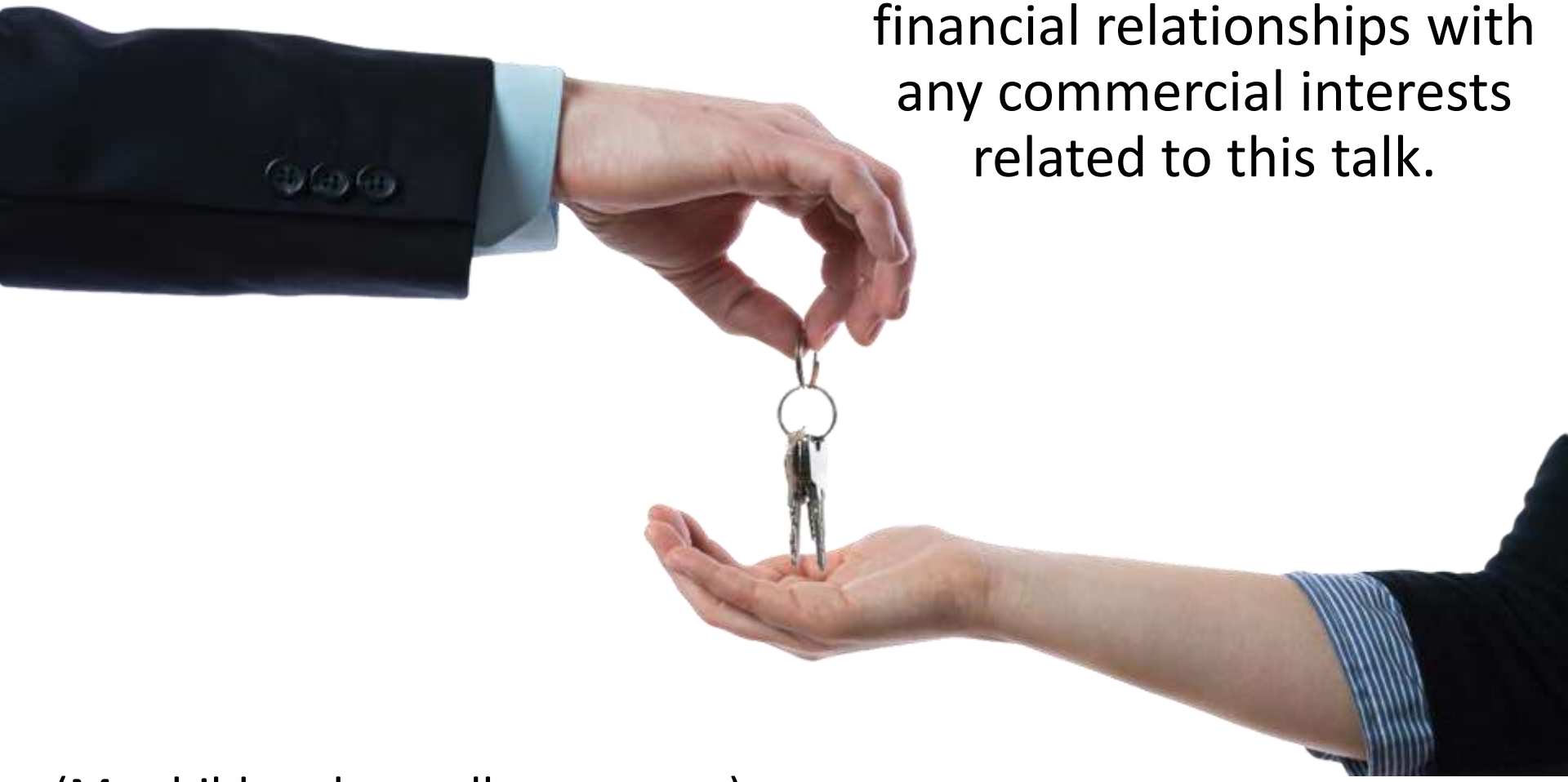
The Latest in Alzheimer's Disease Research: 2018

Bruno Giordani, PhD
Associate Director, Michigan Alzheimer's Disease Center
Senior Director, Mary A. Rackham Institute
Professor, Psychiatry, Neurology, Psychology, and School of Nursing
Board Member and Past Chair, Michigan Great Lakes Chapter, Alzheimer's Association

Disclosure of Financial Relationships

I do not have any relevant financial relationships with any commercial interests related to this talk.



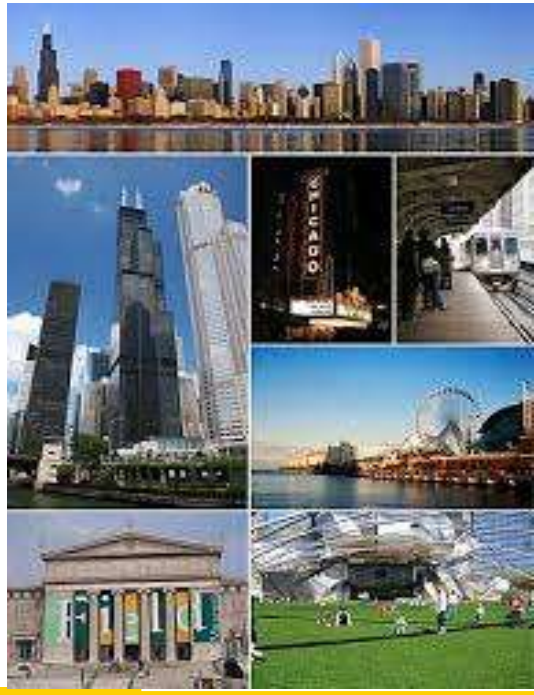
(My children have all my money)

Before We Go Any Further!

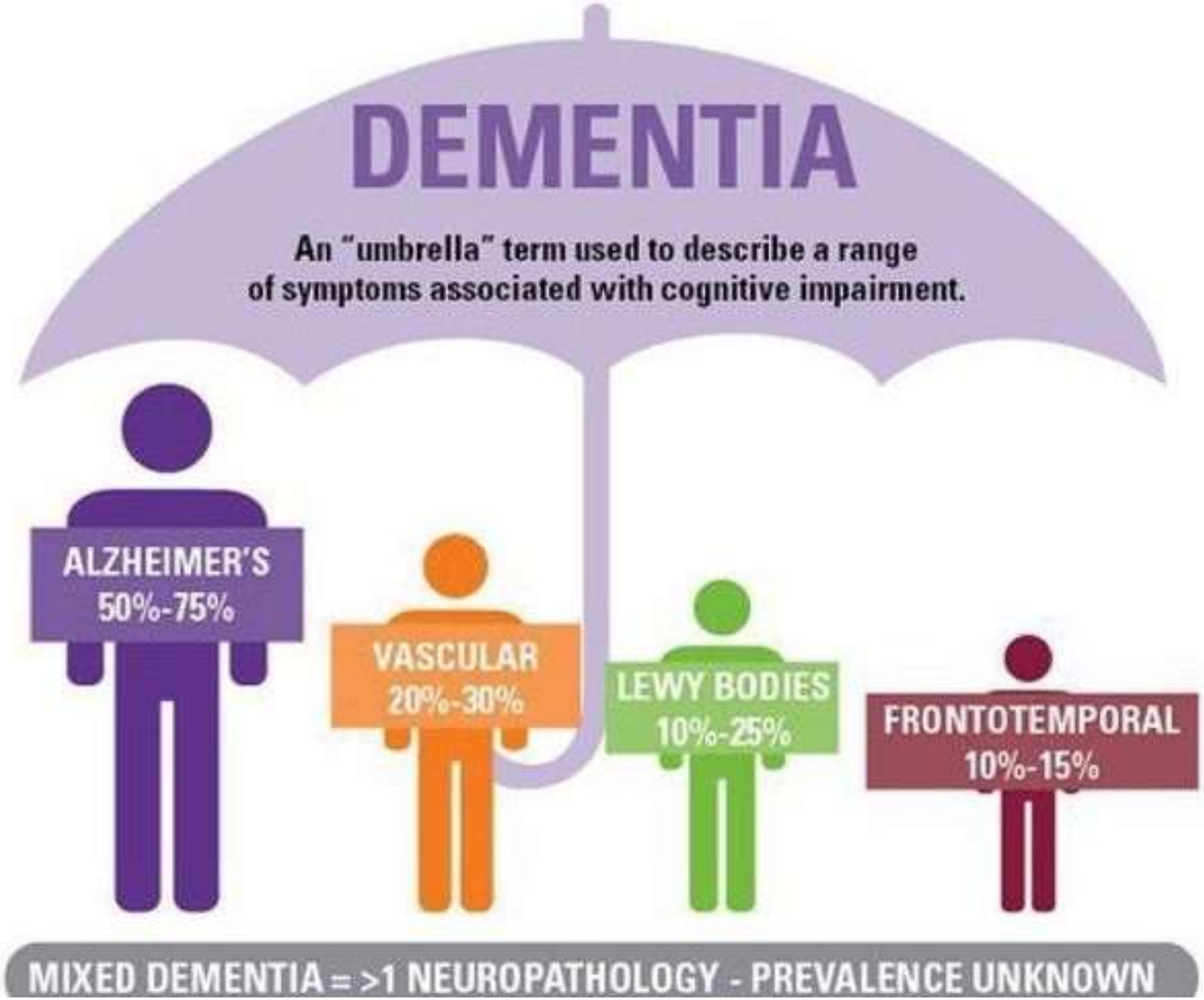
THANK YOU!

Tonight's Agenda

- The growing problem of Alzheimer's disease
- The science of Alzheimer's disease
- How advocacy and fundraising impact research
- The latest research from the Alzheimer's Association International Conference (July 2018)
- Local research opportunities



What is Alzheimer's disease?



Growth of AD in the USA

No known way to stop, slow, or prevent this disease

ALZHEIMER'S STATISTICS

MICHIGAN

HOSPICE (2015)

8,247

# of people in hospice with a primary diagnosis of dementia

16%

of people in hospice have a primary diagnosis of dementia

HOSPITALS (2015)

1,598

# of emergency department visits per 1,000 people with dementia

23.4%

dementia patient hospital readmission rate

NUMBER OF DEATHS FROM ALZHEIMER'S DISEASE (2015)

3,771

6th *leading cause of death in Michigan*

129% *increase in Alzheimer's deaths since 2000*

CAREGIVING (2017)

514,000
Number of Caregivers

586,000,000
Total Hours of Unpaid Care

$7,395,000,000
Total Value of Unpaid Care

$363,000,000
Higher Health Costs of Caregivers

65+ NUMBER OF PEOPLE AGED 65 AND OLDER WITH ALZHEIMER'S BY AGE*

* *Totals may not add due to rounding*

Year	65-74	75-84	85+	TOTAL
2018	28,000	78,000	79,000	180,000
2020	30,000	82,000	80,000	190,000
2025	34,000	100,000	85,000	220,000

Estimated percentage change

MEDICAID

$1.368 BILLION
Medicaid costs of caring for people with Alzheimer's (2018)

24.8%
change in costs from 2018 to 2025

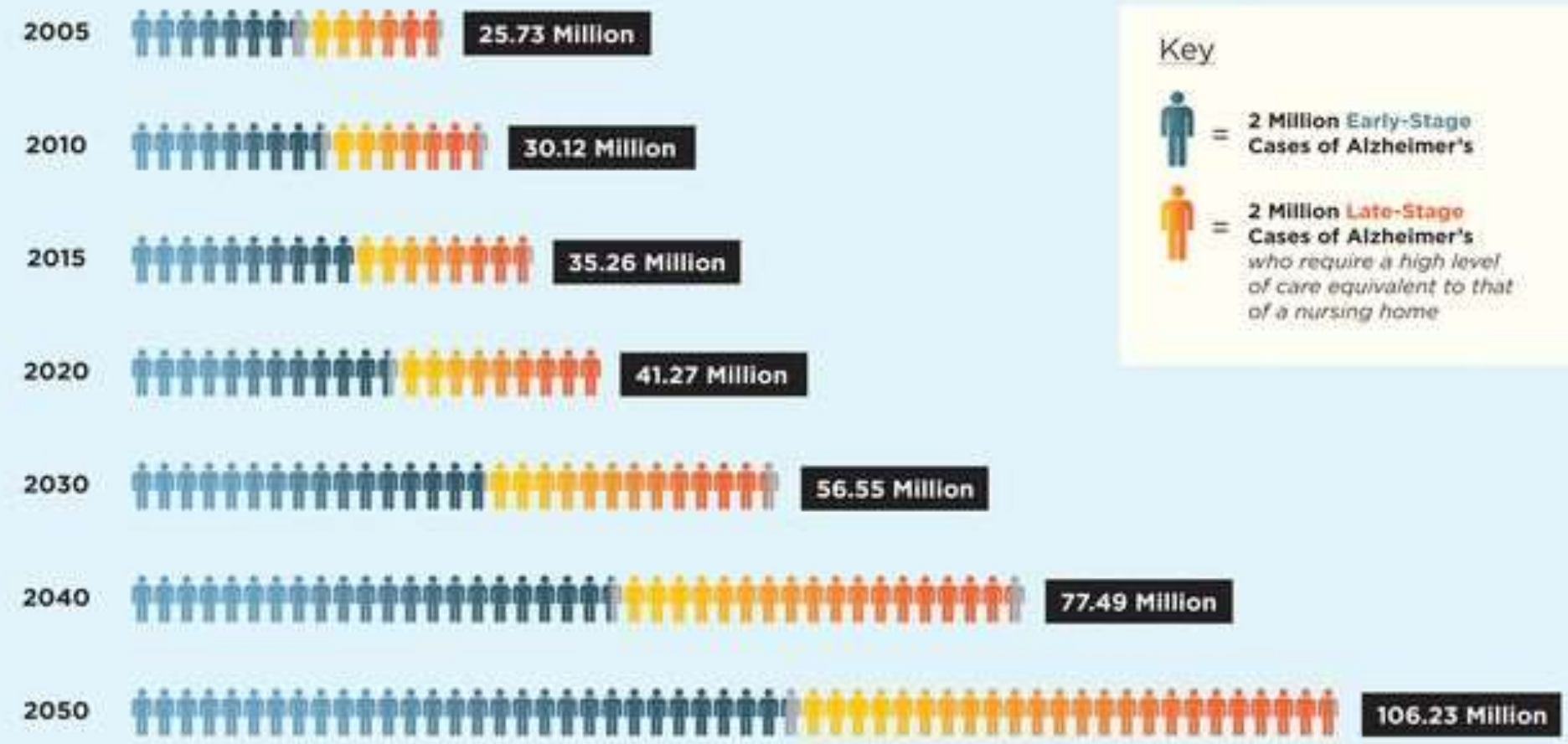
MEDICARE

$26,717
per capita Medicare spending on people with dementia (2017)

AIM
ALZHEIMER'S IMPACT MOVEMENT
alzheimer's association

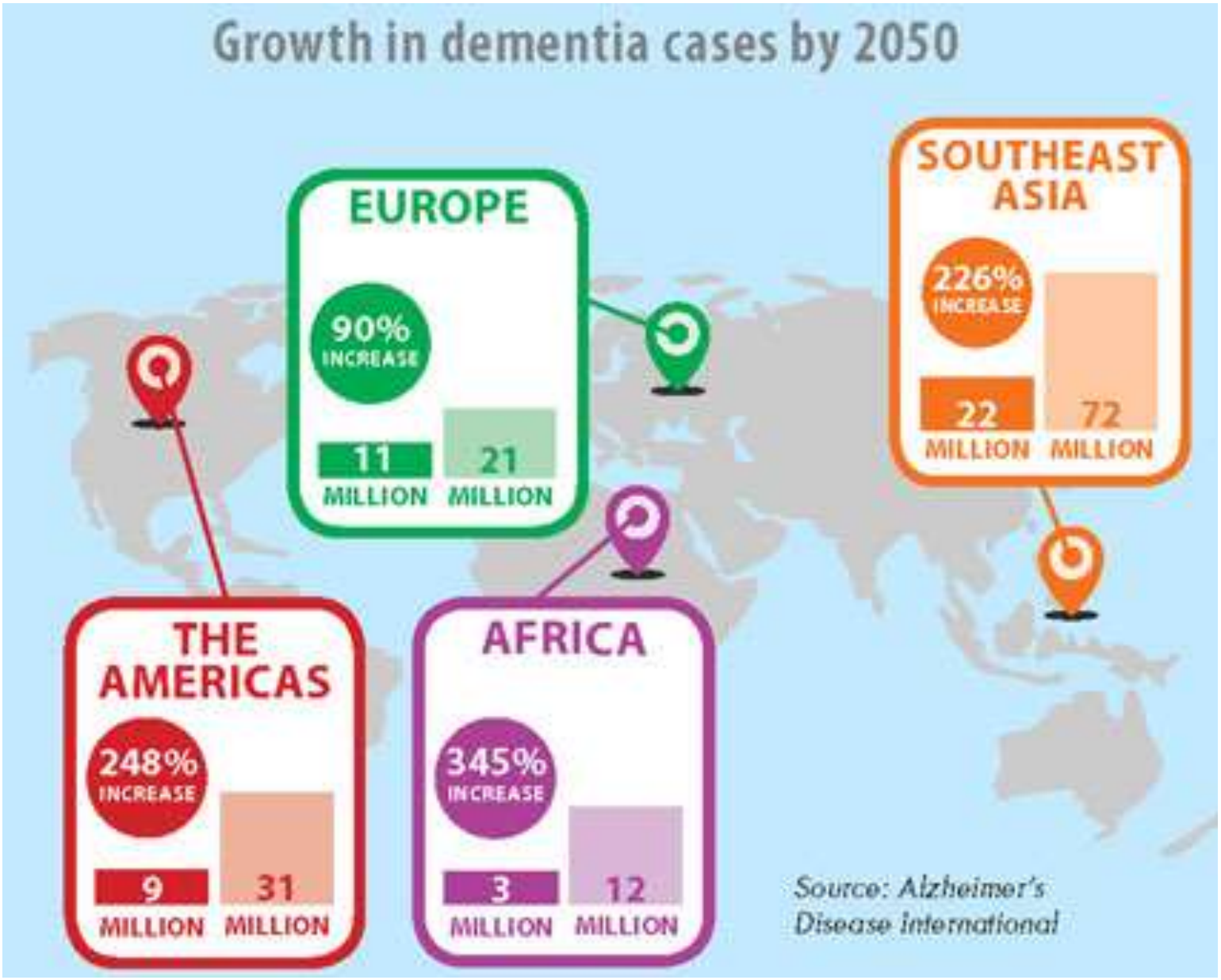
WORLDWIDE PROJECTIONS OF ALZHEIMER'S PREVALENCE

FOR THE YEARS 2005–2050, BY STAGE OF DISEASE (IN MILLIONS)



Adapted from "Forecasting the global burden of Alzheimer's disease," by Ron Brookmeyer, Elizabeth Johnson, Kathryn Ziegler-Graham, and H. Michael Arrighi, 2007, Alzheimer's & Dementia, volume 3, p. 189. Copyright 2007 by The Alzheimer's Association.

