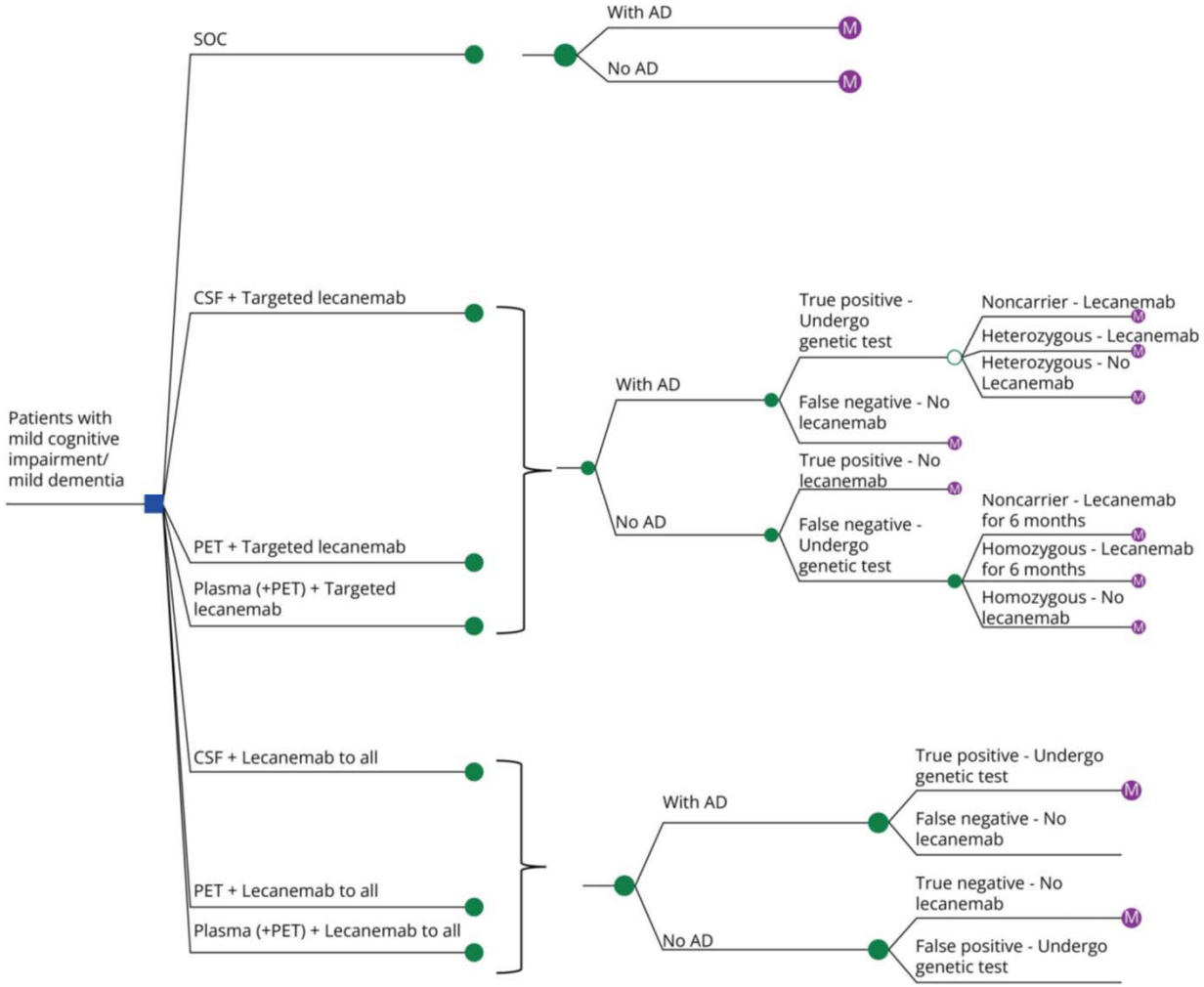
Is lecanemab worth it?

The affordability of lecanemab, an amyloid-targeting therapy for Alzheimer's disease: an EADC-EC viewpoint

Linus Jönsson,[a,*] Anders Wimo,[a] Ron Handels,[a,b] Gunilla Johansson,[a] Mercè Boada,[c] Sebastiaan Engelborghs,[d] Lutz Frölich,[e] Frank Jessen,[f] Patrick Gavin Kehoe,[g] Milica Kramberger,[h] Alexandre de Mendonça,[i] Pierre Jean Ousset,[j] Nikolaos Scarmeas,[k,l] Pieter Jelle Visser,[m] Gunhild Waldemar,[n,o] and Bengt Winblad[a,p]

the population potentially eligible for treatment with lecanemab in the 27 EU countries to 5.4 million individuals. Treatment costs would exceed 133 billion EUR per year if the drug is priced similarly as in the United States, amounting to over half of the total pharmaceutical expenditures in the EU. This pricing would be unsustainable; the ability to pay for high-priced therapies varies substantially across countries. Pricing similarly to what has been announced for the United States may place the drug out of reach for patients in some European countries. Disparities

Cost-benefit analysis vs standard of care



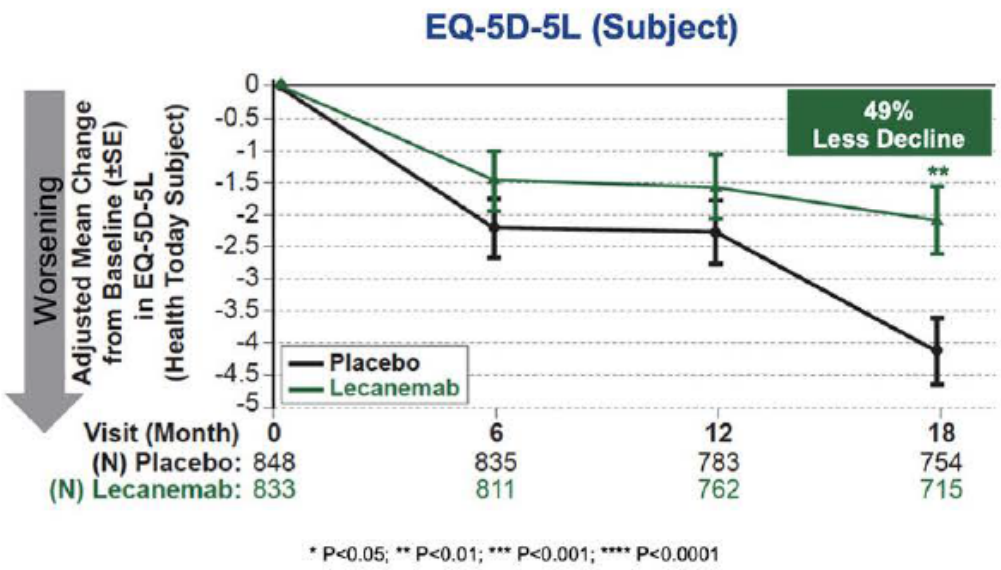
1. CSF testing was the most effective diagnostic (vs blood tests or amyloid PET)
2. Limiting treatment to APOE e4 noncarriers may be more effective
3. Including all costs, the payment for lecanemab should be $5100/year … *other studies have estimated about $9000/year*

J Prev Alz Dis 2023;
Published online September 29, 2023, http://dx.doi.org/10.14283/jpad.2023.123

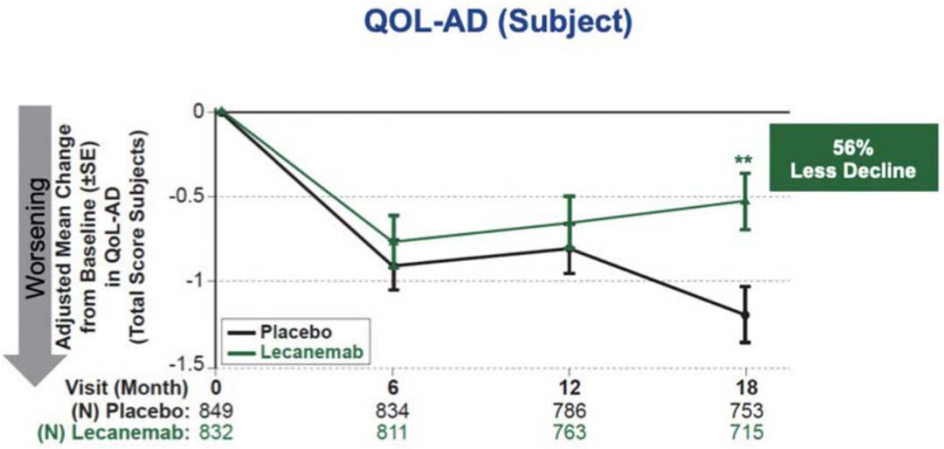
Original Research

Lecanemab Clarity AD: Quality-of-Life Results from a Randomized, Double-Blind Phase 3 Trial in Early Alzheimer's Disease