Global Growth of AD



Symptoms of Alzheimer's Disease

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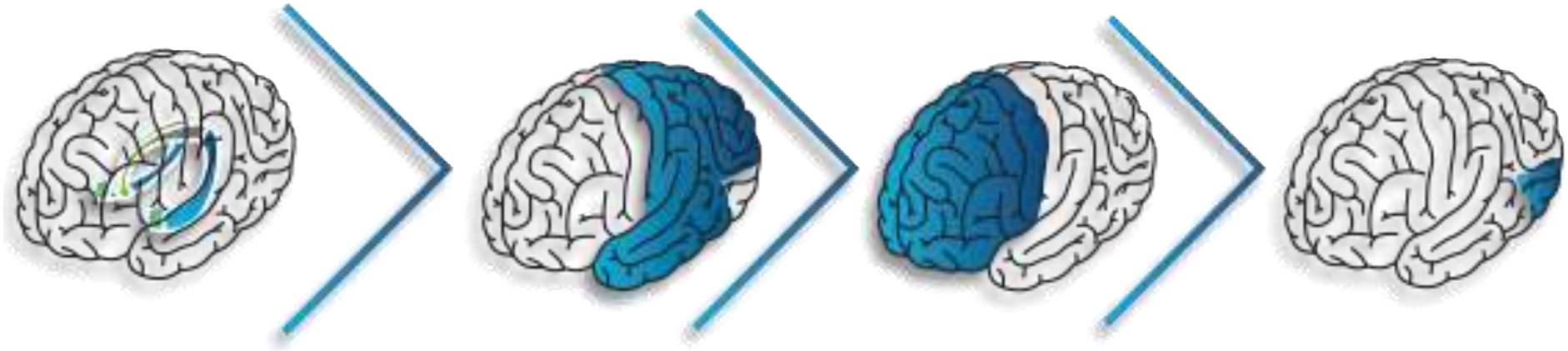
Progression of Alzheimer's Disease



Mild Cognitive Impairment

Duration: 7 years

Disease begins in Medial Temporal Lobe

Symptoms:
- Short-term memory loss

Mild Alzheimer's

Duration: 2 years

Disease spreads to Lateral Temporal & Parietal Lobes

Symptoms include:
- Reading problems
- Poor object recognition
- Poor direction sense

Moderate Alzheimer's

Duration: 2 years

Disease spreads to Frontal Lobe

Symptoms include:
- Poor judgment
- Implusivity
- Short attention

Severe Alzheimer's

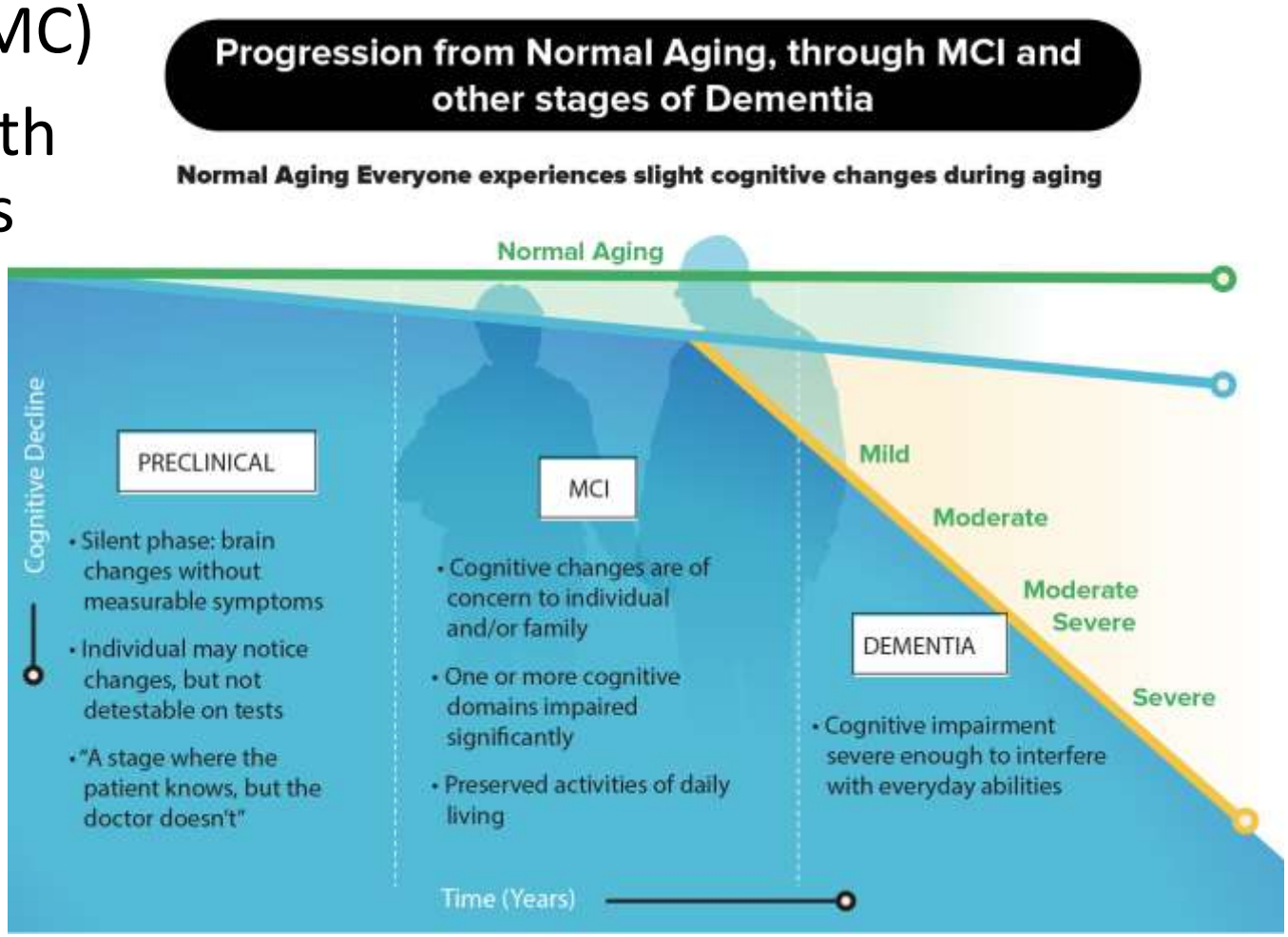
Duration: 3 years

Disease spreads to Occipital Lobe

Symptoms include:
- Visual problems

Earliest Signs of Problems

- Subjective Memory Complaint (SMC)
- Difficulties with daily activities



Brain Facts

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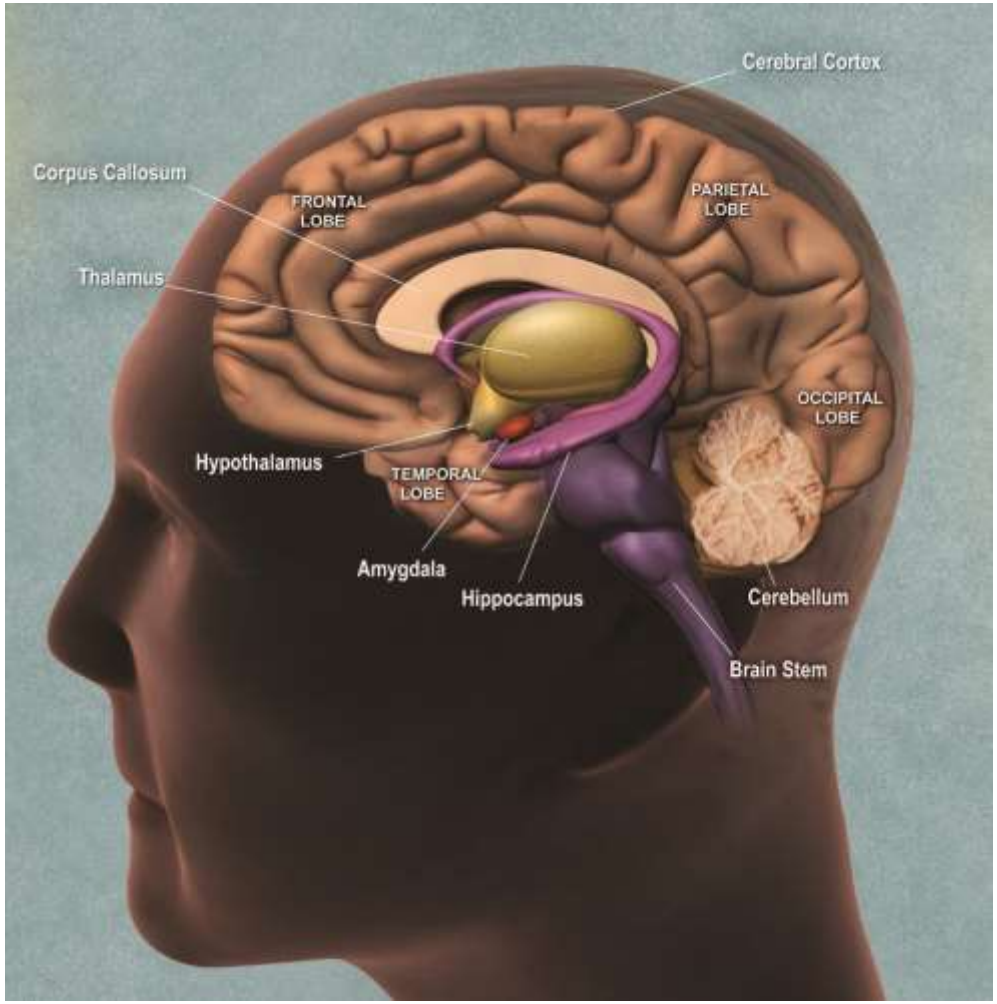
The Brain's Vital Statistics

Adult Weight:
About 3 pounds

Adult Size:
A medium cauliflower

Brain represents 1 to 1.5% of the body's mass, yet needs 20% of the oxygen we breathe

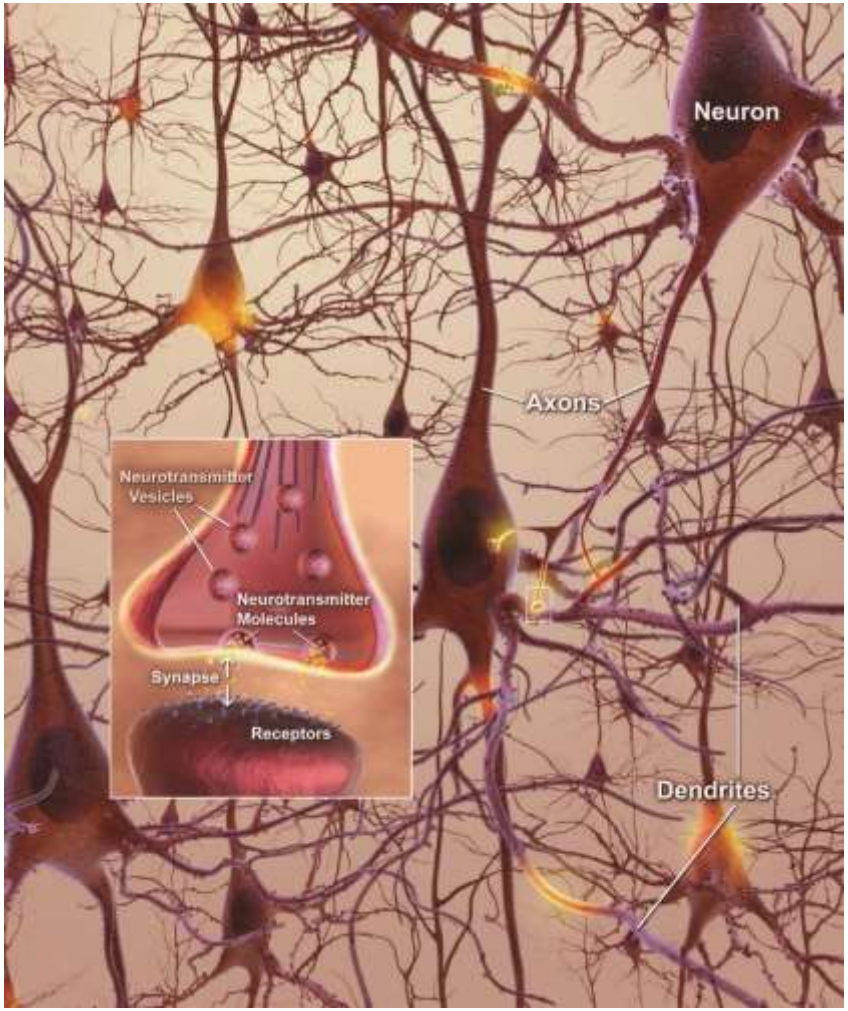


Inside the Brain: Neurons

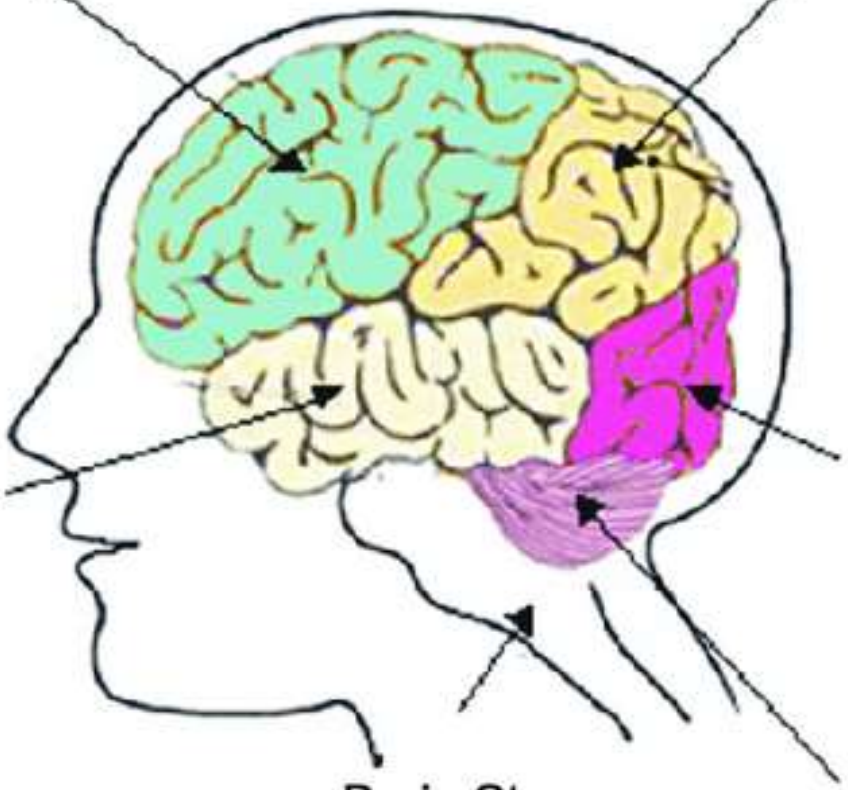
The brain has over a billion neurons, each with an axon and many dendrites

Number of synapses (gap between axons): over 100 trillion

To stay healthy, neurons must communicate with each other and repair themselves



Brain Mind Relation



Frontal Lobe

Planning
Reasoning
Problem solving
Morality
Personality
Social Skills
Recognising and
Regulating Emotions
Motor Functions
Motor speech area
of Broca

Parietal Lobe

Recognising sensation,
body position and objects
Sense of time and space
Reading and Comprehension area
Association between
functions of other
lobes

Temporal Lobe

Understanding
Language
Hearing
Speach
Memory
Learning
Sensory speech area
of Wernicke

Occipital Lobe

Vision and Integrating
visual information
(colour, shape and
distance)

Brain Stem

Regulation of heart
beats, respiration,
body temperature
and other essential
body functions

Cerebellum

Balance
Muscular co-ordination

What Happens in the Brain with AD?