S. Cohen[1], C.H. van Dyck[2], M. Gee[3], T. Doherty[3], M. Kanekiyo[4], S. Dhadda[4], D. Li[4], S. Hersch[4], M. Irizarry[4], L.D. Kramer[4]

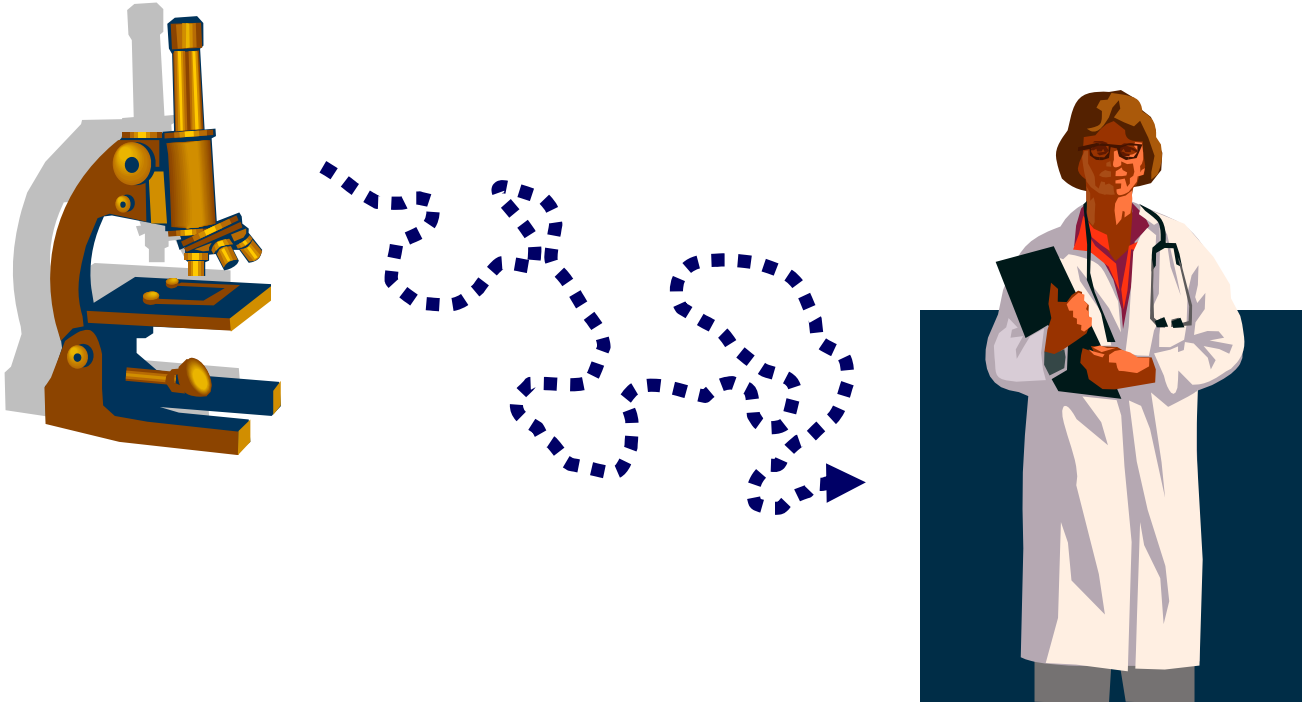


* P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001



* P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001

We need to continue to develop new treatments

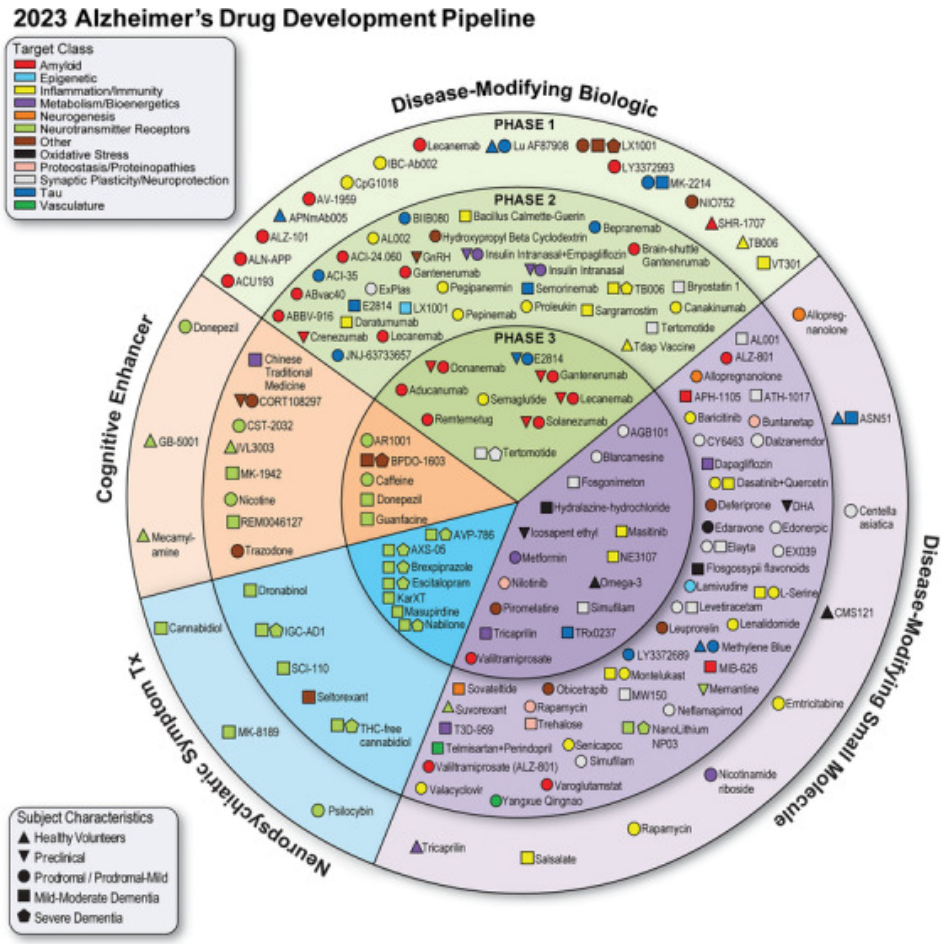


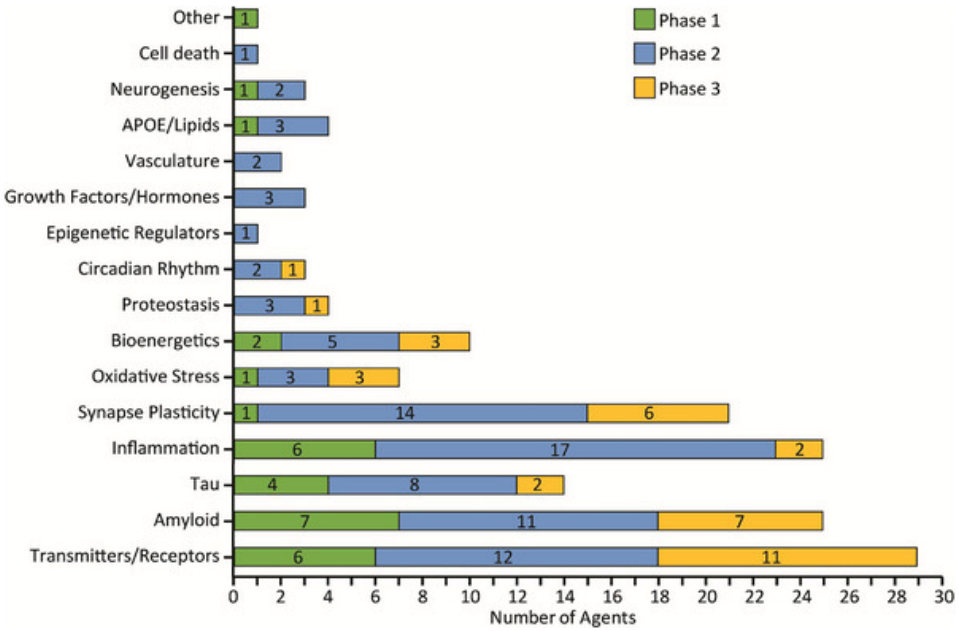
Further developments in Amyloid therapy

- Subcutaneous Leqembi – may allow home administration
- Prevention trials of lecanemab and donanemab
- Combination of anti-amyloid and tau antibody Rx:
  - has started in autosomal dominant AD (DIAN-TU)
- New anti-amyloid antibodies: Prothena, Acumen
- Active immunization: AC Immune, Vaxxinity, Prothena
- Other approaches: block formation of pyroglu-A-beta;