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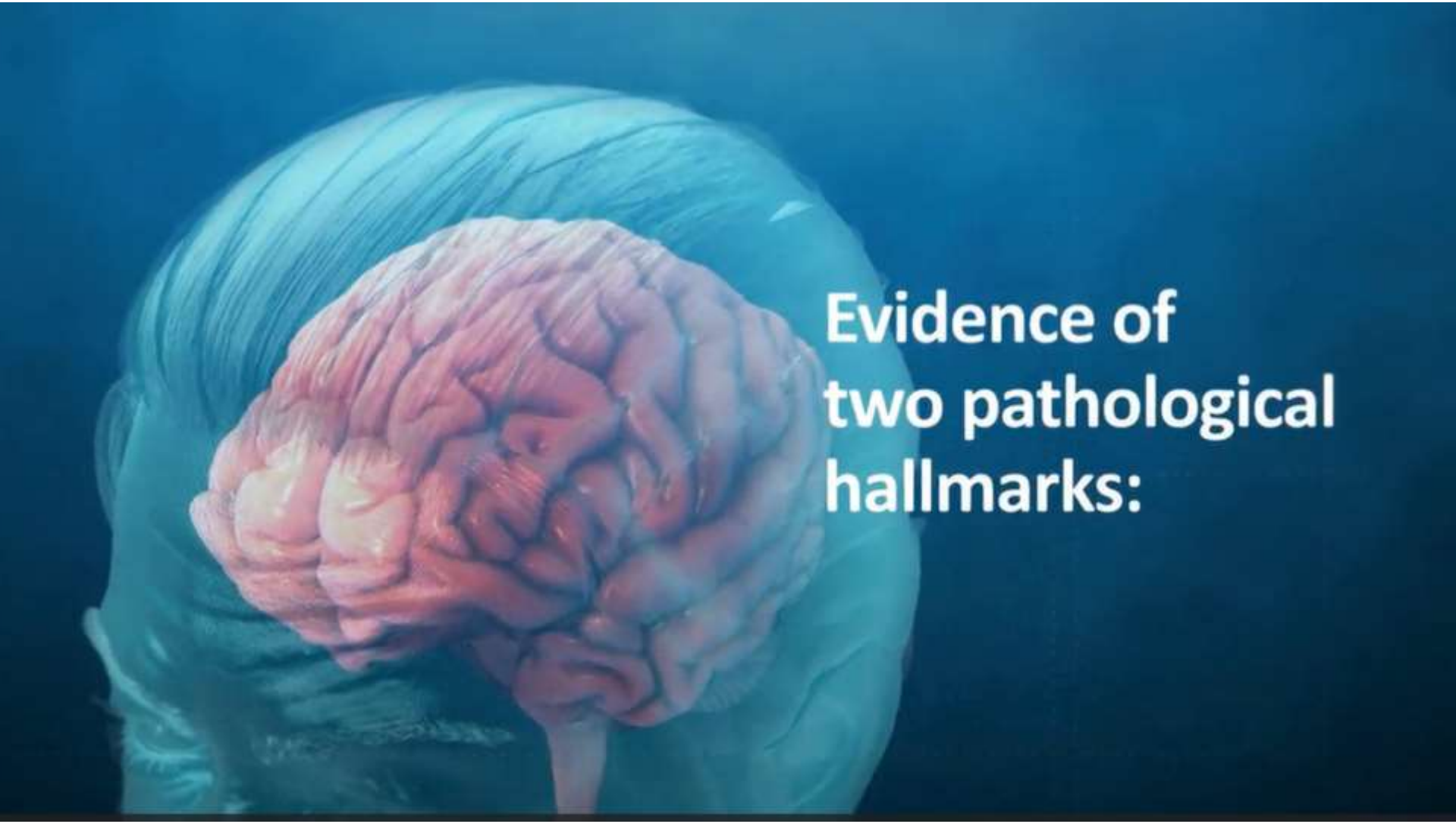
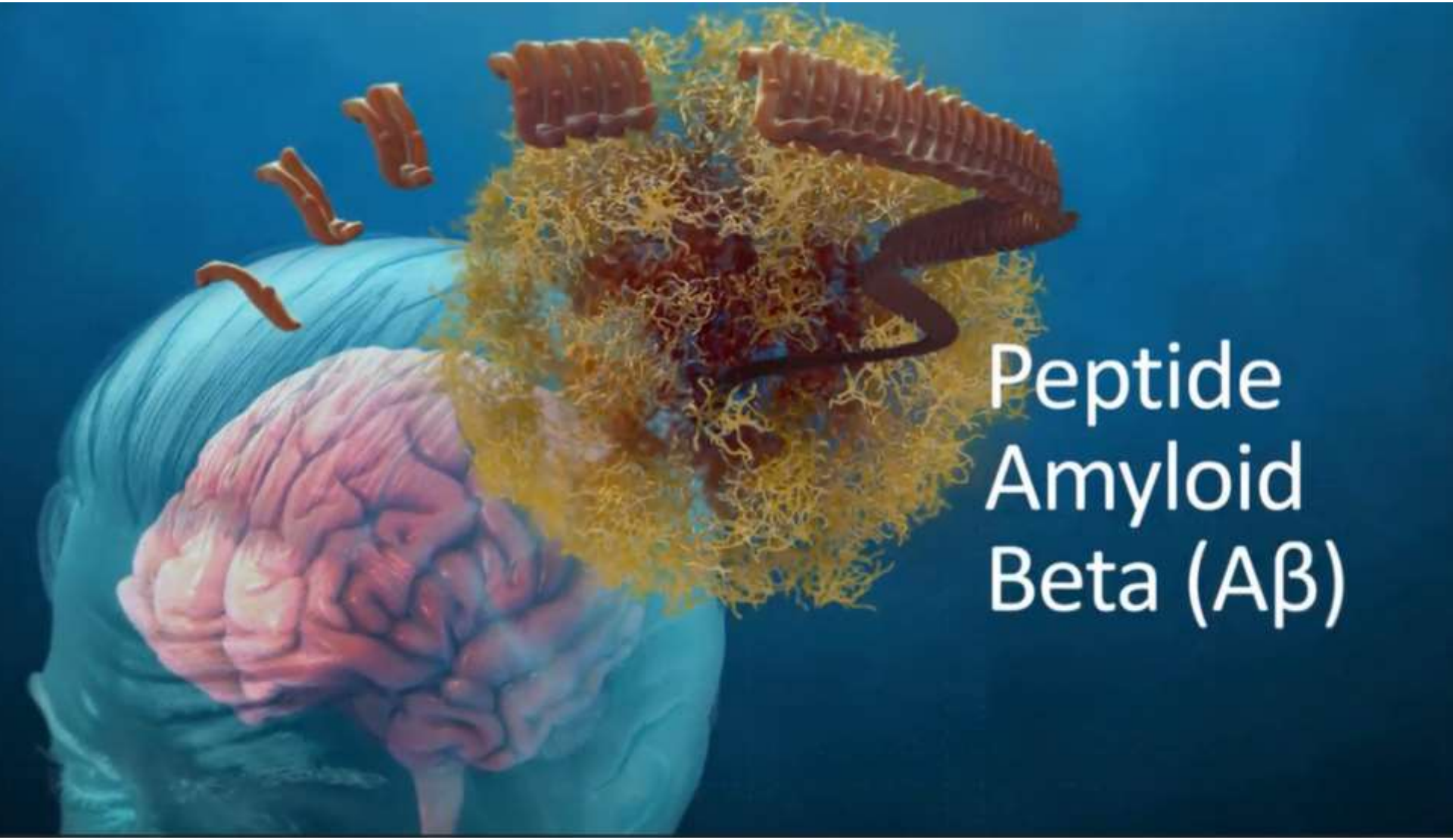
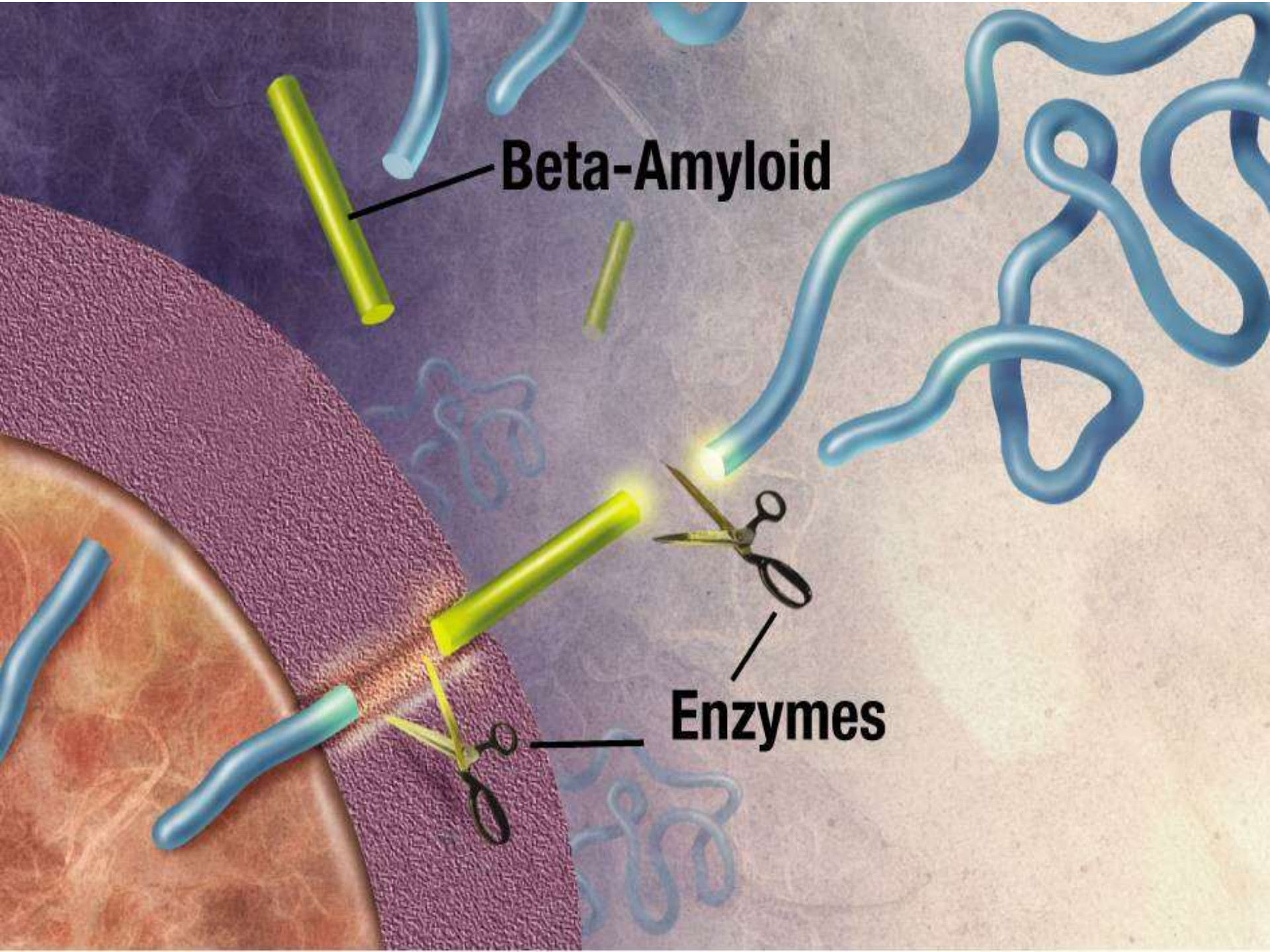
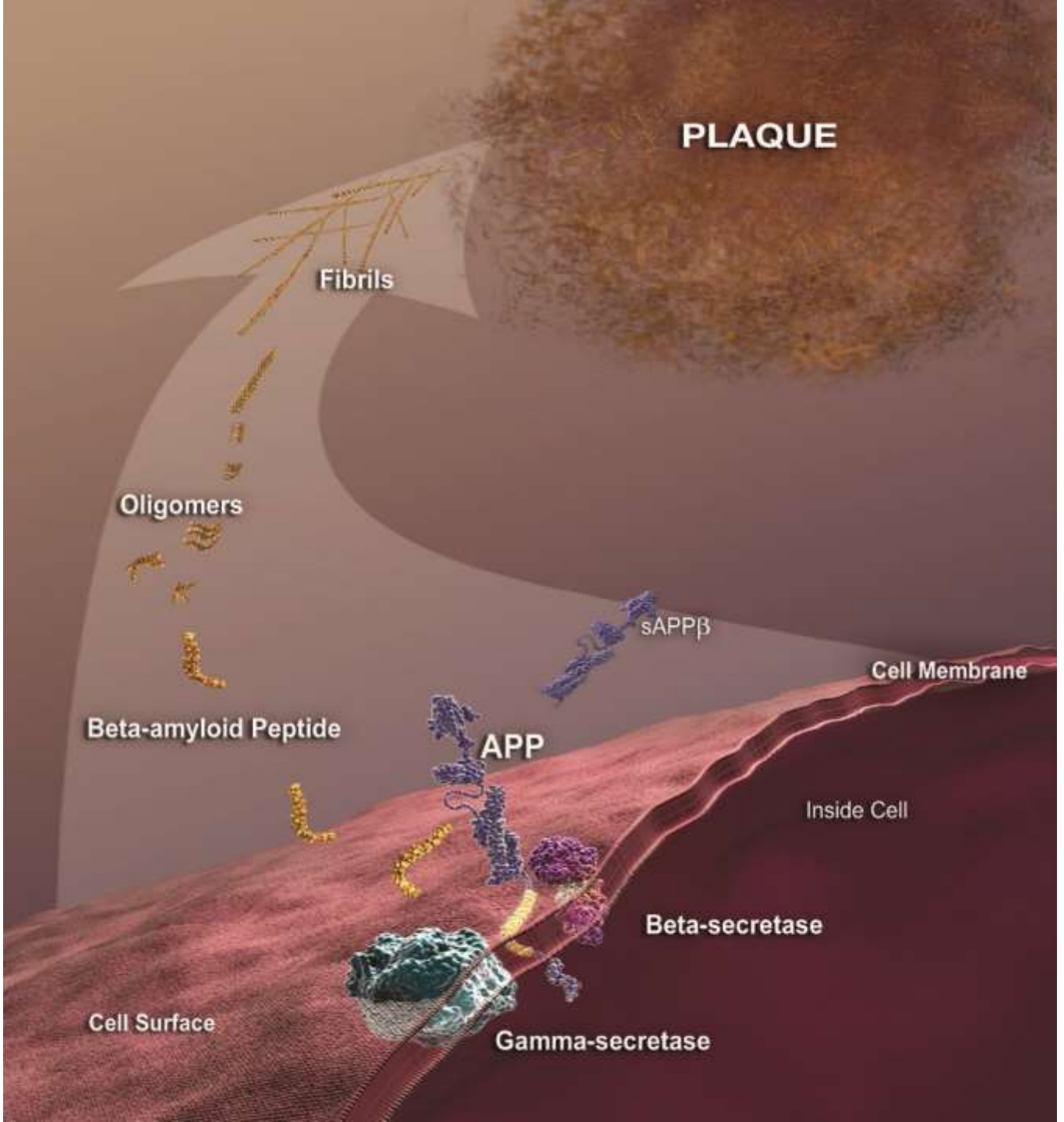
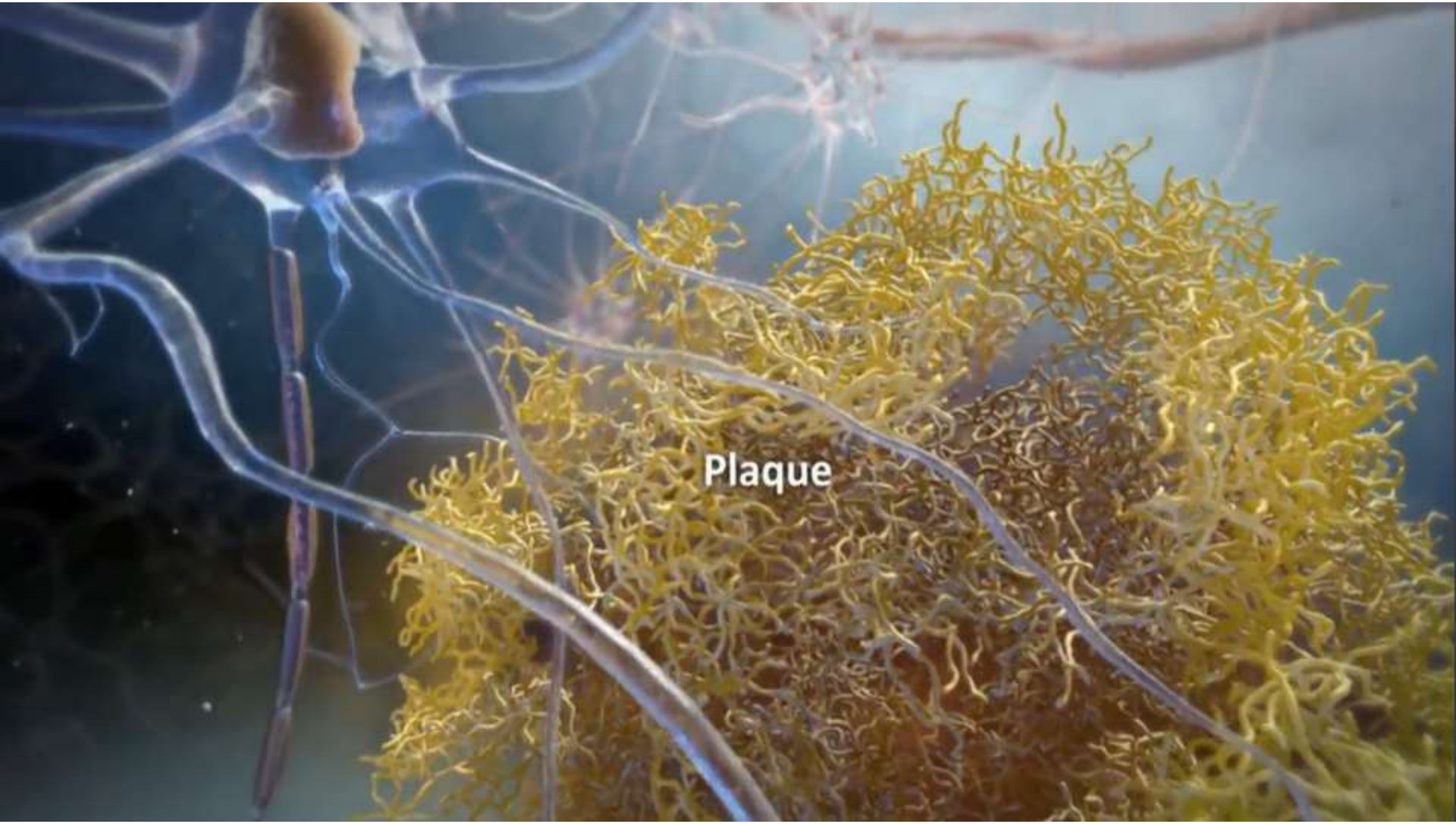
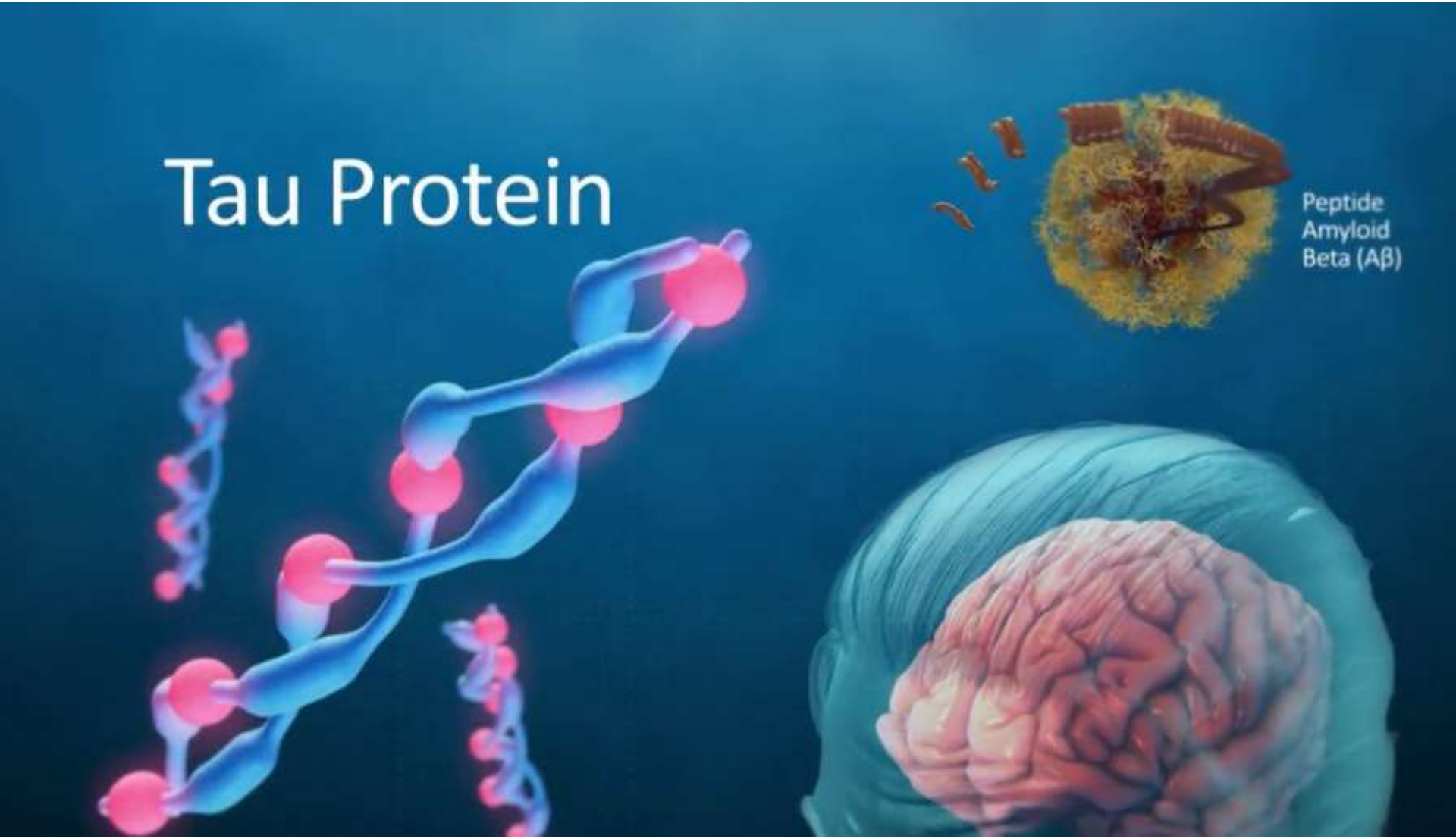

Evidence of
two pathological
hallmarks:

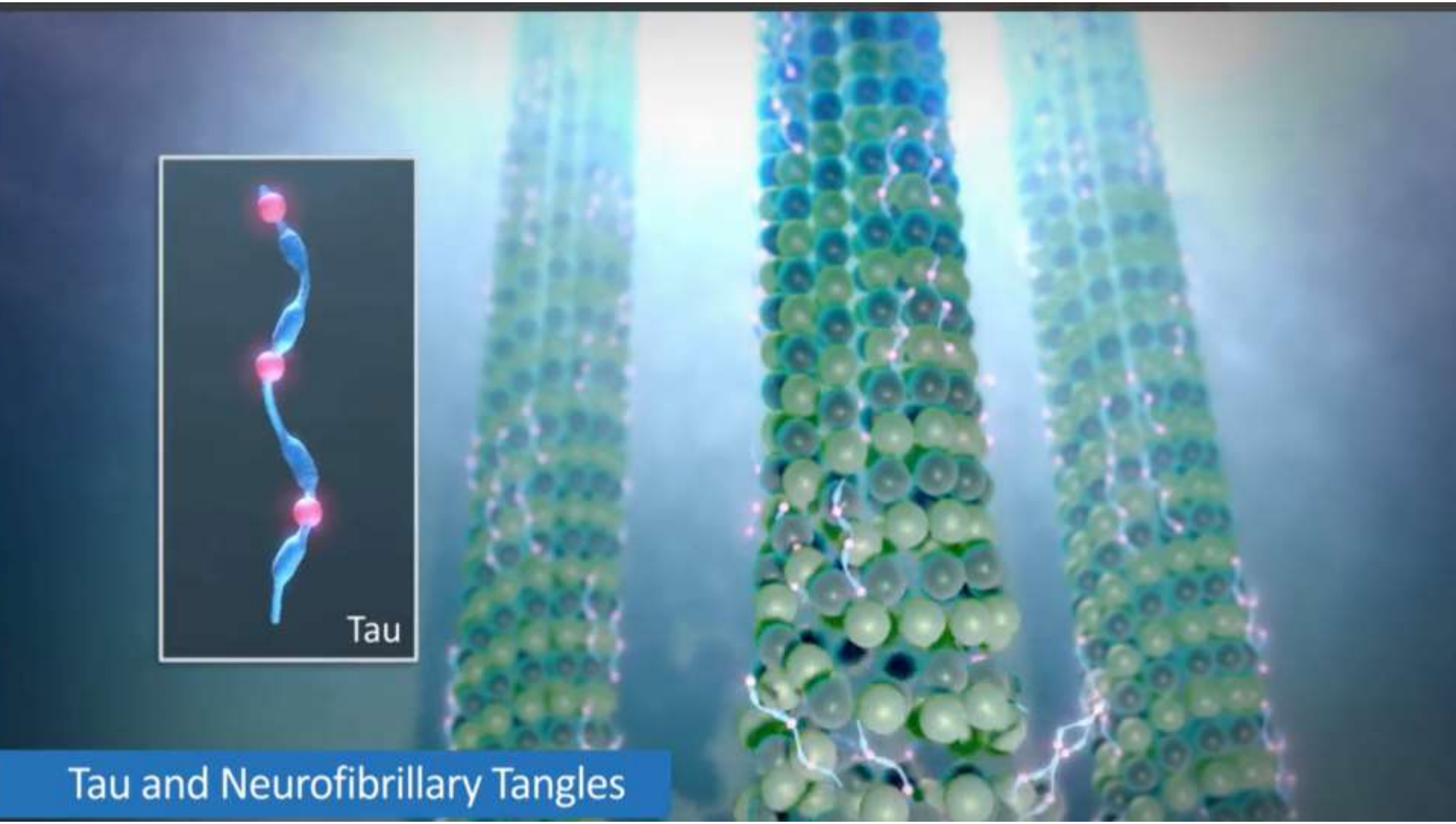

Peptide
Amyloid
Beta (Aβ)

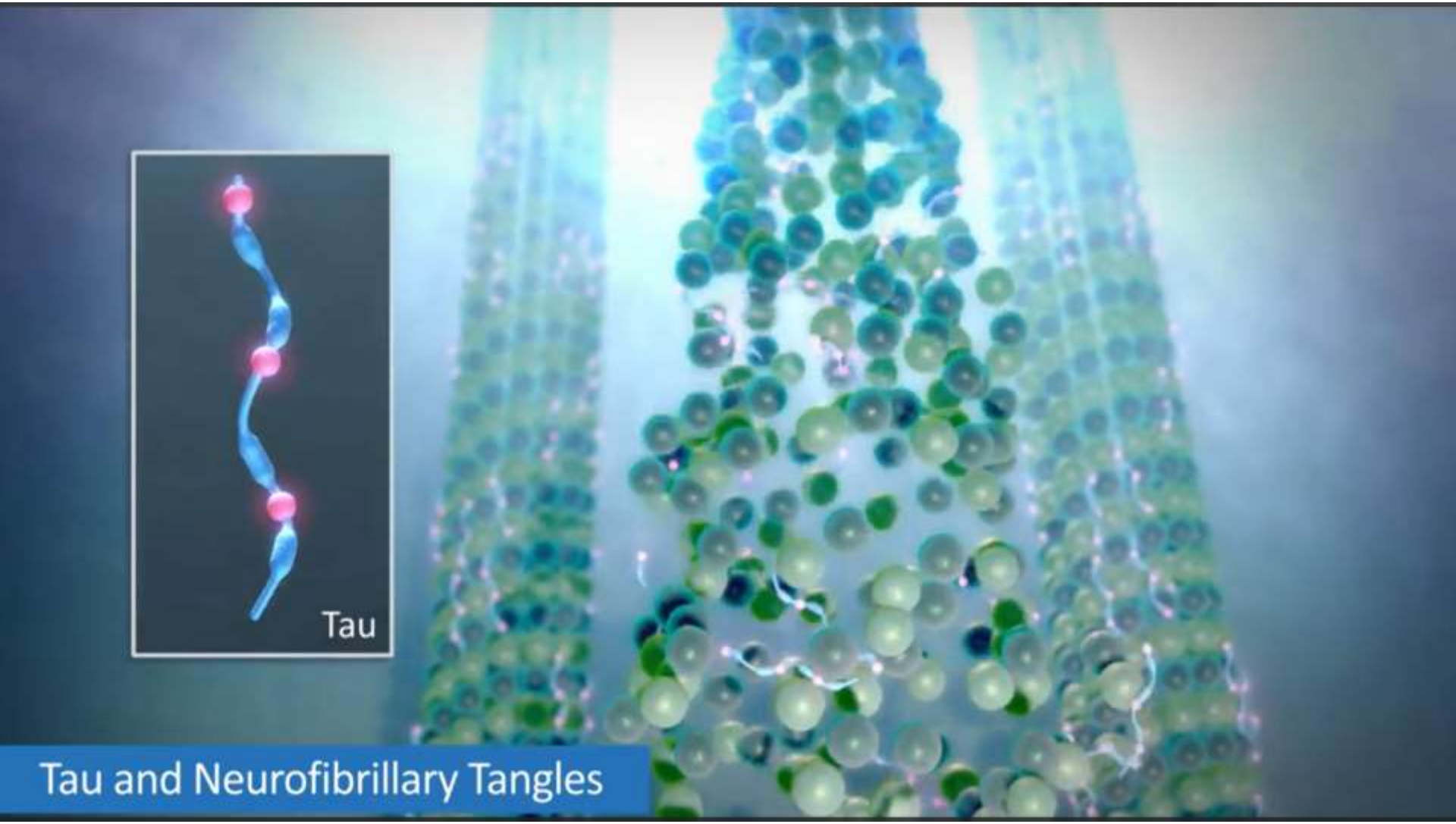

Beta-Amyloid
Enzymes

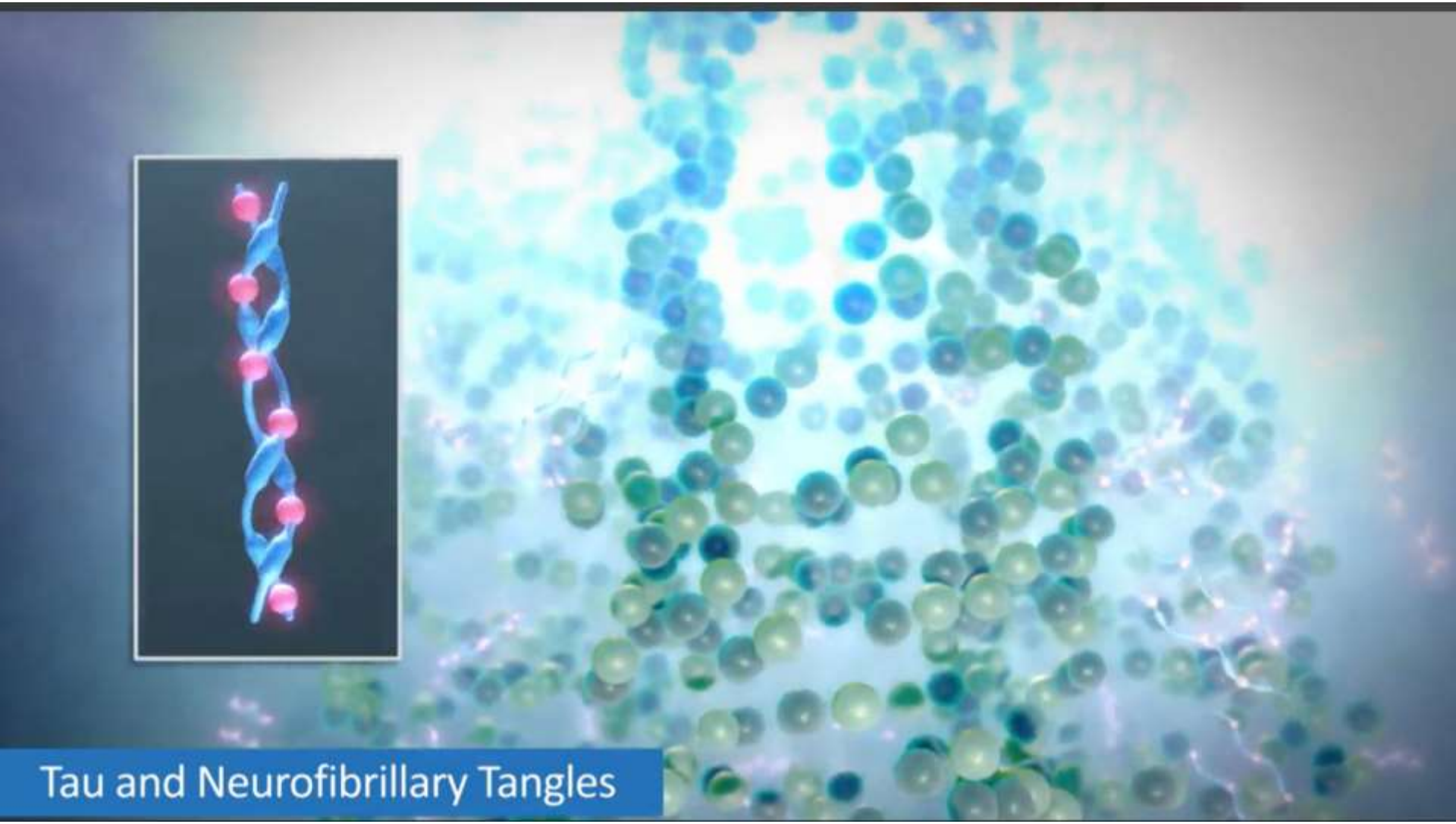

PLAQUE
Fibrils
Oligomers
Beta-amyloid Peptide
sAPPβ
APP
Cell Membrane
Inside Cell
Beta-secretase
Gamma-secretase
Cell Surface

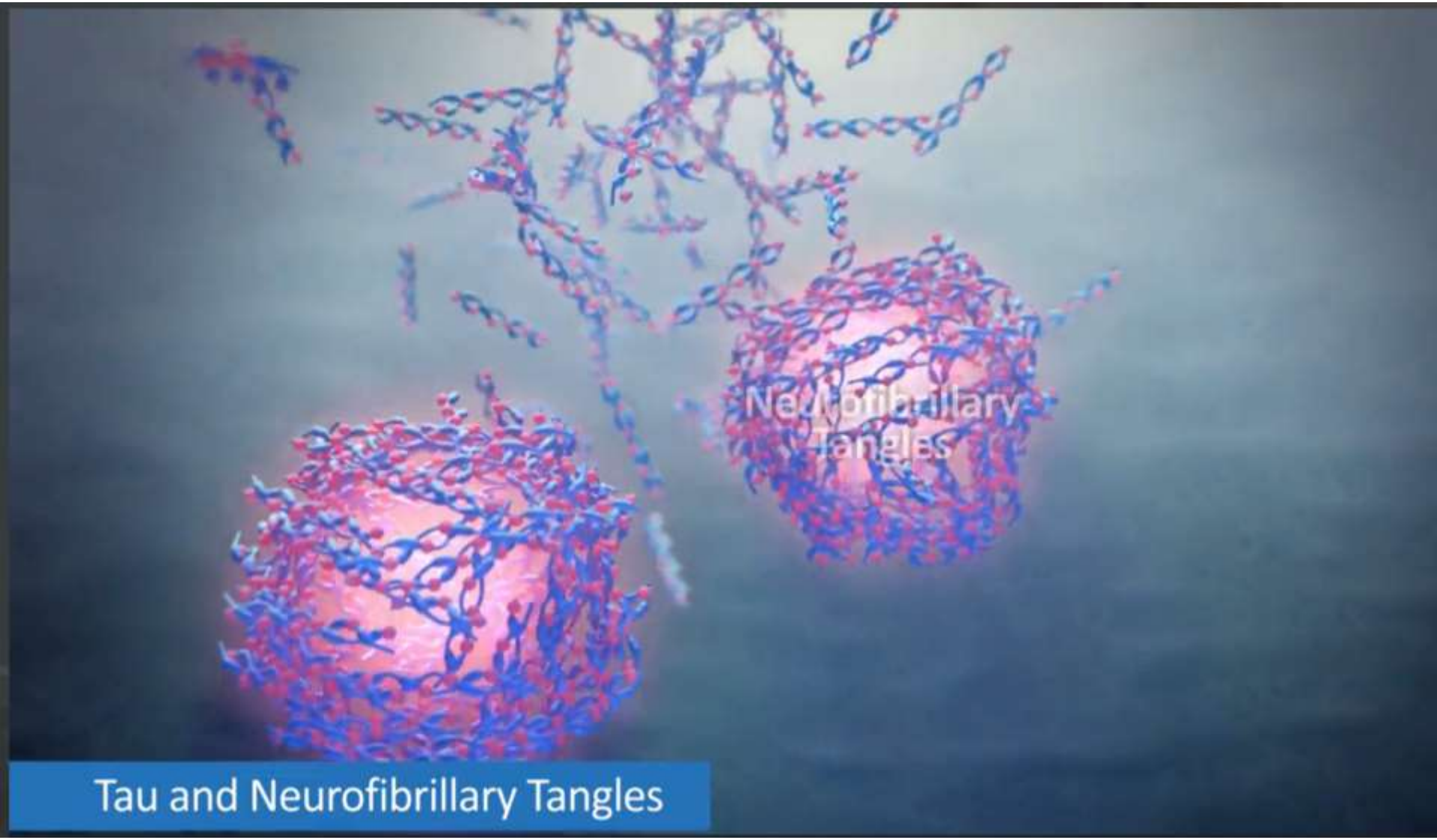

Plaque


Tau Protein
Peptide
Amyloid
Beta (Aβ)