  gamma-secretase modulator; decrease APP with ASO

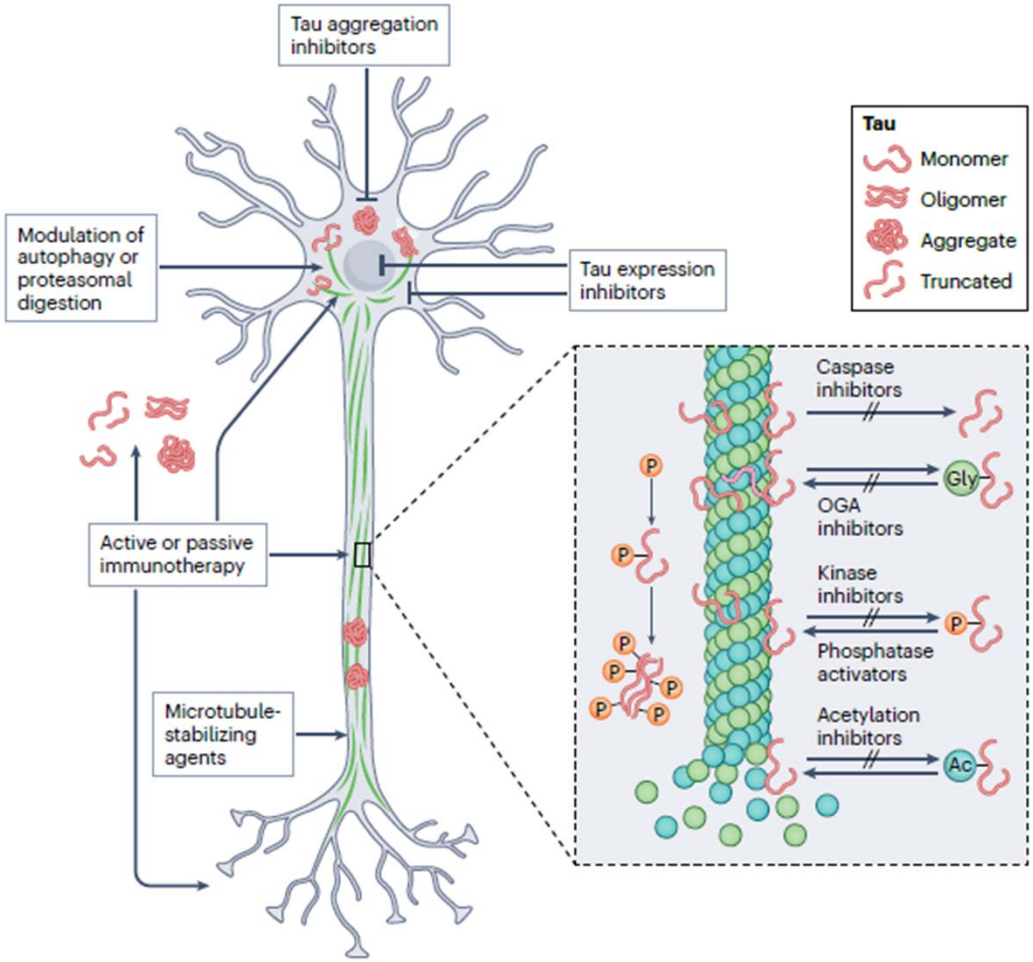
What next for Alzheimer's? Many treatment targets and ongoing clinical trials





Cummings J et al, Alzheimer's and Dementia 2023

Can tau be a therapeutic target?



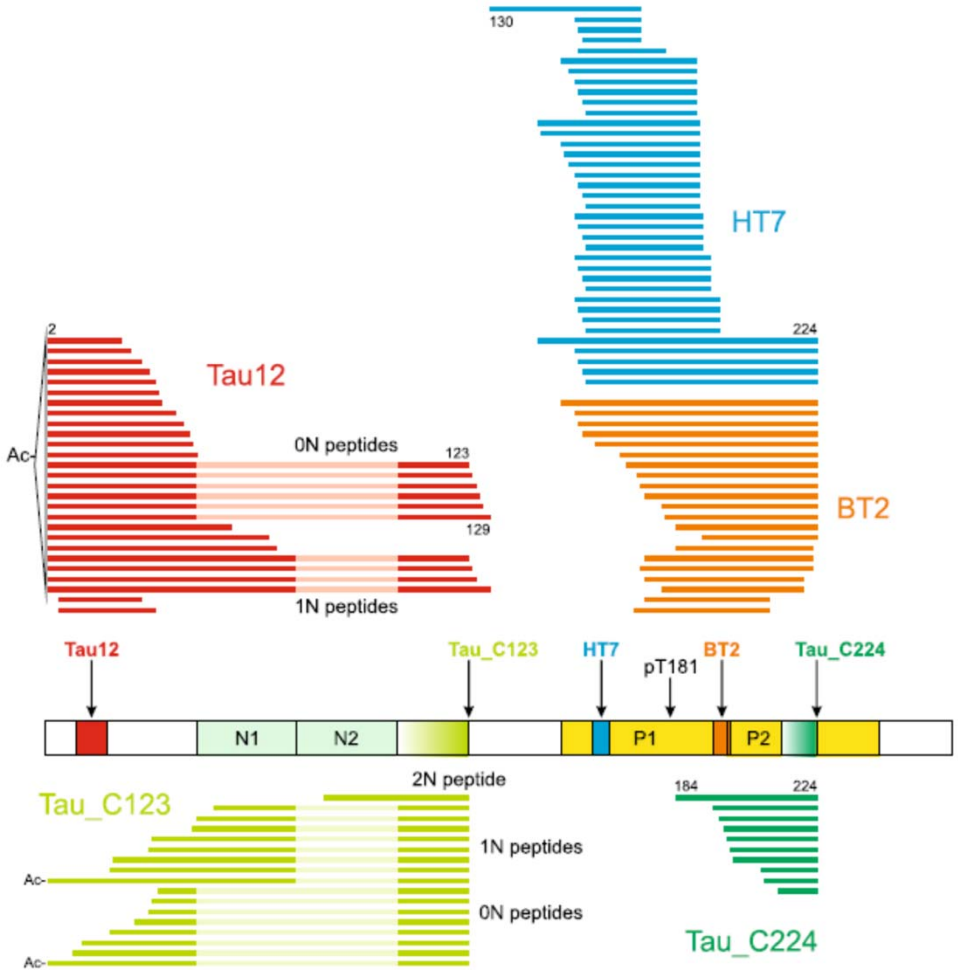
Phase 2 or 3 trials are testing:

1. Whether antibodies can block the spread of tau
   - includes active immunization

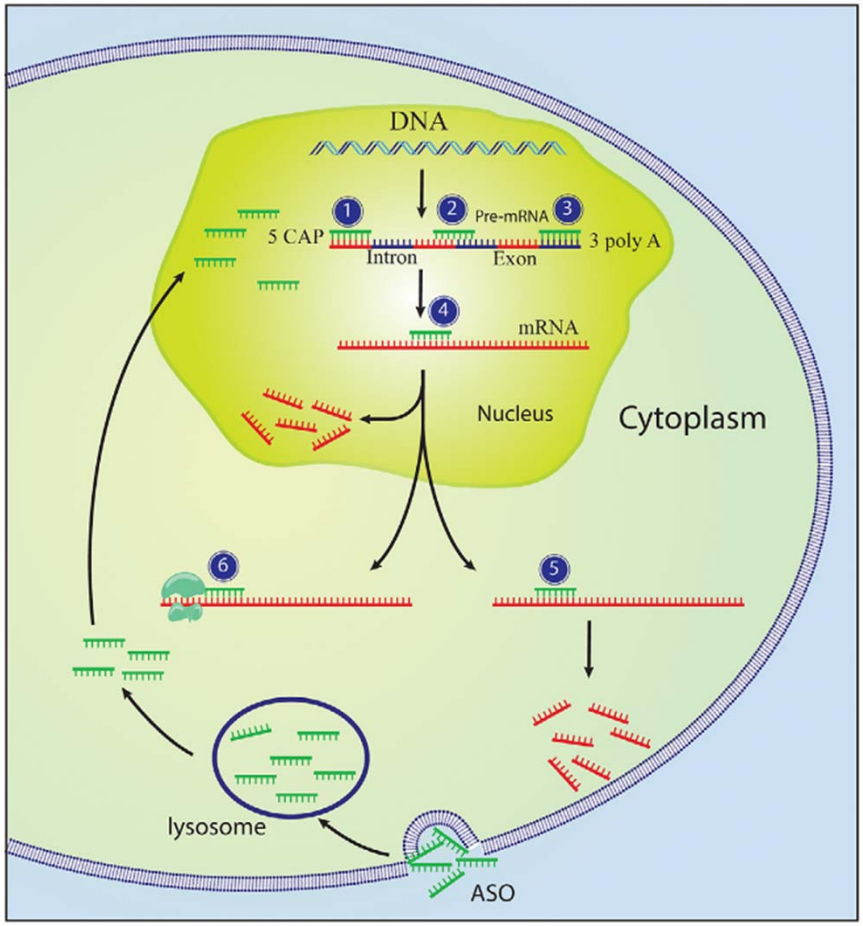
2. whether lowering tau using ASOs may slow progression