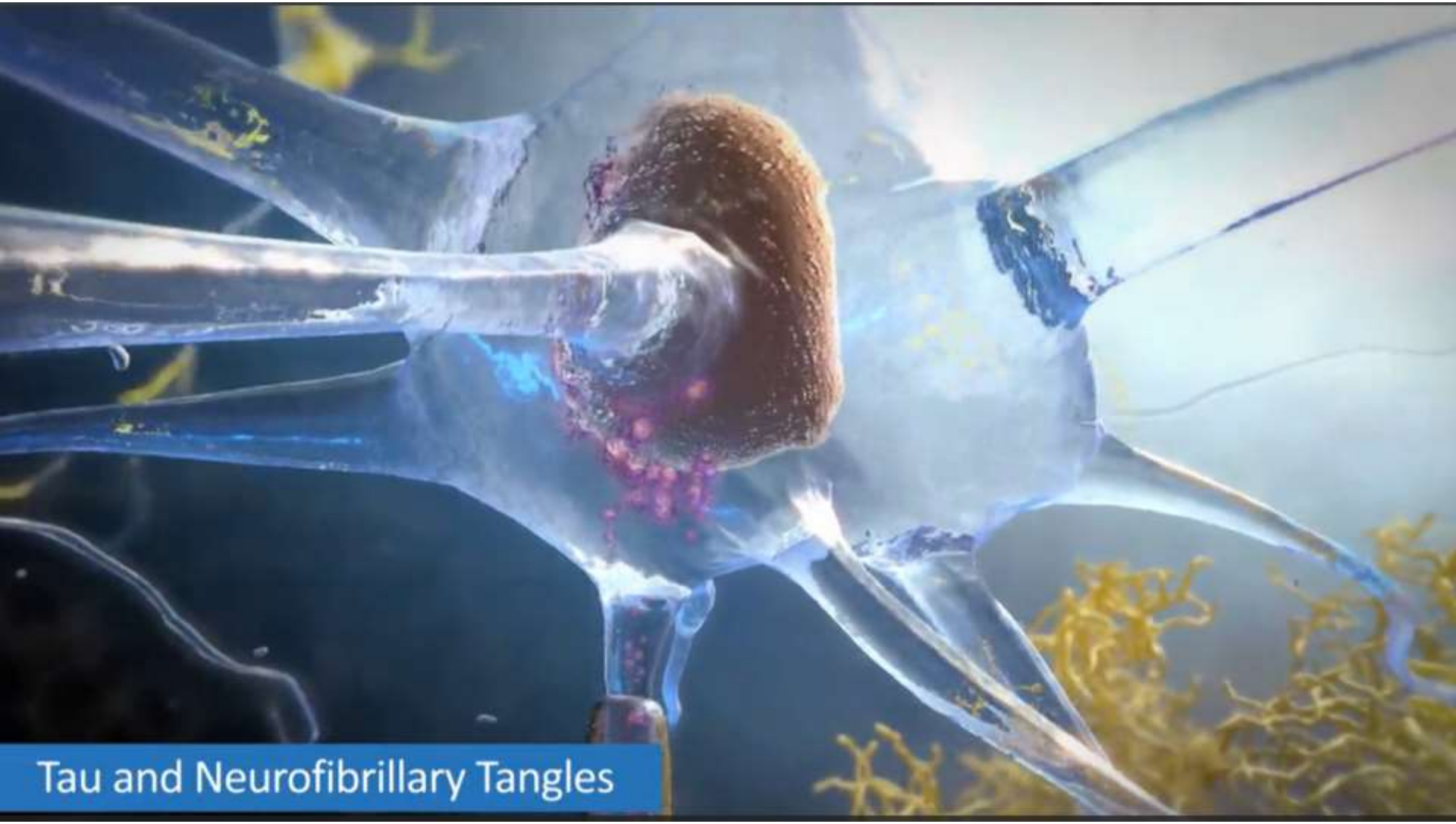

Tau
Tau and Neurofibrillary Tangles


Tau
Tau and Neurofibrillary Tangles

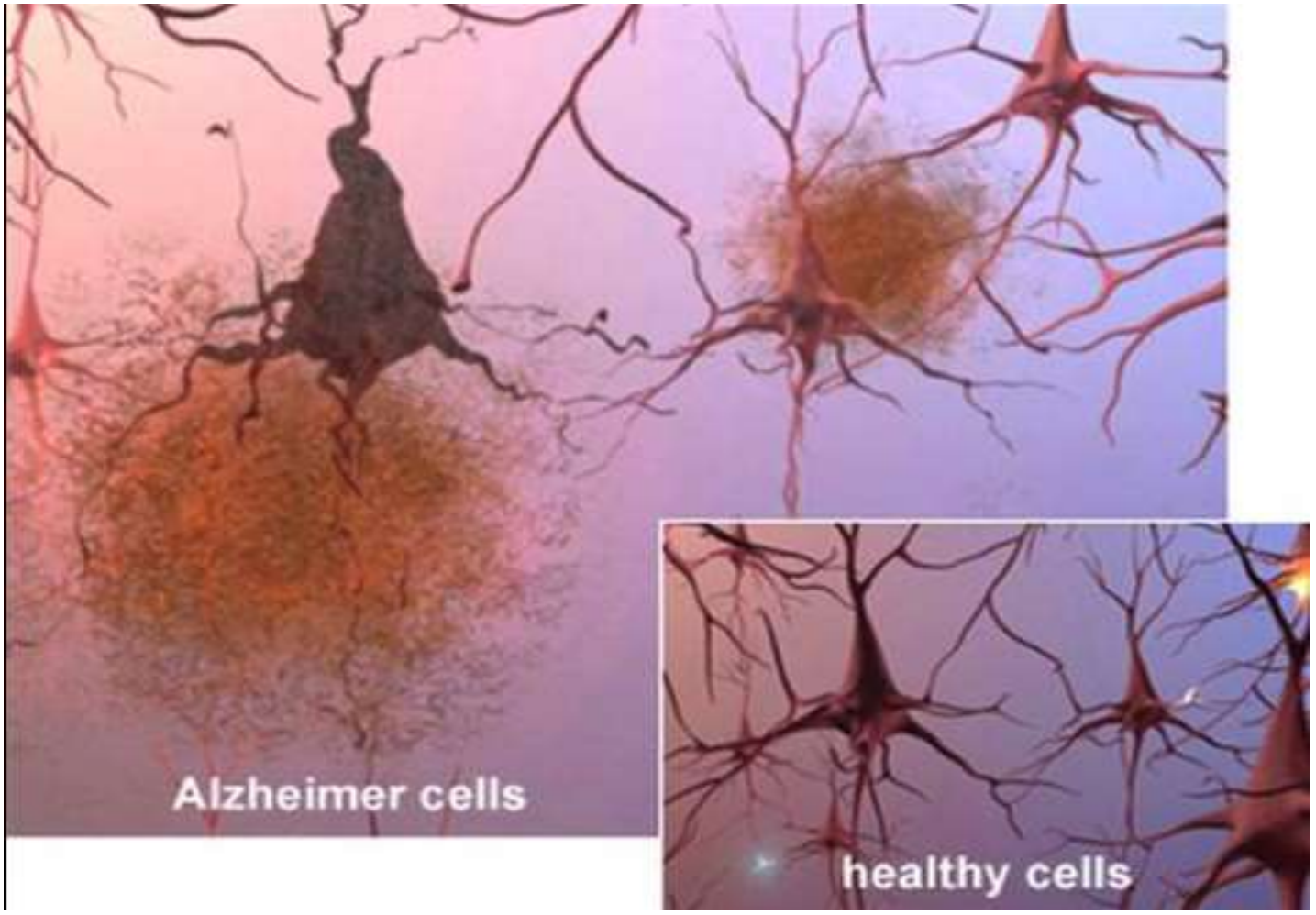

Tau and Neurofibrillary Tangles



Tau and Neurofibrillary Tangles

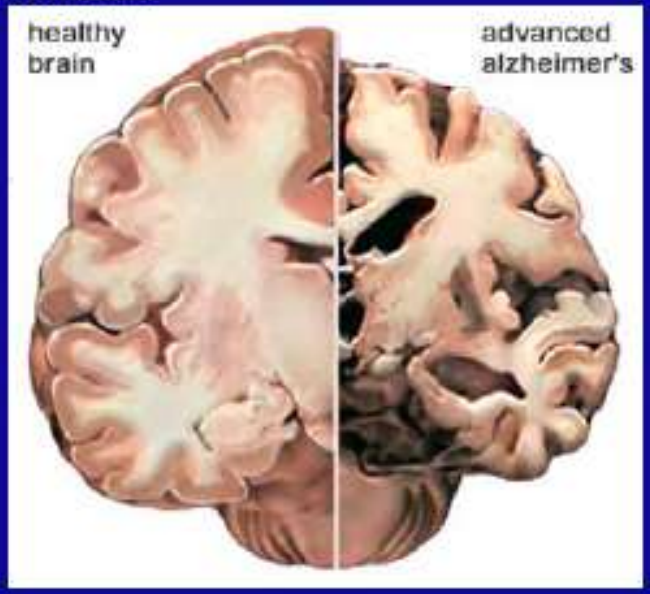

Tau and Neurofibrillary Tangles

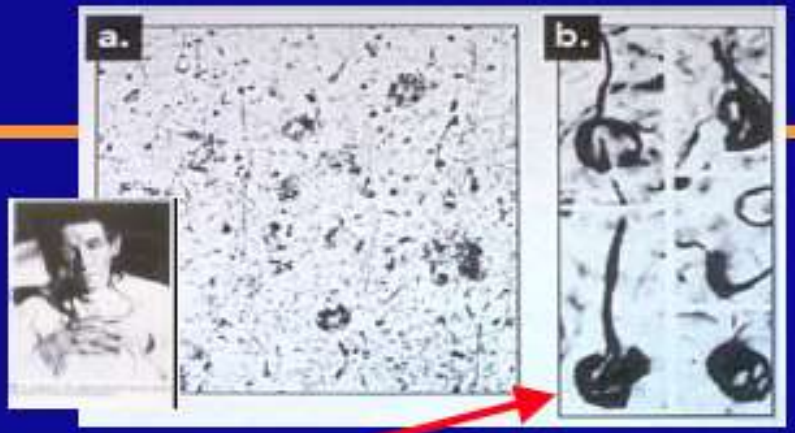
Amyloid Deposition - Plaques



Neuropathology of AD

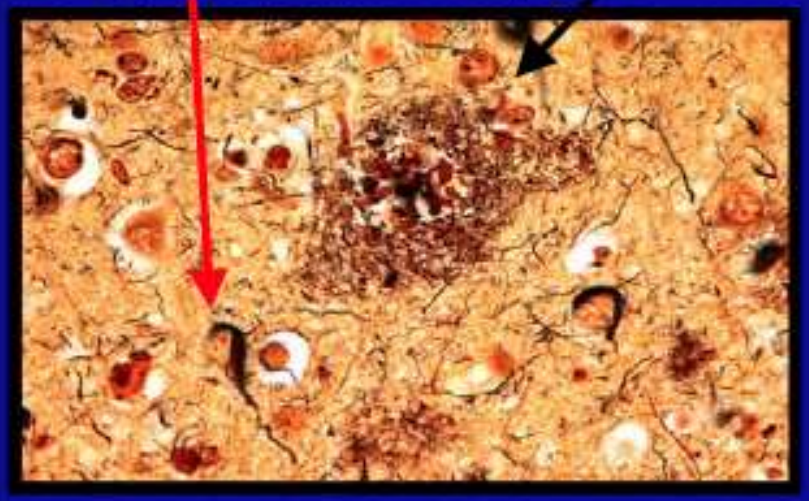
- Plaques (Amyloid-ß)
- Neurofibrillary tangles (NFT) (tau)
- Nerve cell and synapse dysfunction, loss of connections, cell death, brain shrinkage
- Inflammation

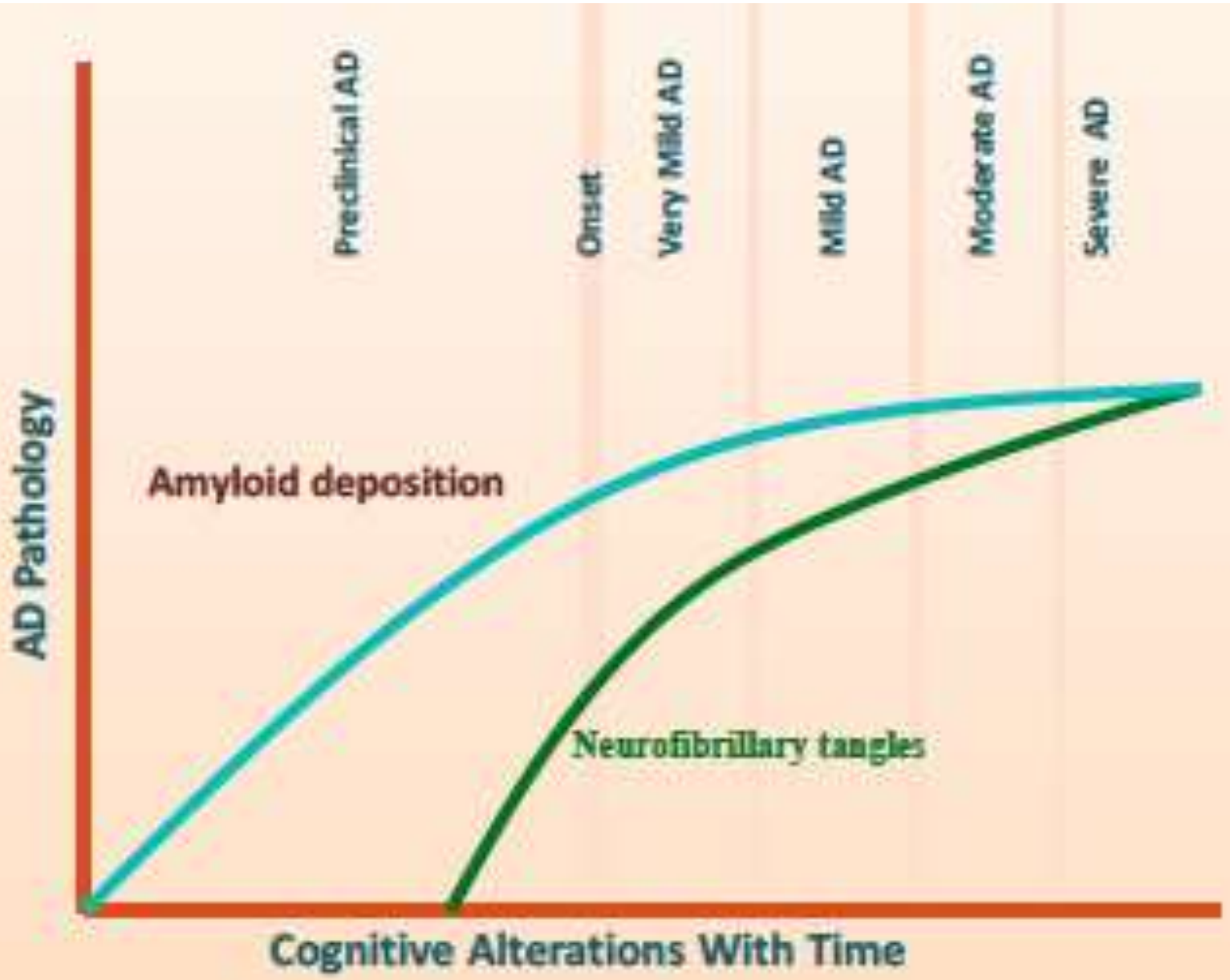




Tangles

Plaques



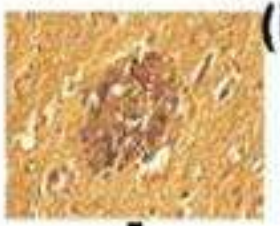

Preclinical AD
Onset
Very Mild AD
Mild AD
Moderate AD
Severe AD
AD Pathology
Amyloid deposition
Neurofibrillary tangles
Cognitive Alterations With Time

PATHOLOGIES ASSOCIATED WITH AD

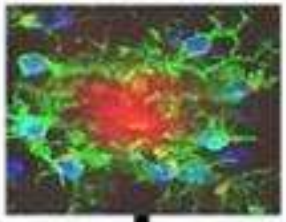
AGE

30
40
50
60
70
80
90
100

β-amyloid Deposition (plaques)



Microglial Activation (inflammation)

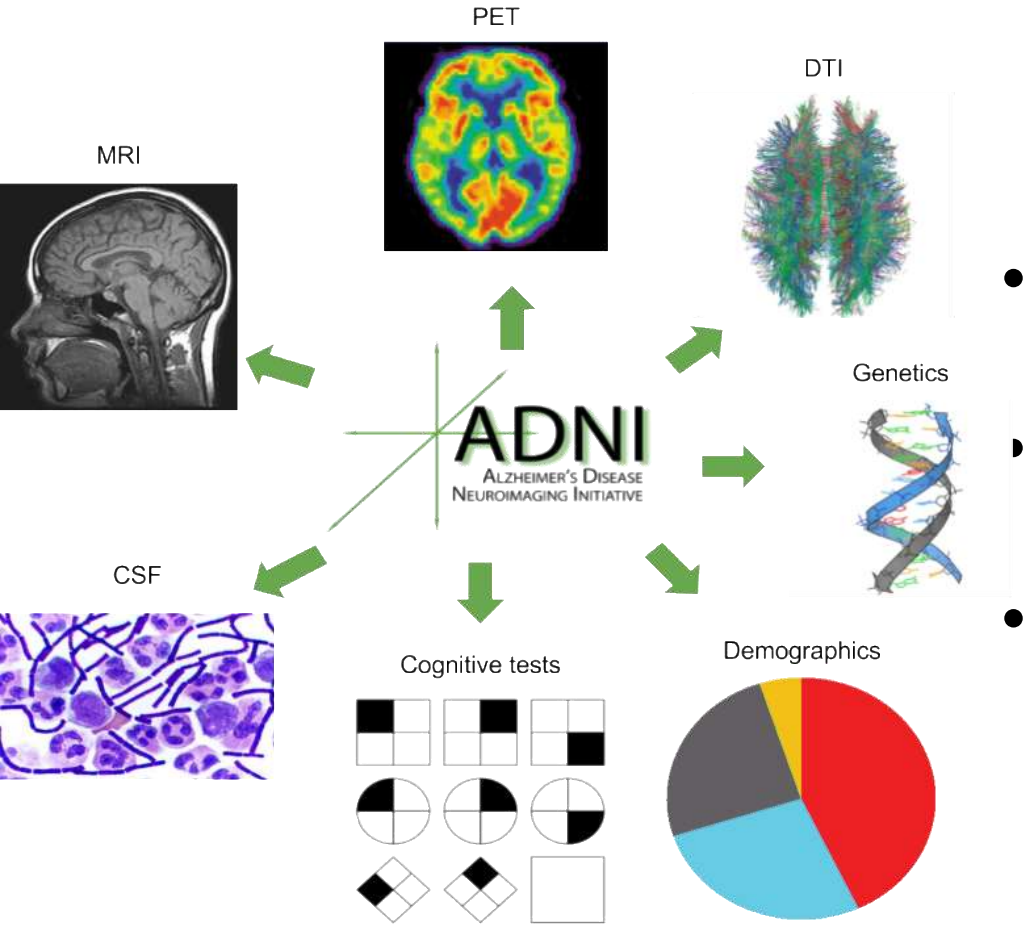


NFTs (tangles)

Neuronal Loss (atrophy)

Symptoms

ADNI
Alzheimer's Disease Neuroimaging Initiative



- Currently in its third phase
- Now including older controls and SMC
- Developed Standardized MRI, PET. CSF, DTI, and neuropsychological test measures
- Identified earliest biomarker changes in AD
- Elucidated patterns & rates of change
- Identified at-risk populations

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Naturalistic Study of AD Progression

All data in public database: UCLA/LONI/ADNI

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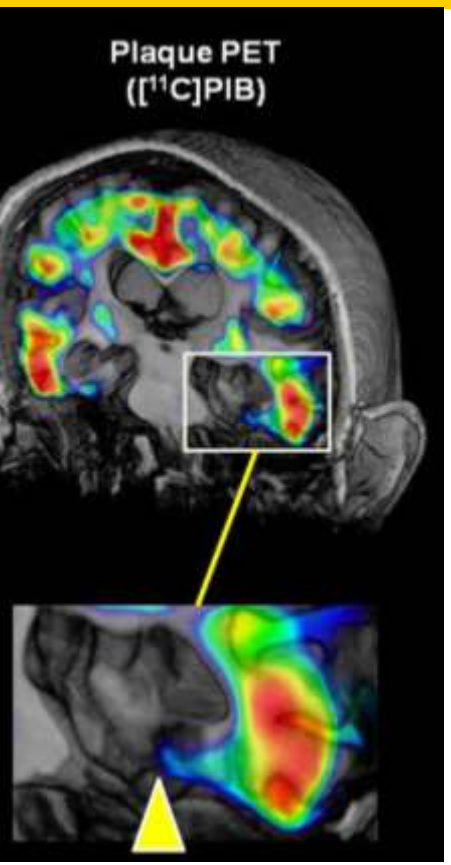
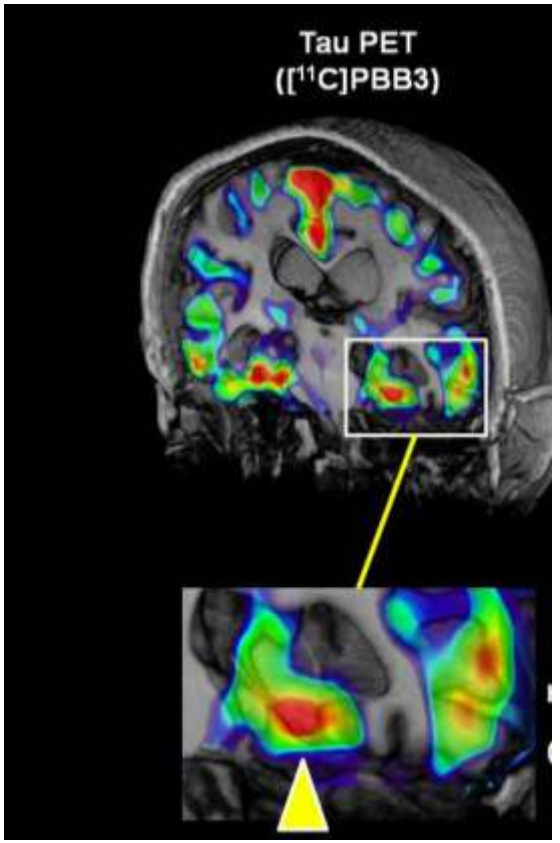
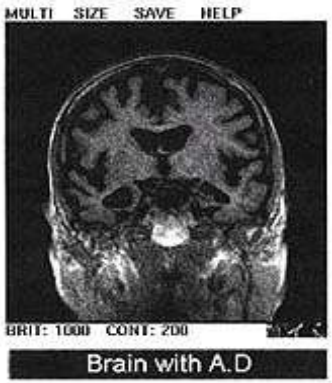


Imaging Classification Markers

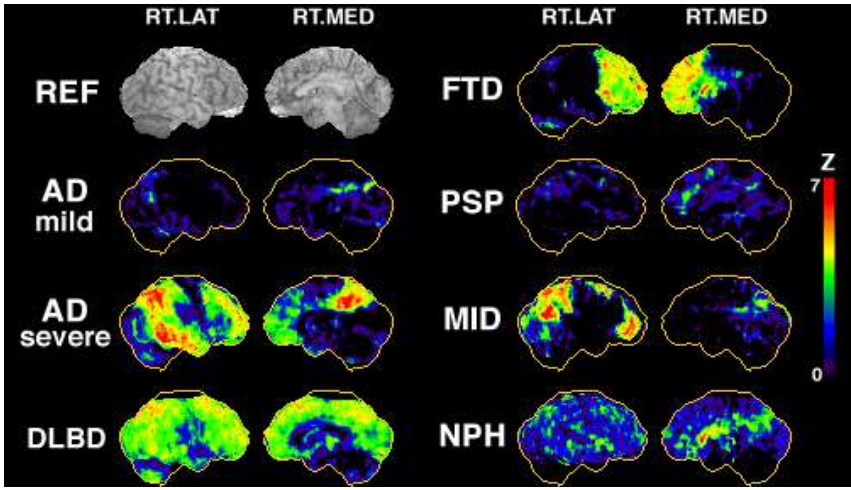


Amyloid PET Biomarker*

Tau Pathology Biomarker*

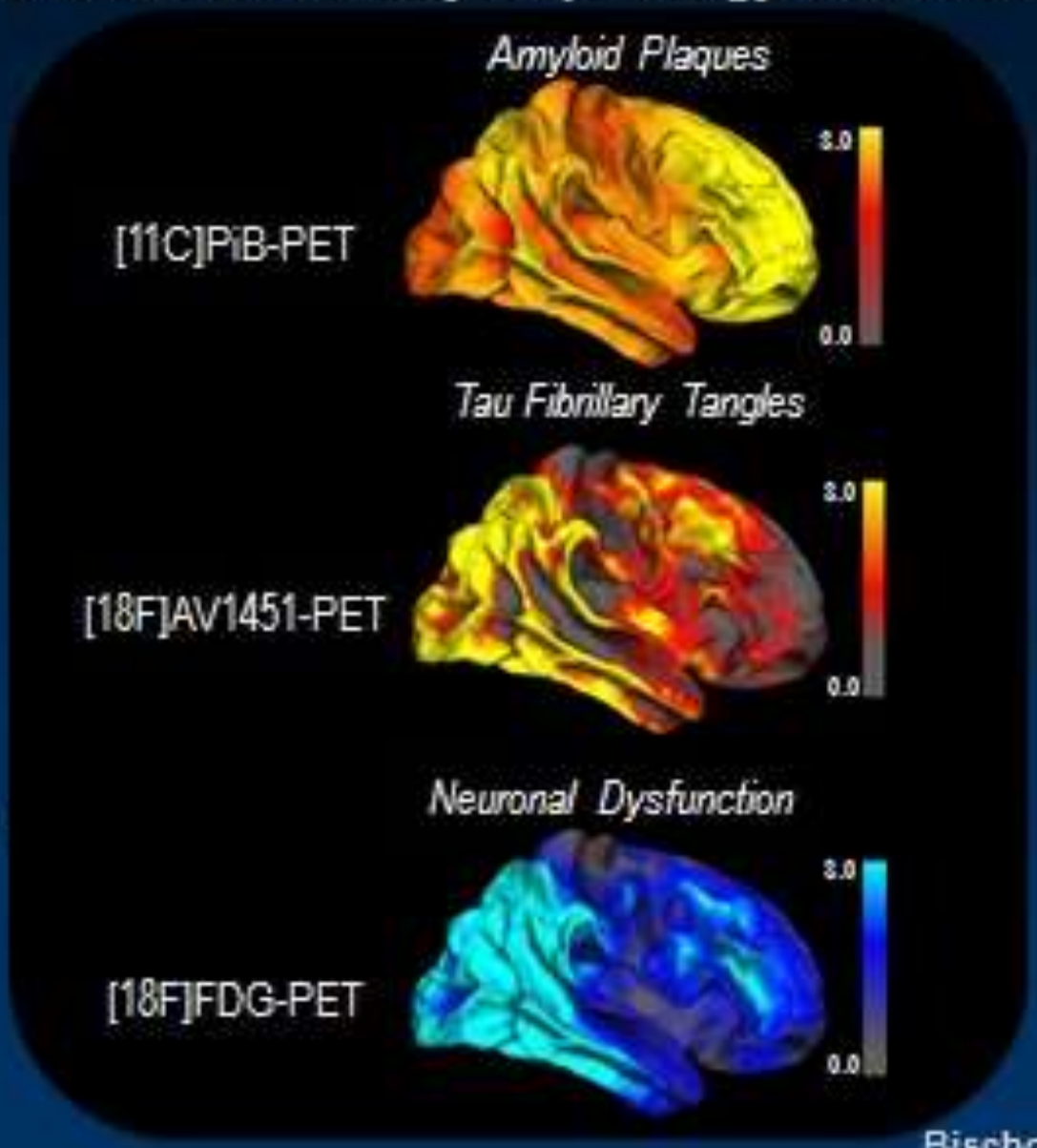


Neurodegeneration Markers



*CSF does both

Correspondence of tau- but not amyloid-pathology with neuronal dysfunction



Right lateral surface of projected z-score images, reflecting deviation from healthy controls

Yellow/red: higher uptake

blue: lower uptake as compared to controls

Bischof et al. Pub. No.: 124.

New Proposed Criteria: A/T/N Classification

- **Research classification** strictly based on 3 binary (yes/no, +/-) biological markers
- A: Amyloid Biomarker
  - Amyloid PET or CSF $A\beta_{42}$
- T: Tau pathology biomarker
  - CSF p-tau or tau PET
- N: Quantitative or topographic biomarker of neurodegeneration or neuronal injury (CSF t-tau, FDG-PET, structural MRI)
- Example: A+/ T+/ N+

	+	-
A		
T		
N		

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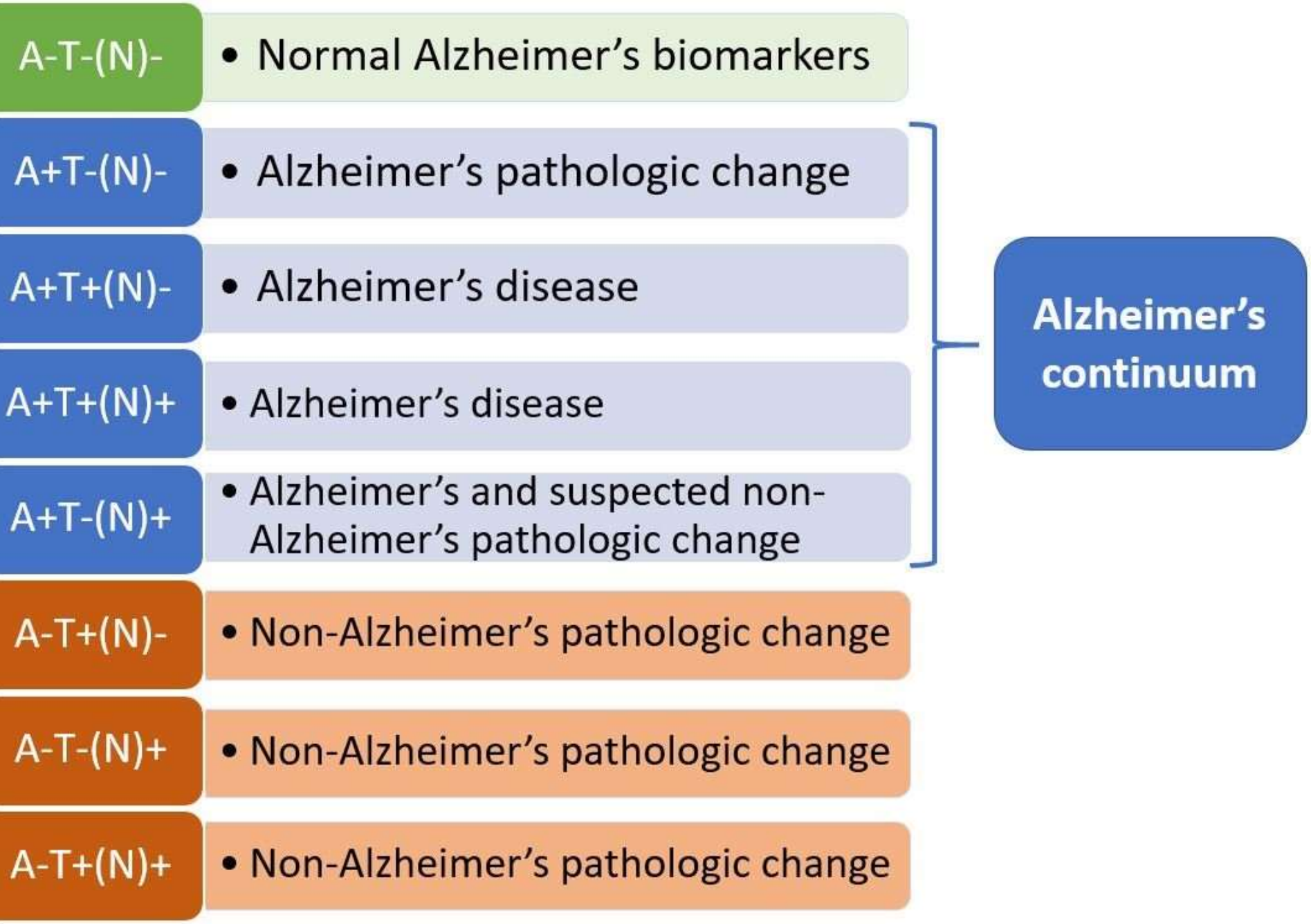
A-T-(N)-
• Normal Alzheimer's biomarkers
A+T-(N)-
• Alzheimer's pathologic change
A+T+(N)-
• Alzheimer's disease
A+T+(N)+
• Alzheimer's disease
A+T-(N)+
• Alzheimer's and suspected non-Alzheimer's pathologic change
Alzheimer's continuum
A-T+(N)-
• Non-Alzheimer's pathologic change
A-T-(N)+
• Non-Alzheimer's pathologic change
A-T+(N)+
• Non-Alzheimer's pathologic change

Risk Issues & Genetics

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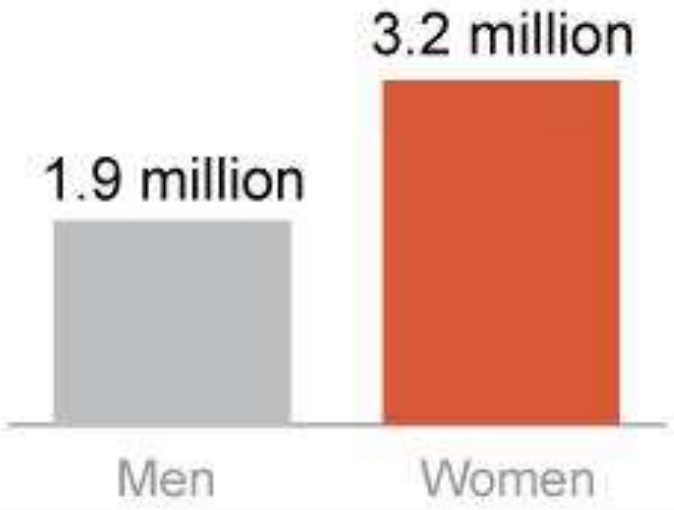
You Are at Higher Risk of Alzheimer's Disease, IF…..

- Are over the age of 65
- Have had a serious head injury, particularly repeated injuries
- Have genes that are involved with the development of Alzheimer's disease
- Are Hispanic or Black
- Have an immediate family history of a person with Alzheimer's disease
- Experience other health conditions such as heart disease, high blood pressure, high cholesterol, diabetes, or if you have had a stroke

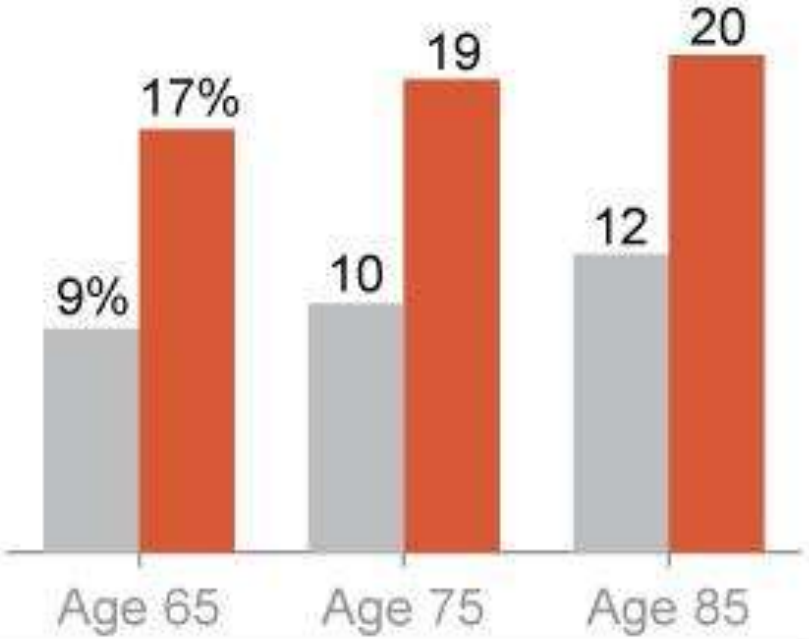
Gender and Alzheimer's disease

Women make up a larger share of Alzheimer's patients than men and have a greater risk of developing the disease as they age.