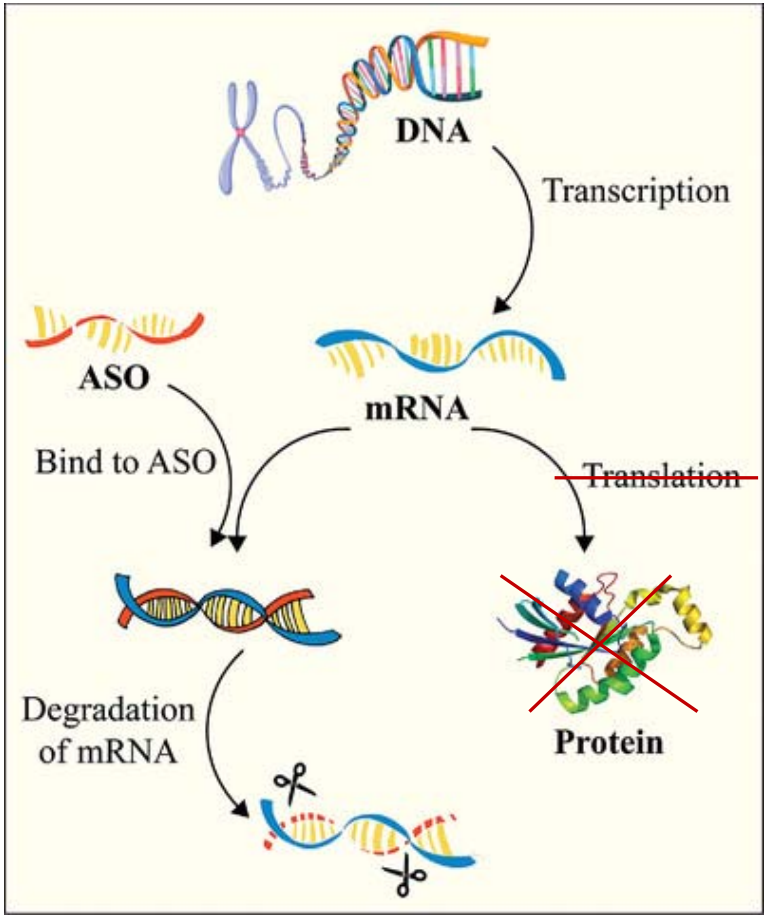
Tau antibody therapy

- Antibodies against the N-terminal end of tau failed in AD and PSP trials.
- New wave of trials targets the microtubule binding region, which is critical for tau to aggregate and form tangles
- Trial programs under way by Eisai, Janssen, BMS.



Lower Tau in the brain using Antisense Oligonucleotides (ASOs)





ASOs FDA Approved

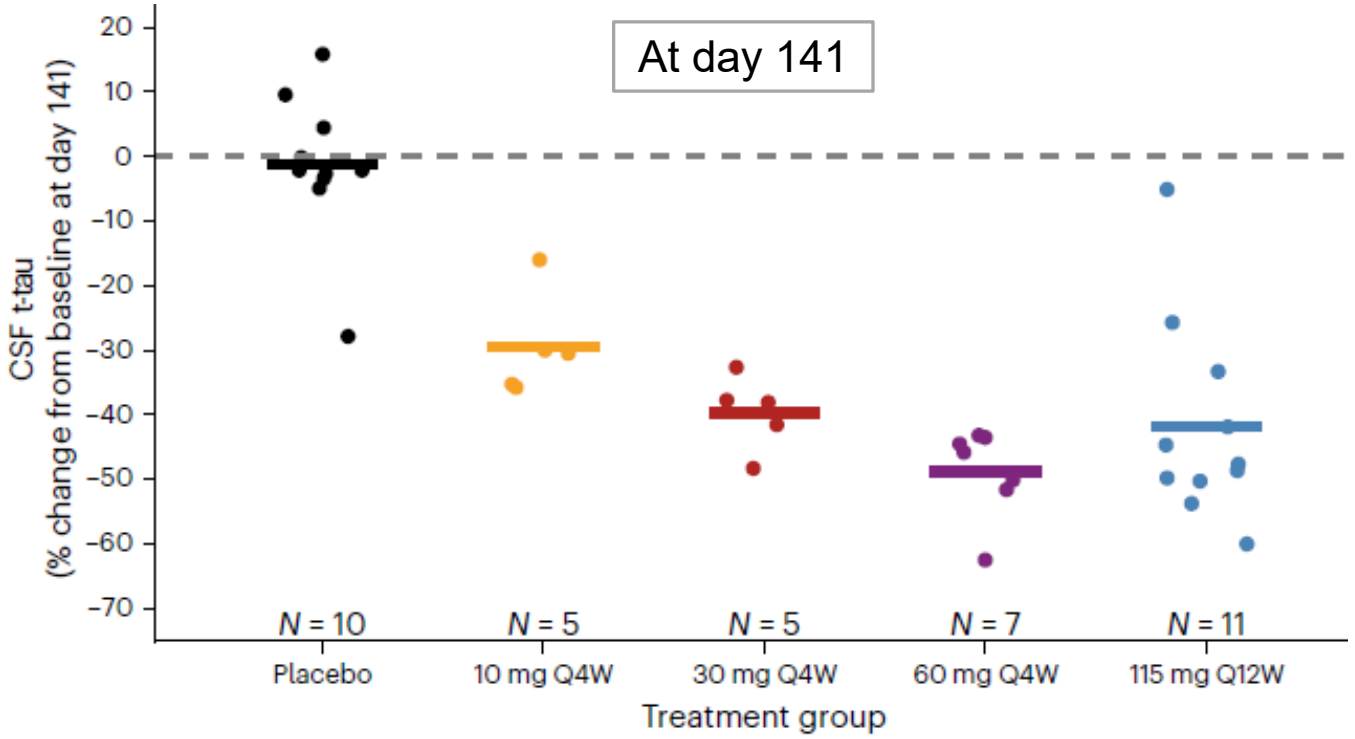
Spinal Muscular Atrophy

ALS with SOD 1 mutations

Gheibi-Hayat SM, Jamialahmadi K. BAB 2020. DOI: 10.1002/bab.2028

UC San Diego
School of Medicine

An ASO to the Tau gene lowers CSF concentrations of t-tau Protein



Phase 2 trial is starting and UCSD is a site

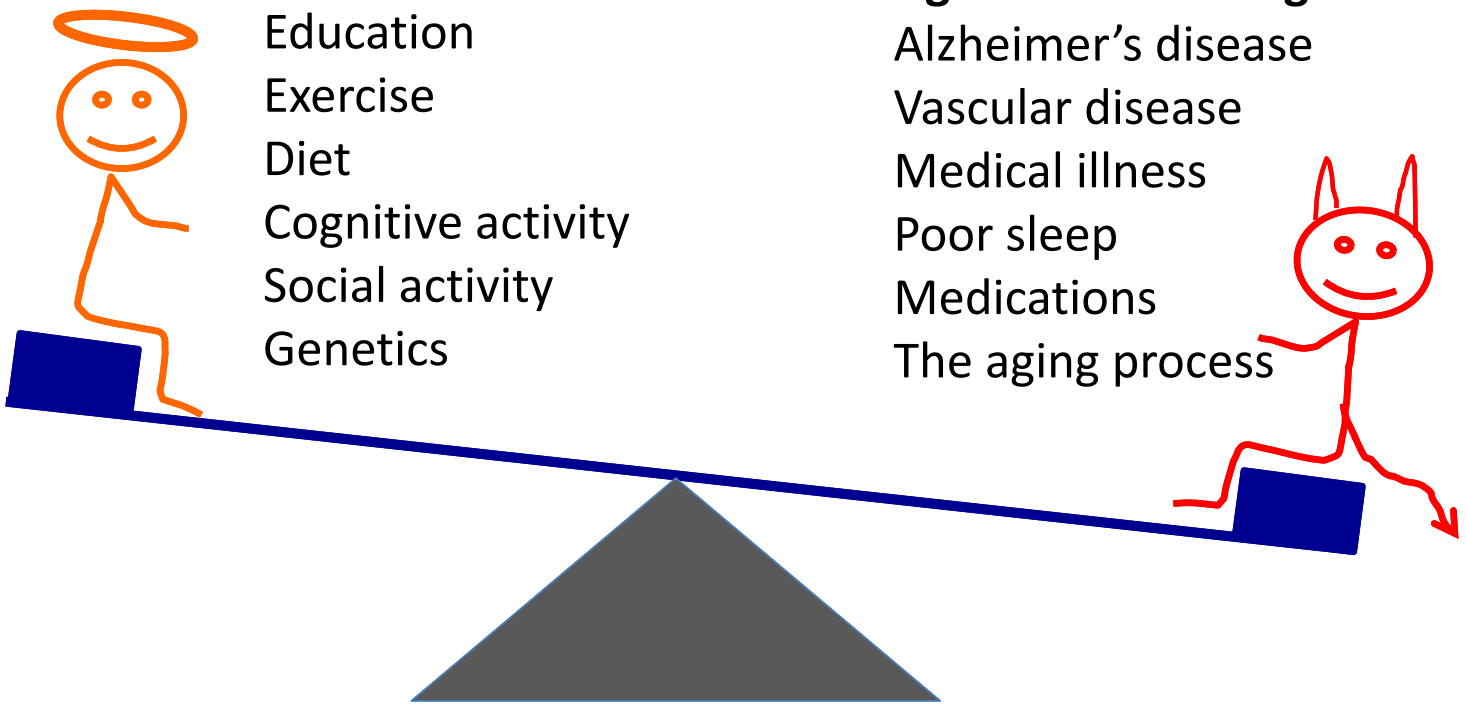
Mummery, C.J., et al. Nat Med (2023). https://doi.org/10.1038/s41591-023-02326-3