Number of people ages 65 and older in the U.S. with Alzheimer's:



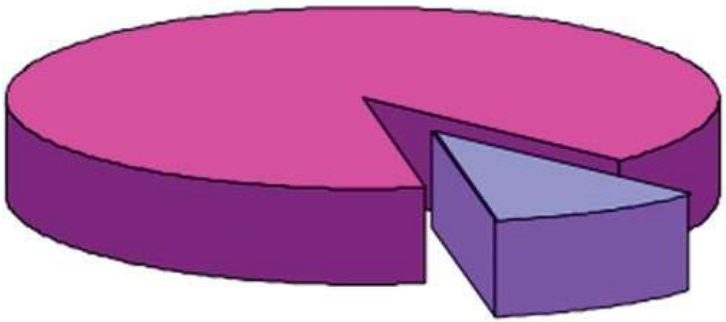
Percent chance a person will develop Alzheimer's during his or her remaining lifetime:



GENETICS

LOAD>60 years

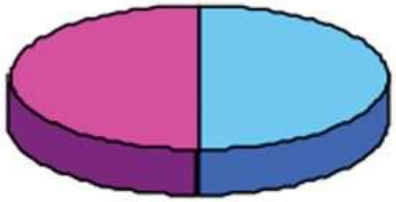
90%



10%

EOAD <60 years

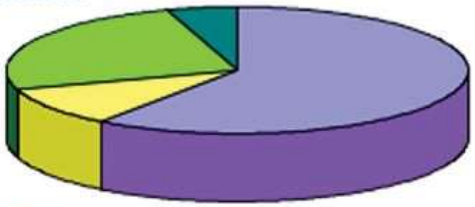
APOE4: 50%
Chromosome 19



Other: 50%

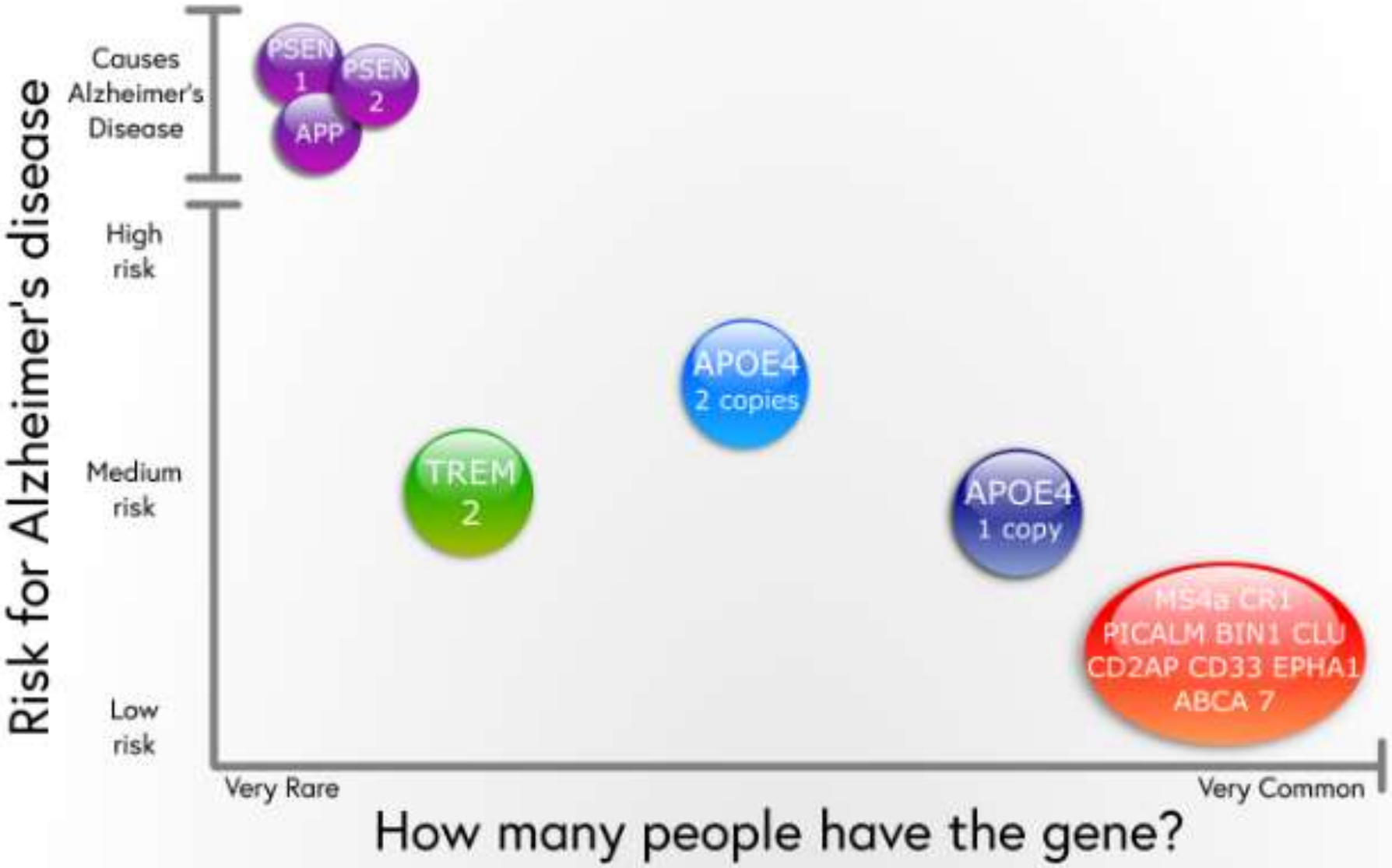
Presenilin-2: 5%
Chromosome 1

Other: 30%

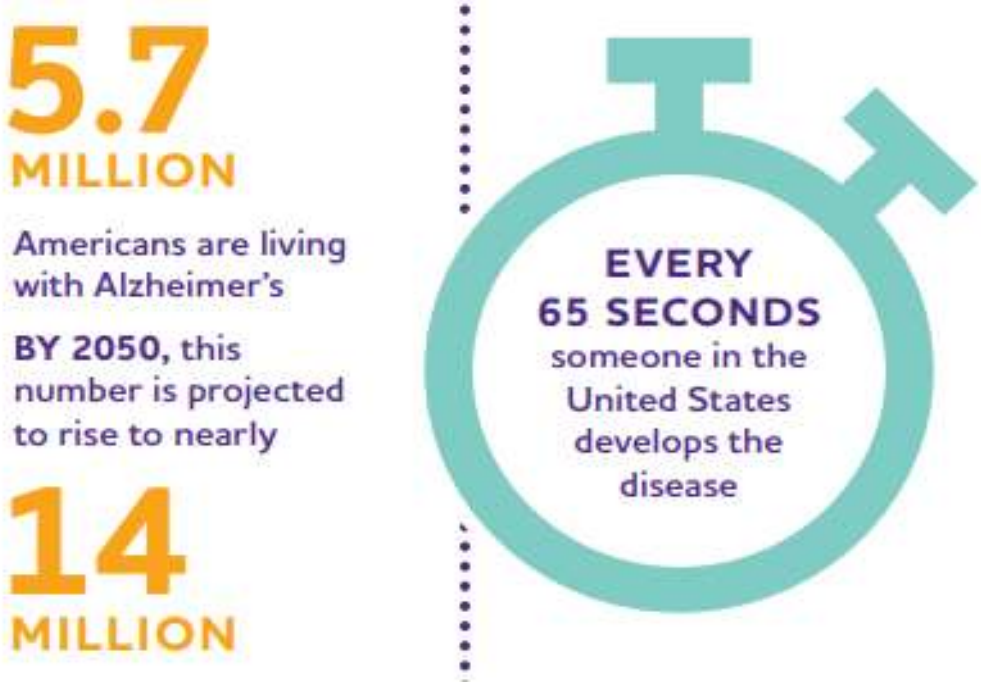


APP: 5%
Chromosome 21

Presenilin-1: 60%
Chromosome 14


Risk for Alzheimer's disease
Causes Alzheimer's Disease
High risk
Medium risk
Low risk
PSEN 1
PSEN 2
APP
TREM 2
APOE4 2 copies
APOE4 1 copy
MS4a CR1 PICALM BIN1 CLU CD2AP CD33 EPHA1 ABCA 7
Very Rare
Very Common
How many people have the gene?

Thinking about the Financial Impact



IN 2018, Alzheimer's and other dementias will cost the nation

$277 BILLION

BY 2050, these costs could rise as high as

$1.1 TRILLION

EARLY AND ACCURATE DIAGNOSIS COULD SAVE UP TO

$7.9 TRILLION

in medical and care costs

How Advocacy & Fundraising Impact Research

Jennifer Howard
Executive Director,
Alzheimer's Association Michigan Great Lakes Chapter

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How do we fund Alzheimer's research through the Association?

Alzheimer's Association Leadership

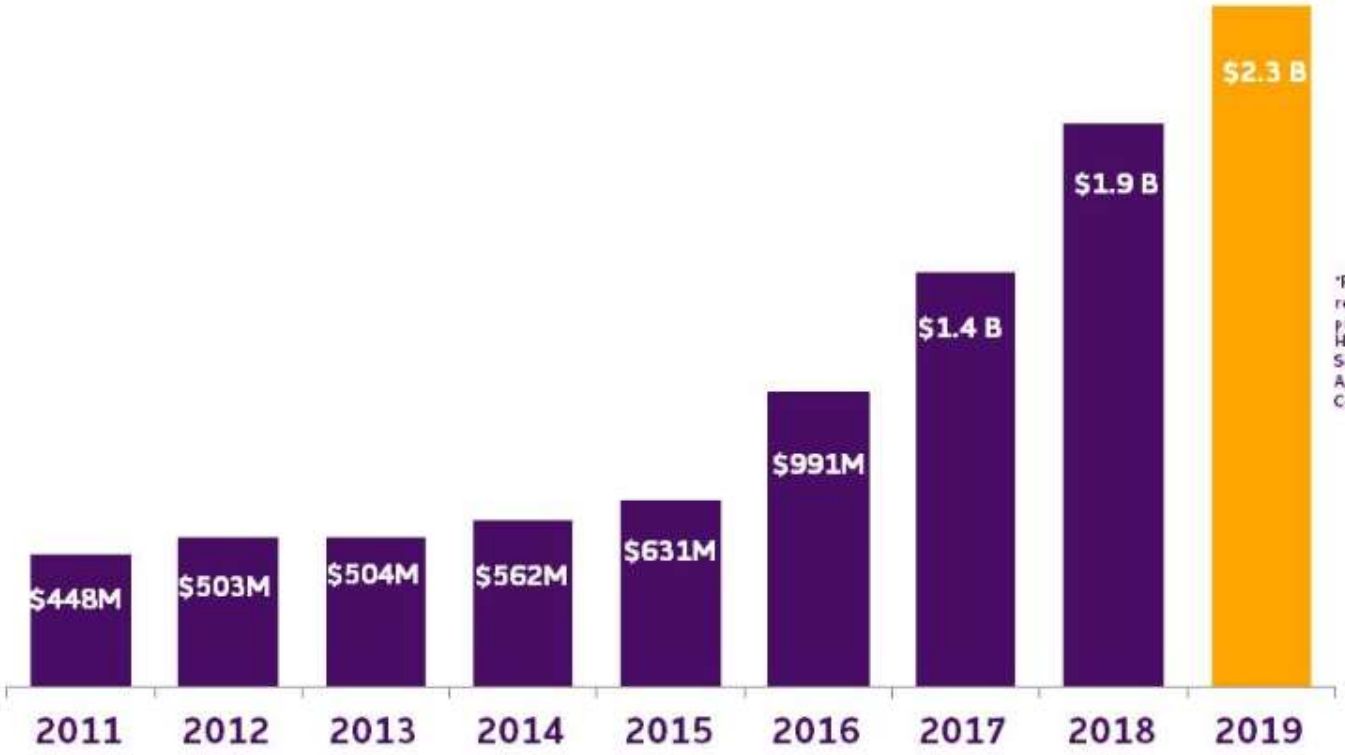
- $110 Million in 400+ current active studies located in 19 countries
- $440 Million total direct funding
- Over $5 Million total in MI

U.S. POINTER Study

U.S. Study Protecting Brain Health through Lifestyle Intervention to Reduce Risk

Alzheimer's and Related Dementia Research Funding at the NIH

AIM
ALZHEIMER'S IMPACT MOVEMENT
alzheimer's association



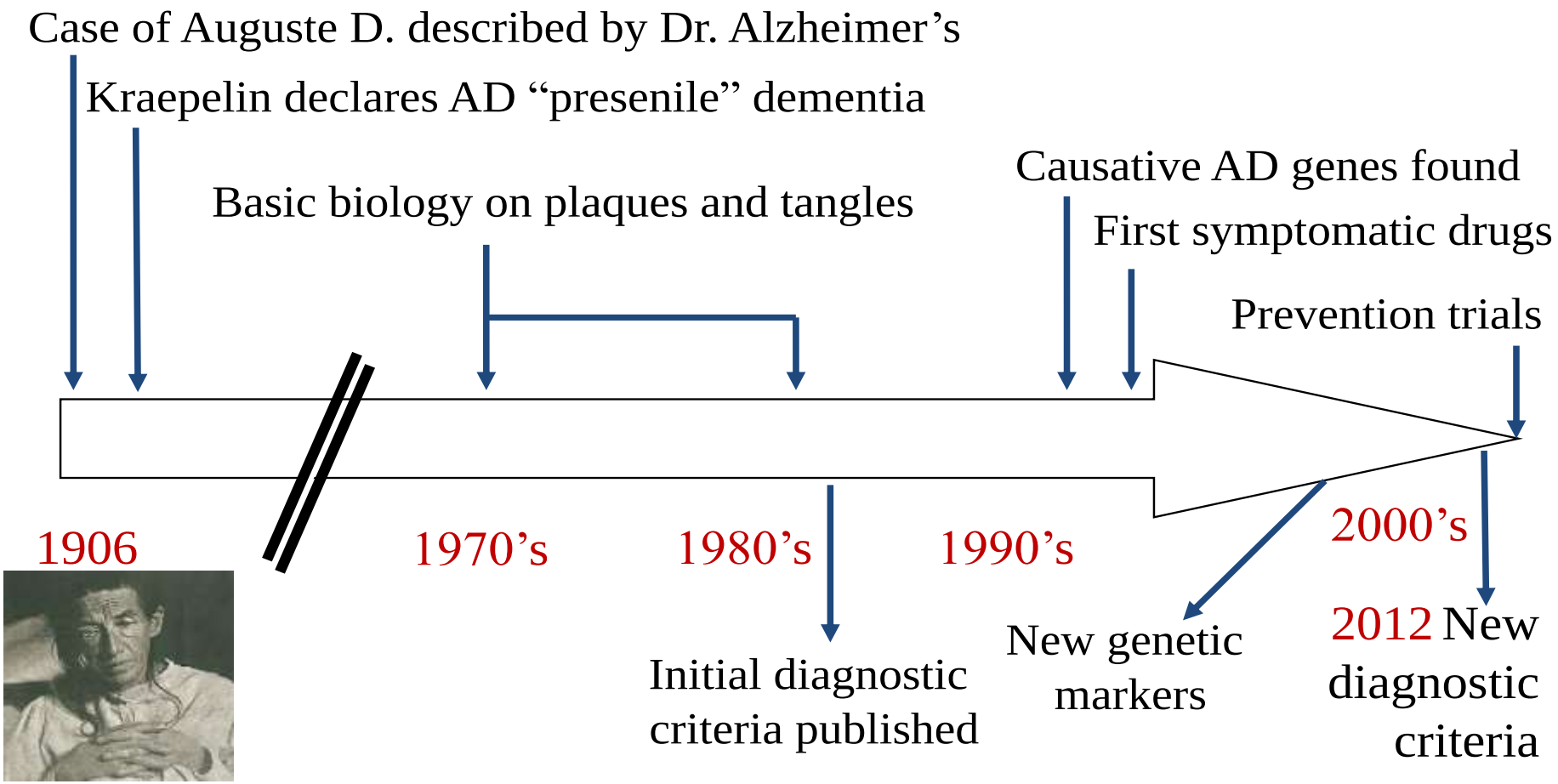
*FY2019 reflects current proposal by House and Senate Appropriations Committees

Thank You Jennifer Howard

(If you went over, I get 10 more minutes)

Alzheimer’s Association International Conference 2018!