UC San Diego
School of Medicine

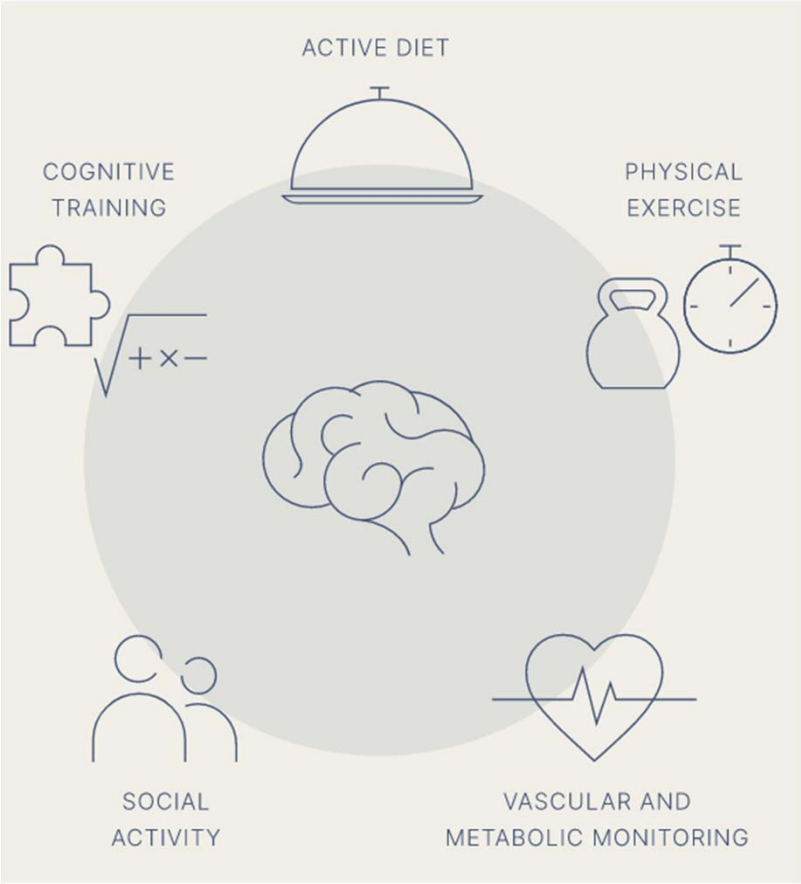
Lifestyle, brain aging and cognition

Brain health
Development
Education
Exercise
Diet
Cognitive activity
Social activity
Genetics

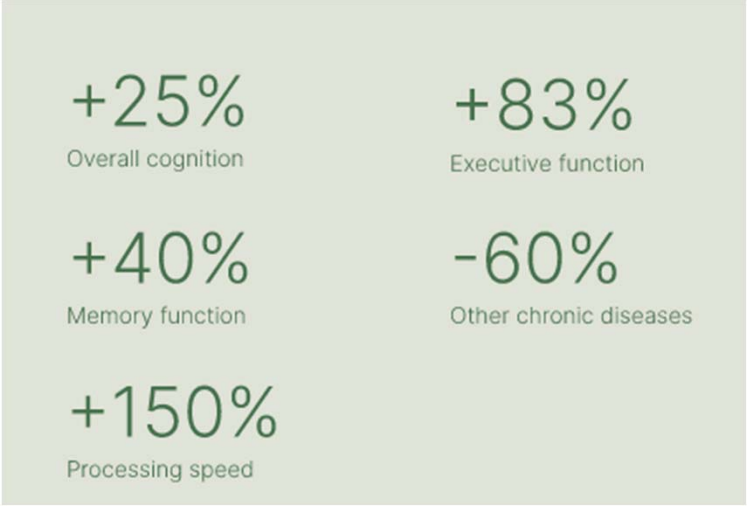
Age-related damage
Alzheimer's disease
Vascular disease
Medical illness
Poor sleep
Medications
The aging process



Finnish Geriatric Intervention Study to prevent Cognitive Impairment and Disability (FINGER)



Started in 2011
Enrolled 1260 people aged 60 – 77 based on a cardiovascular risk score
Randomized x 2 years
Outcome measures: cognition, general health



Plasma p-tau181 as an outcome and predictor of multidomain intervention effects: a secondary analysis of a randomised, controlled, dementia prevention trial

*Nicola Coley, Henrik Zetterberg, Christelle Cantet, Sophie Guyonnet, Nicholas J Ashton, Bruno Vellas, Kaj Blennow, Sandrine Andrieu for the MAPT study group**

	Multidomain intervention plus omega-3 (n=132)	Omega-3 (n=121)	Multidomain intervention (n=119)	Control (n=133)
Observed mean change from baseline	0·08 (−0·49 to 0·66)	0·27 (−0·44 to 0·98)	0·52 (−0·22 to 1·27)	−0·48 (−1·16 to 0·19)
Estimated unadjusted mean difference (95% CI) in change from baseline compared to control group	0·69 (−0·19 to 1·56)	0·83 (−0·07 to 1·72)	1·04 (0·13 to 1·94)	NA
p value*	0·13	0·11	0·075	..
Estimated mean difference (95% CI) in change from baseline compared to control group, adjusted for baseline p-tau, age, gender, and kidney function	0·63 (−0·23 to 1·49)	0·64 (−0·24 to 1·52)	0·89 (0·00 to 1·78)	NA
p value*	0·15	0·15	0·15	..
Estimated mean difference (95% CI) in change from baseline compared to control group, adjusted for baseline p-tau, age, gender, kidney function, and *APOE* genotype	0·65 (−0·21 to 1·51)	0·67 (−0·21 to 1·55)	0·91 (0·02 to 1·80)	NA
p value*	0·14	0·14	0·14	..

p-tau181=plasma tau phosphorylated at threonine 181. NA=not applicable. *Mean differences are estimated from a linear mixed model, and p values are adjusted for multiple comparisons using the Hochberg procedure.

Table 2: **Mean (95% CI) changes from baseline to 3 years in p-tau181 (pg/mL) by intervention group**

36 month multidomain intervention: Group-based cognitive training, advice and education on physical activity and nutrition, and an annual preventative consultation +/- omega-3.

No effect of intervention of longitudinal plasma p_Tau181

Coley N, et al, Lancet Healthy Longevity 2024

Summary

- Anti-amyloid antibodies can result in slowing of clinical progression in MCI/mild AD
- Leqembi is FDA and CMS-approved and donanemab awaits a hearing
- Blood-based biomarkers are starting to have clinical roll-out
- Additional clinical trials targeting amyloid, some targeting Tau, and one combination study. Are under way.
- A pipeline of drugs in development has many targets beyond amyloid and tau
- Lifestyle interventions show cognitive effects, but no clear impact on biomarkers
- There is progress and hope in Alzheimer therapeutics!

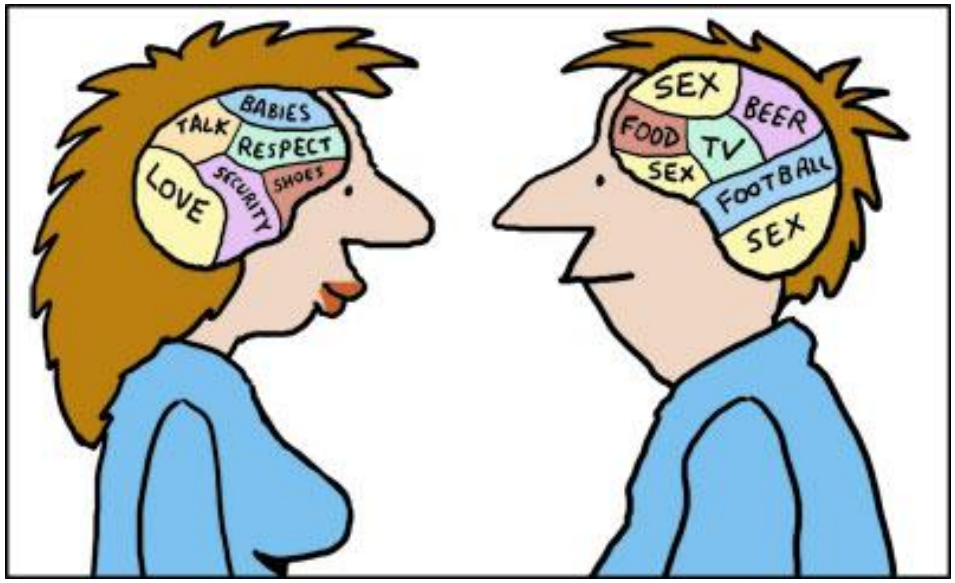
The Influence of Sex/Gender in Alzheimer's Disease

Erin Sundermann, PhD
Associate Professor of Psychiatry
University of California, San Diego
2024 Shiley Marcos ADRC Participant Appreciation Event

First, some terminology…

- Sex – Biological distinction of males versus females that primarily results from gonadal hormones and sex chromosome (XX vs. XY)
- Gender – a social construct referring to how one identifies themselves that can be influenced by environmental, social, and cultural factors

The female and male brains are unique



By Ellid Nadler of Toonpool.com

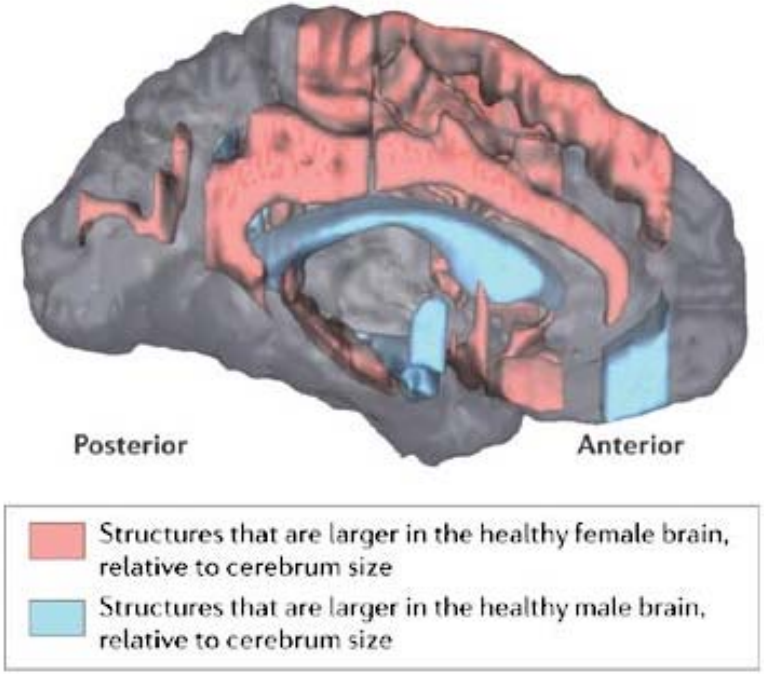
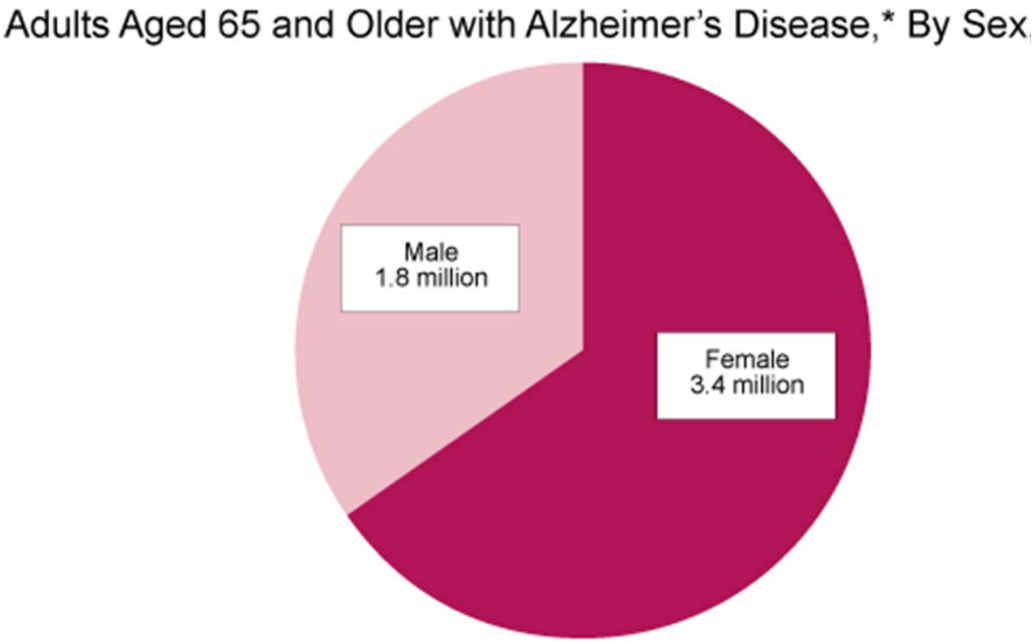


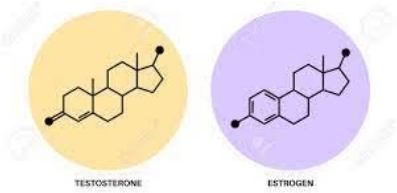
Image from Brainfacts.Org, May 2014

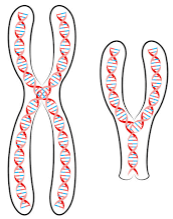
Women are 2/3 of Alzheimer's cases

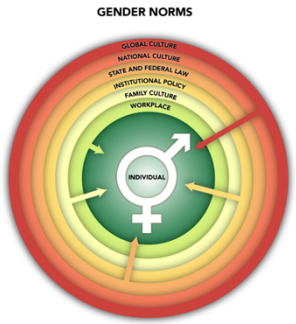


But why?

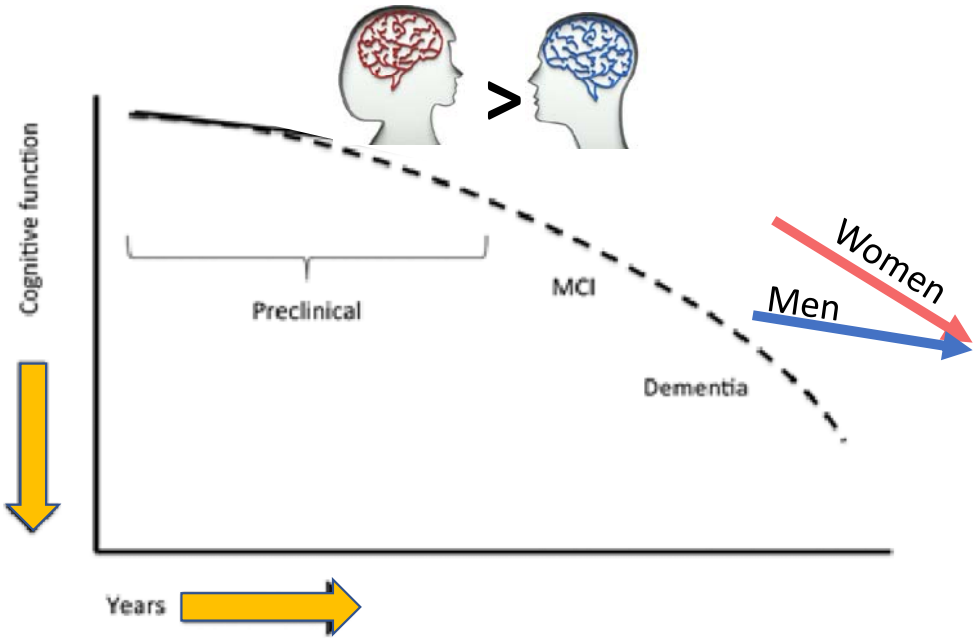
Sex/gender-related factors can provide clues

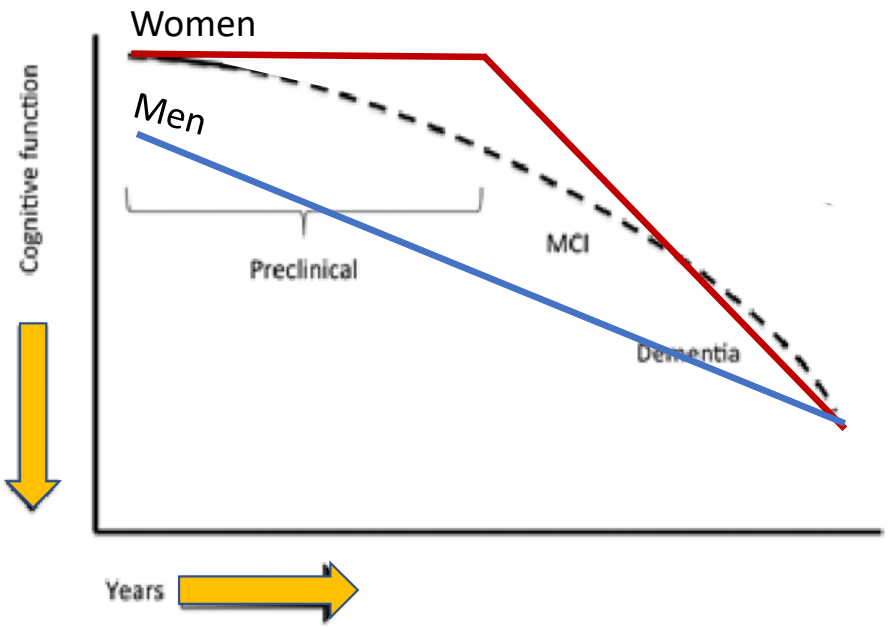






Sex differences in the symptom trajectory of AD





Sex differences in healthy cognition

Verbal memory

Visuospatial skills

Fine motor skills

Gross motor function

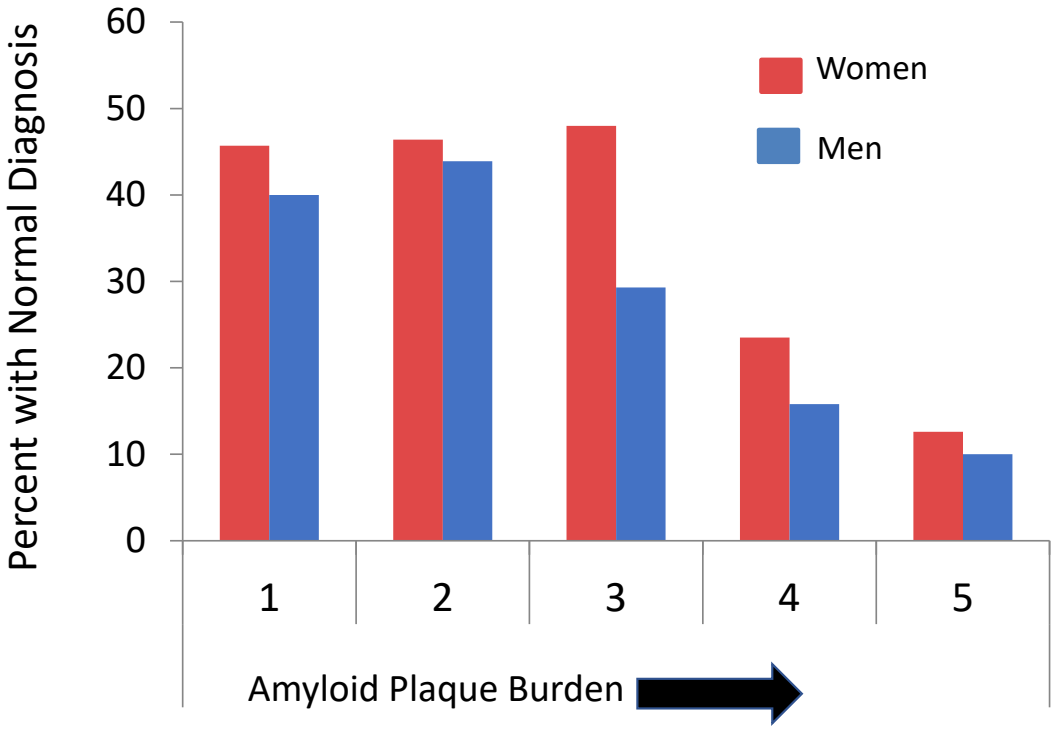
Information processing speed

Mathematical problem solving

Lets suppose you go shopping. I'm going to read a list of items for you to buy…….

drill
banana
jacket
apple
grapes
shirt
…

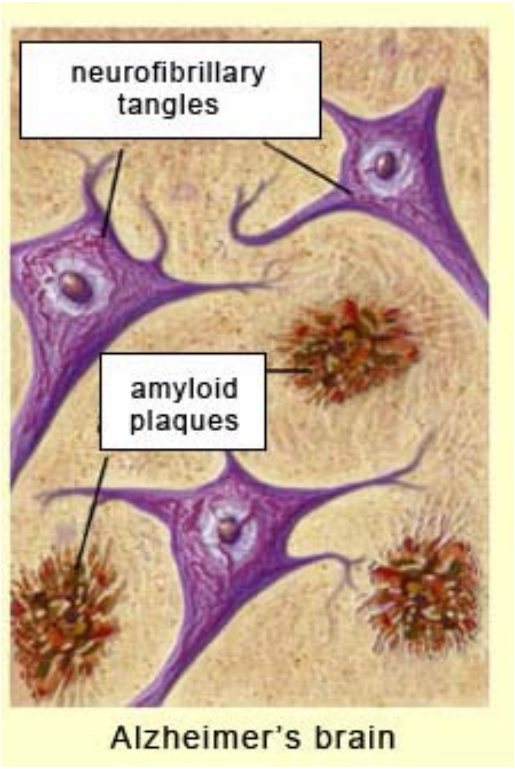
Female cognitive advantage in earlier pathology stages gives way to steeper decline in later stages



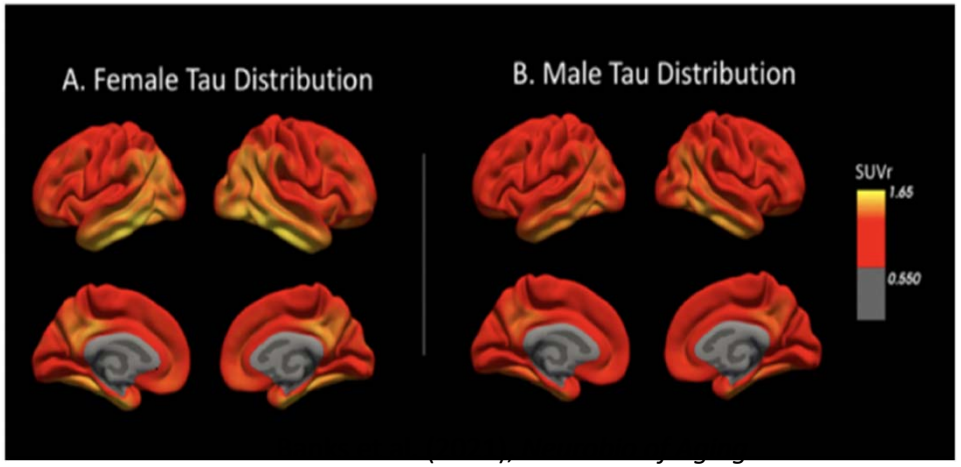
How to improve our ability to detect early-stage AD in women?

- Use of visual memory tests
- Applying sex-specific cut-scores to determine impairment on verbal memory tests
  - Leads to 10% ***more*** women diagnosed with MCI
  - Leads to 10% ***less*** men diagnosed with MCI

Sex differences in AD pathology: greater tau burden (tangles) in women



Alzheimer's brain



Tau, but not amyloid, pathology relates to cognitive function

WHY?...

Could inflammation be a culprit?

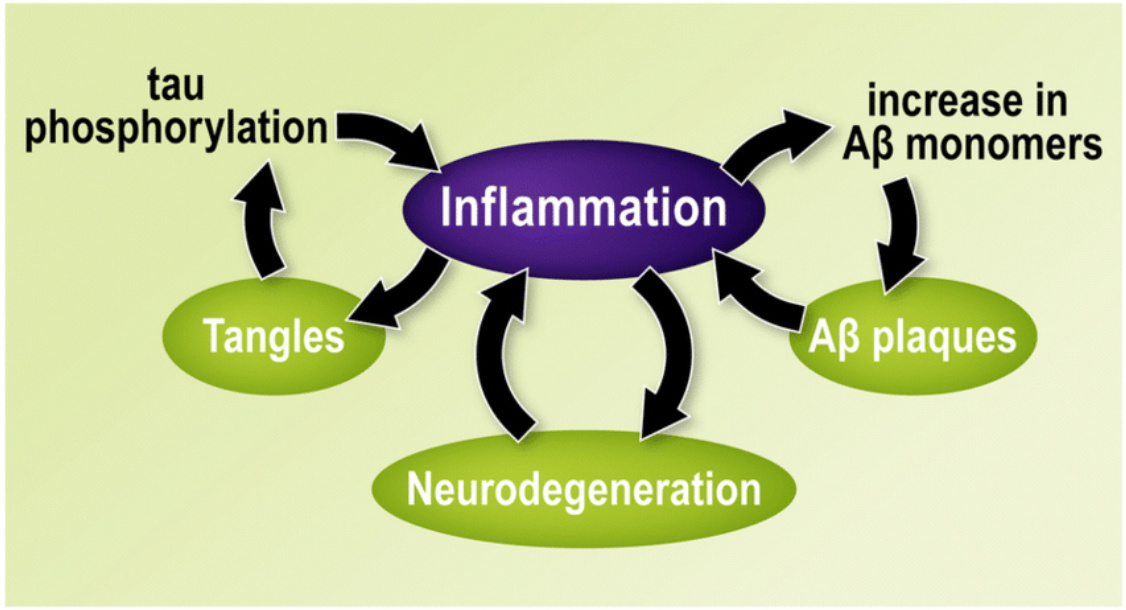
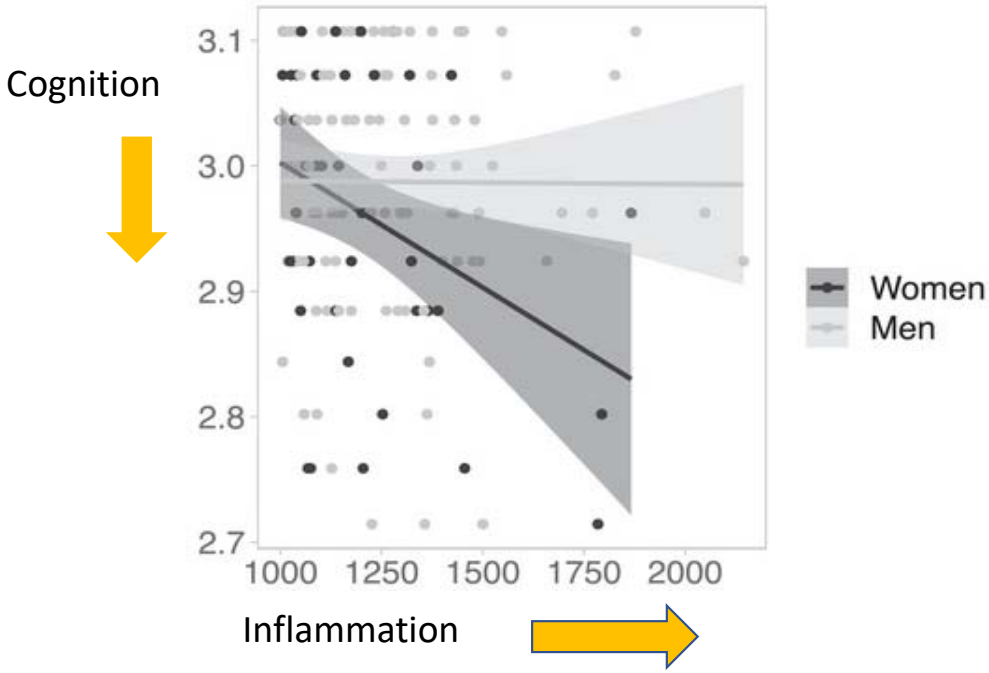


Image from Newcombe et al., 2018, Journal of Neuroinflammation

Could inflammation be a culprit?

Dr. Rachel Bernier

- Women show stronger relationships between neuroinflammatory markers and cognition than men
- The relationship between inflammation and cognition in women was accounted for by Tau



Bernier et al., 2022, *Alzheimer's & Dementia*

The Women: Inflammation & Tau Study (WITS)

- Could inflammation be the key to the greater tau in women, and could understanding that help us learn how to restrict or slow spread of tau?
- How do lifestyle factors that impact inflammation (physical activity, sleep, diet, vascular risk) contribute to the spread of Tau?

WITS
Women: Inflammation and Tau Study

UC San Diego

Led by Drs. Sarah Banks & Erin Sundermann

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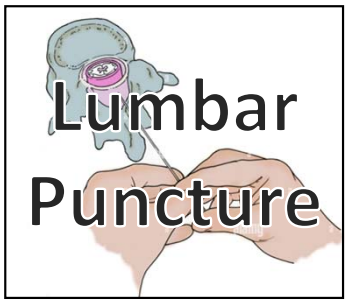

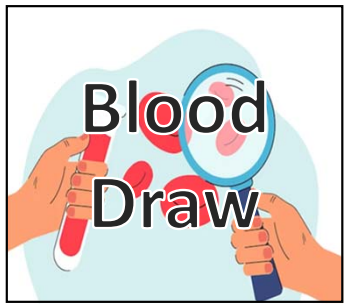

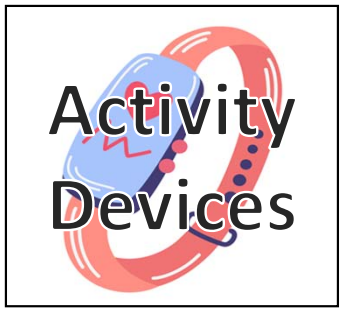

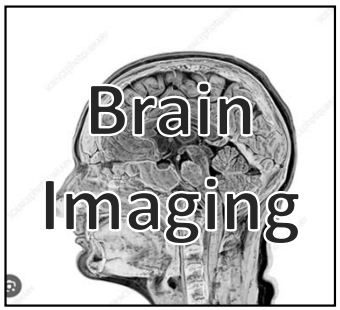

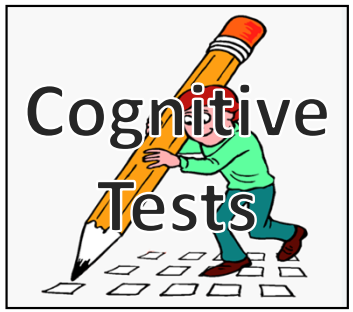

- Neuro-inflammatory
- AD pathology markers
- Sex Hormones
- Sleep Metrics, Sleep Apnea symptoms
- Physical activity
- MRI: Brain volume
- PET: Tau in the brain
- Verbal and visual memory, other cognitive domains

WITS
Women: Inflammation and Tau Study

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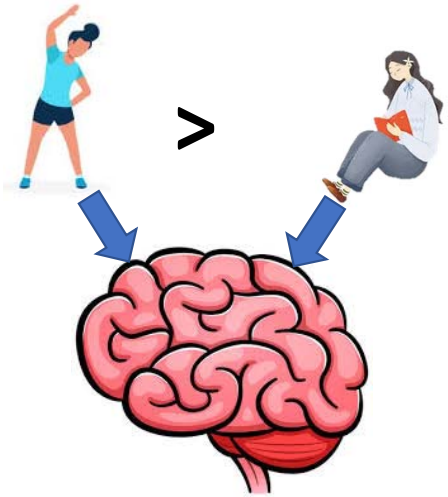
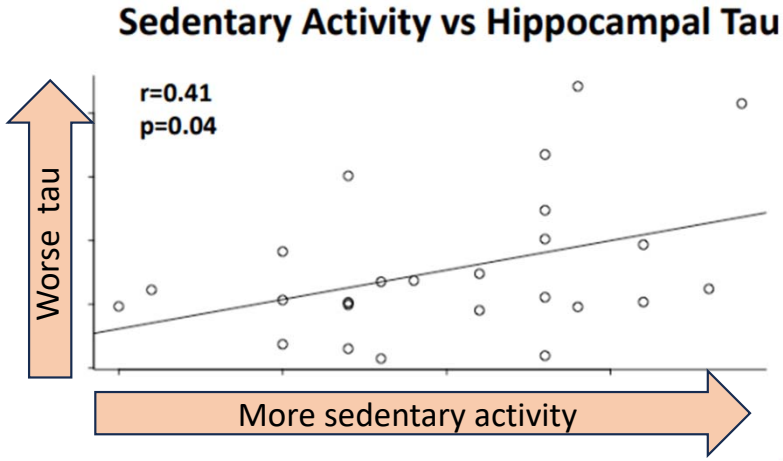
Emma Rice
UCSD School of Med

- WITS participants complete a questionnaire assessing weekly activities

- Responses classified as “Sedentary Activity” (ex: knitting, reading) or “Physical Activity” (ex: pickle ball, walking)





WITS
Women: Inflammation and Tau Study

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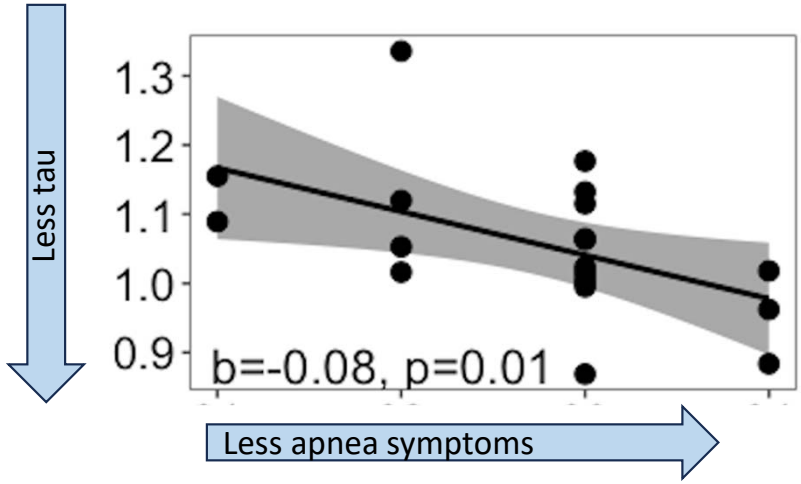
Kitty Lui
SDSU/UCSD
Clinical Psychology

- WITS participants complete a home sleep test measuring sleep apnea indices (e.g., oxygen saturation levels)
- 70% of 39 participants demonstrated at-least mild sleep apnea symptoms



WITS
Women: Inflammation and Tau Study

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WITS
Women: Inflammation and Tau Study

Prescription for Cognitively Healthy Aging