AD Research Now Picking Up Speed



Key takeaways from AAIC 18

- New technology uses in training
- Evidence from new trials
- Lifestyle predictors
  - High blood pressure
  - Gut health
  - Reproductive history, pregnancy, hormone therapy
- Special populations: LGB, Oldest old, Early onset
- Clinical evaluation measures
- Treatment of Non-Cognitive symptoms
- A new take on approaching tau and neurodegeneration
- National recruitment strategy

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Training

- “Bringing Art to Life”
- Virtual reality program presenting two scenarios through continuum of AD
- Among a group of high school students working with seniors
  - Improved empathy
  - Increased enthusiasm
  - Decreased stigma and negative attitudes

- Expanded awareness about what it is like to have Alzheimer's disease and dementia
  - Ongoing project with medical and pharmacy students

New Reports on Medications

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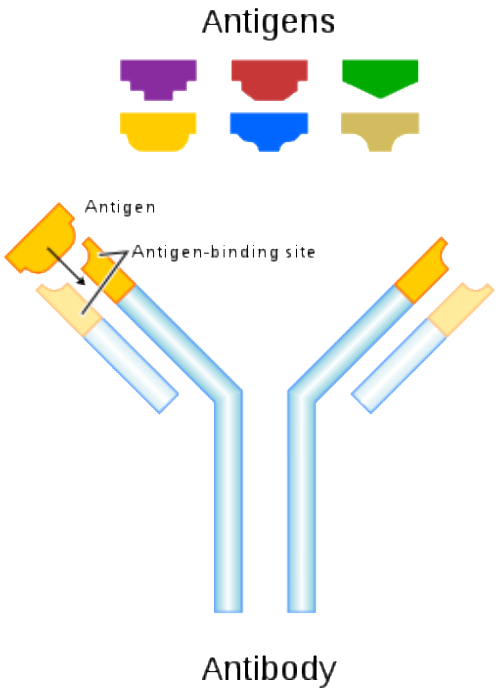
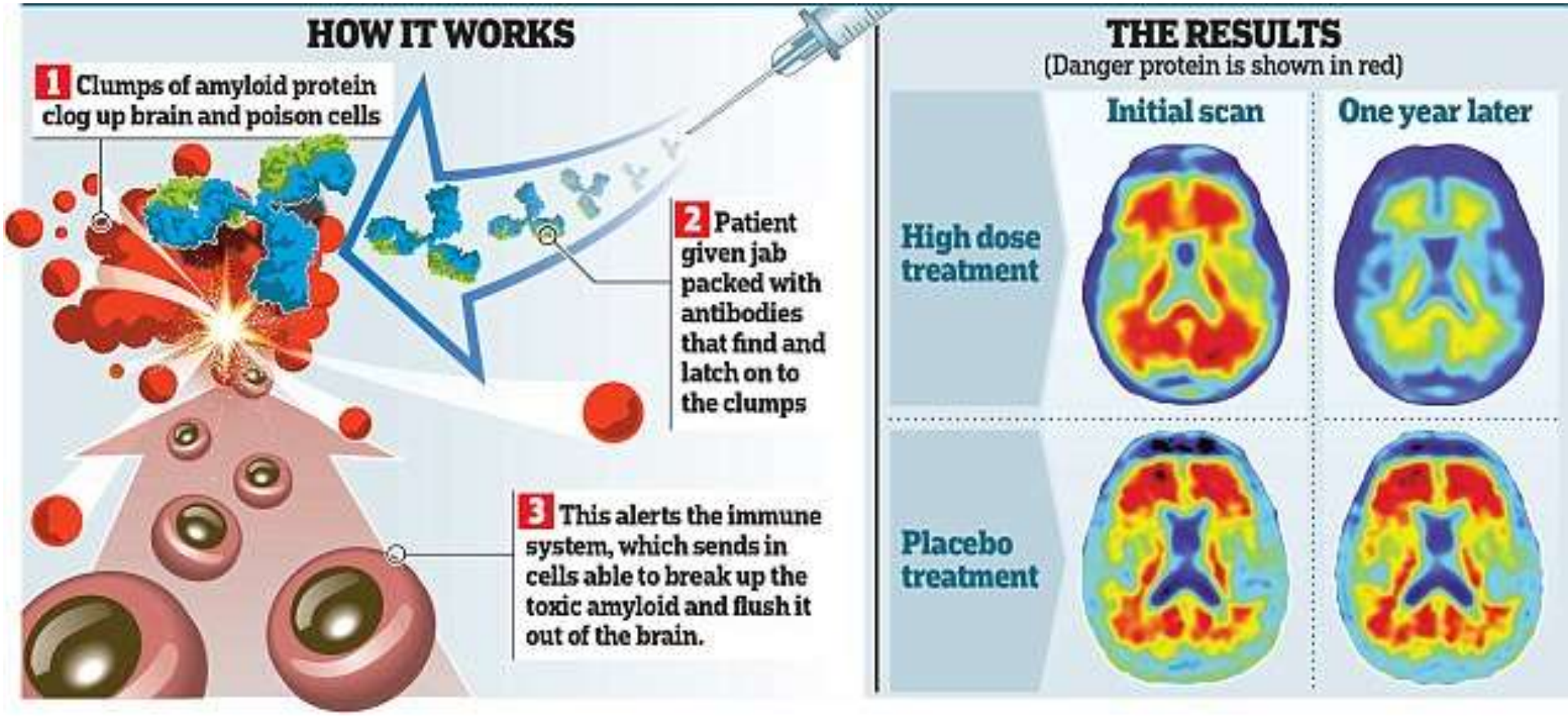
Antibodies (Ab)-- Immunoglobulin (Ig)

- An antibody (Ab), also known as an immunoglobulin (Ig), is a large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to neutralize pathogens
- The antibody recognizes a unique molecule of the pathogen, called an antigen
- Using this binding mechanism, an antibody can:
  - Tag a microbe or an infected cell for attack by other parts of the immune system (e.g., macrophages)
  - Or neutralize its target directly by impeding the biological process causing the disease by coating the pathogen, antibodies stimulate **effector functions** against the pathogen in cells



Aducanumab: “Plaque Busters”



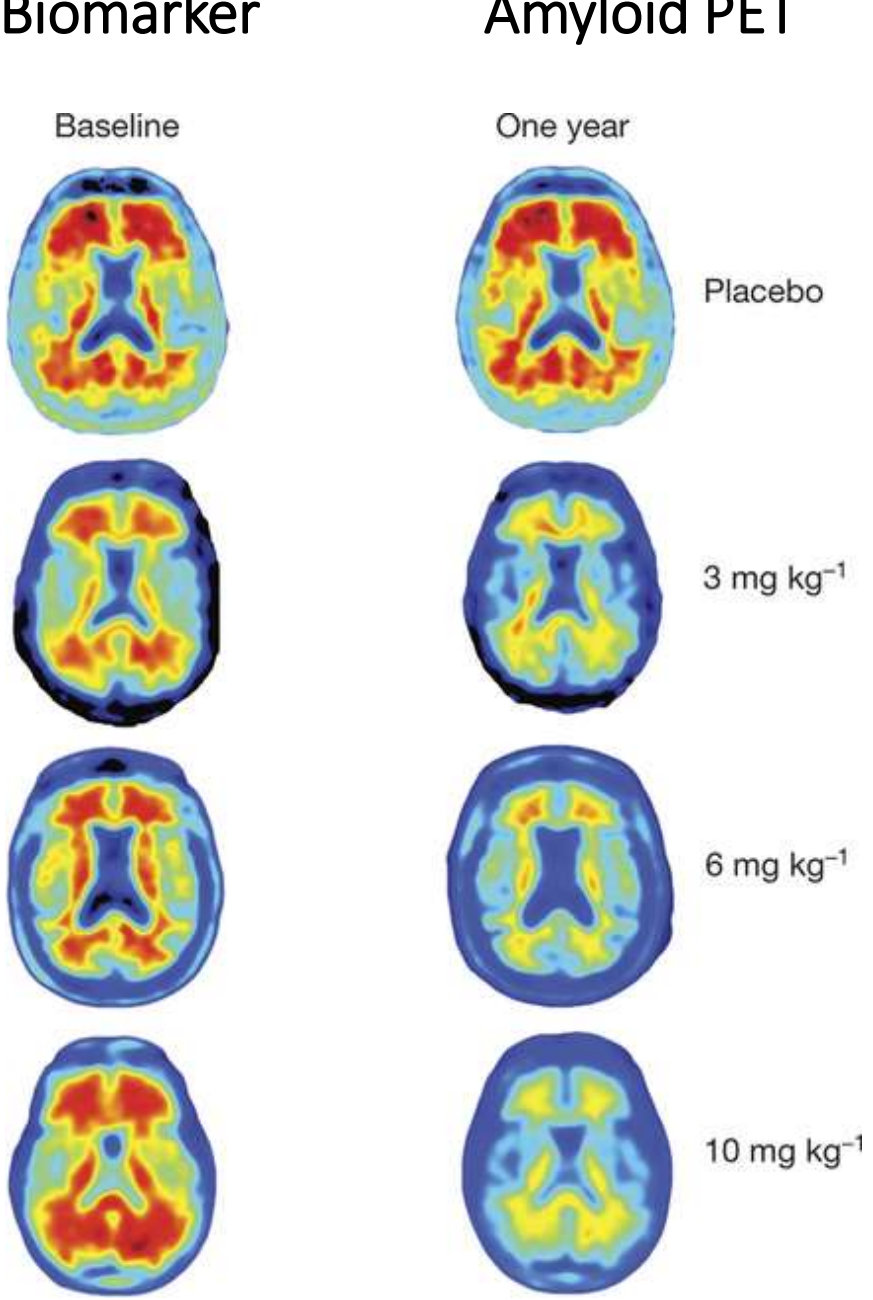
First late-stage study successfully demonstrating potential disease-modifying effects in both clinical function and beta amyloid accumulation

Aducanumab Phase 1b

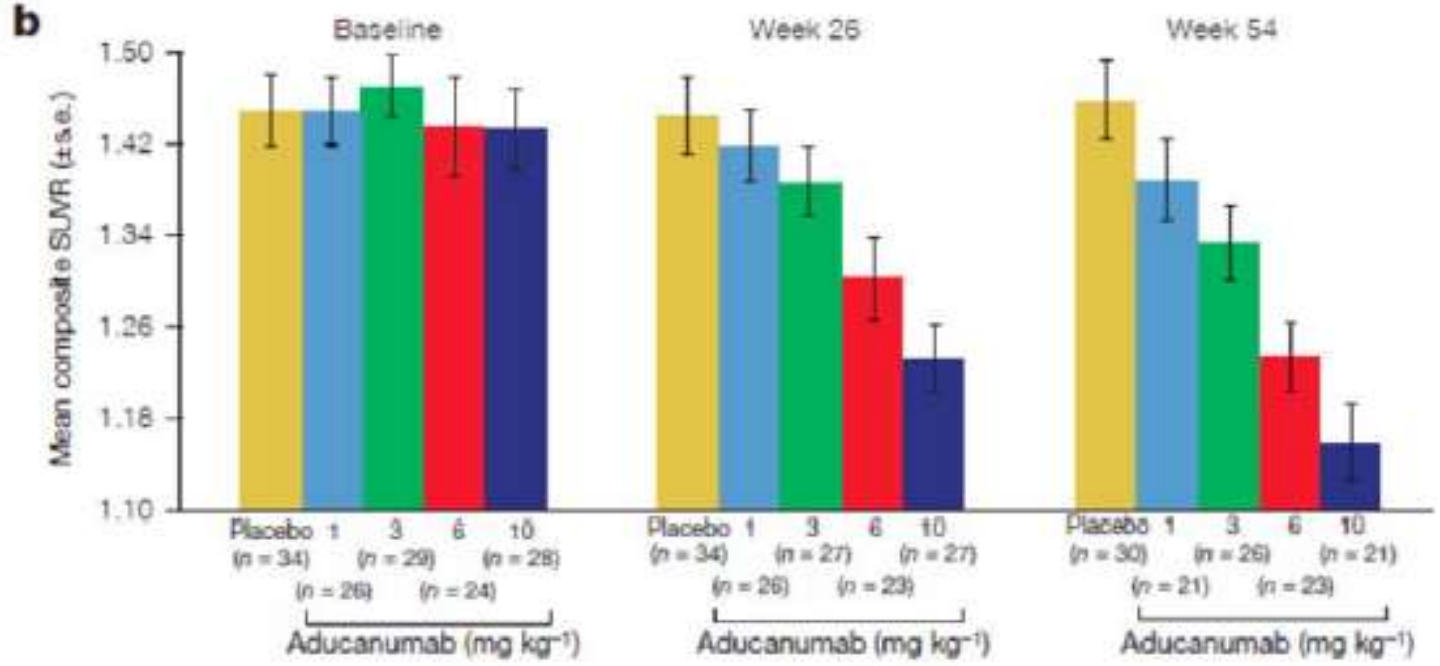
Biogen Pharmaceuticals
165 patients at treated for 1 year
All enrolled were Amyloid PET+
4 dose groups or placebo

Efficacy
Preliminary! Suggestion of better scores in treatment group than placebo group and Improved amyloid imaging

Safety
Higher doses associated with increased Amyloid Related Imaging Abnormality (ARIA)



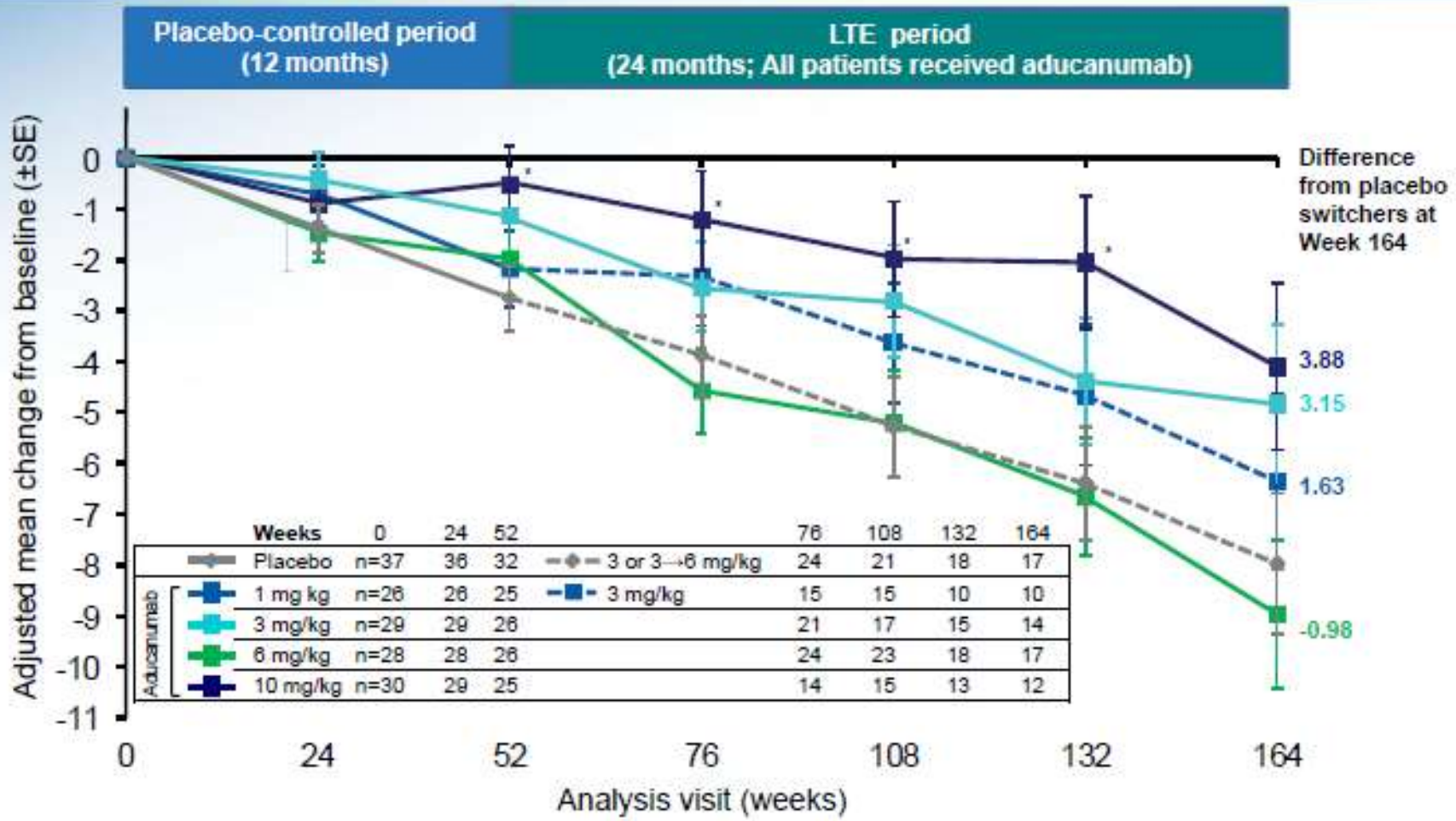
Aducanumab Amyloid PET Results (Phase 1b, early AD)



SUVR=standardized uptake value ratio.

Sevigny J et al. *Nature*. 2016;537(7618):50-56.

Effect of Aducanumab on Clinical Decline as Measured by MMSE (Exploratory Endpoint)

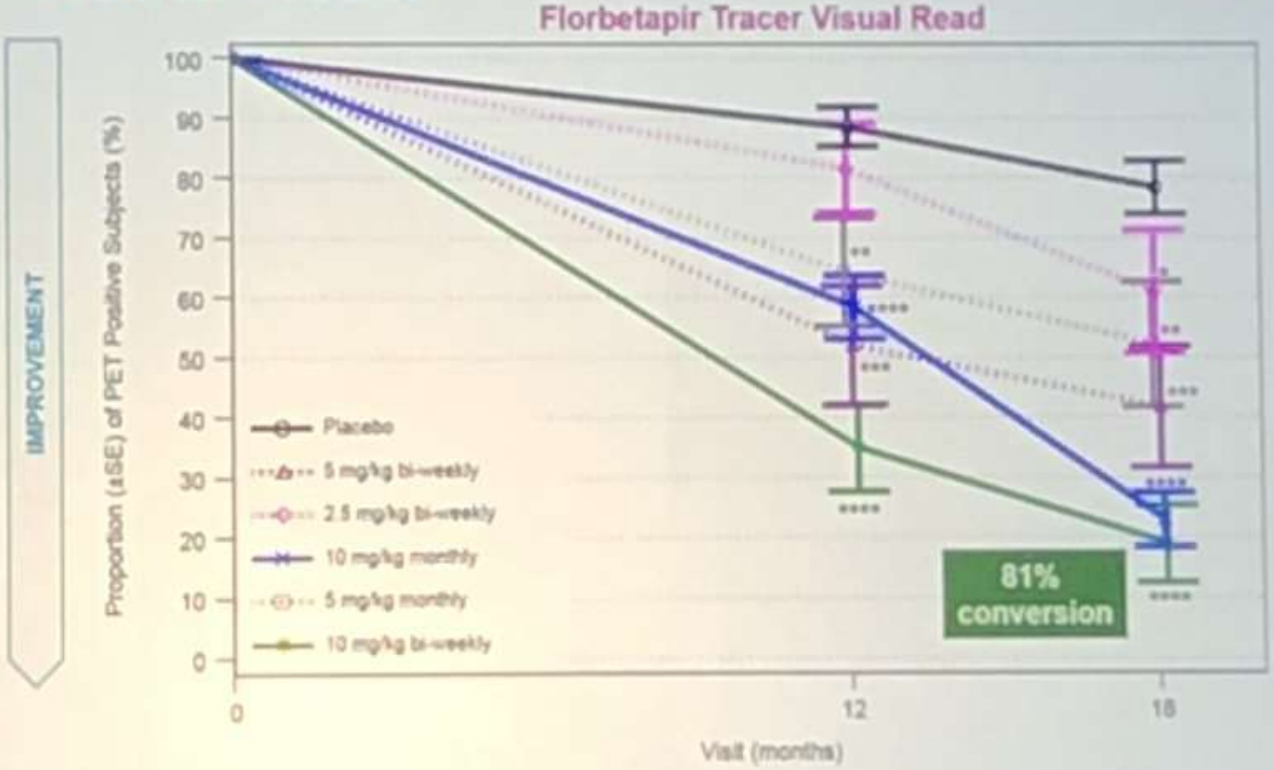


BAN2401 Clinical Trial is Cautiously Optimistic

- "Amyloid hypothesis:" lower levels of beta amyloid in the brain to slow or reverse Alzheimer's in early AD
- 2017: No benefit at 12 months first look analysis
- 2018: Did slow disease course of 18 months which was planned completion based on several indicators
- First late-stage study successfully demonstrating potential disease-modifying effects in both clinical function and beta amyloid accumulation
- Support for beta amyloid as a target for AD therapy

Significant Conversion of Amyloid Positive to Negative With Visual Read

- Dose dependent conversion from amyloid positive to negative vs placebo
- BAN2401 significantly converted subjects from amyloid positive to negative across most doses

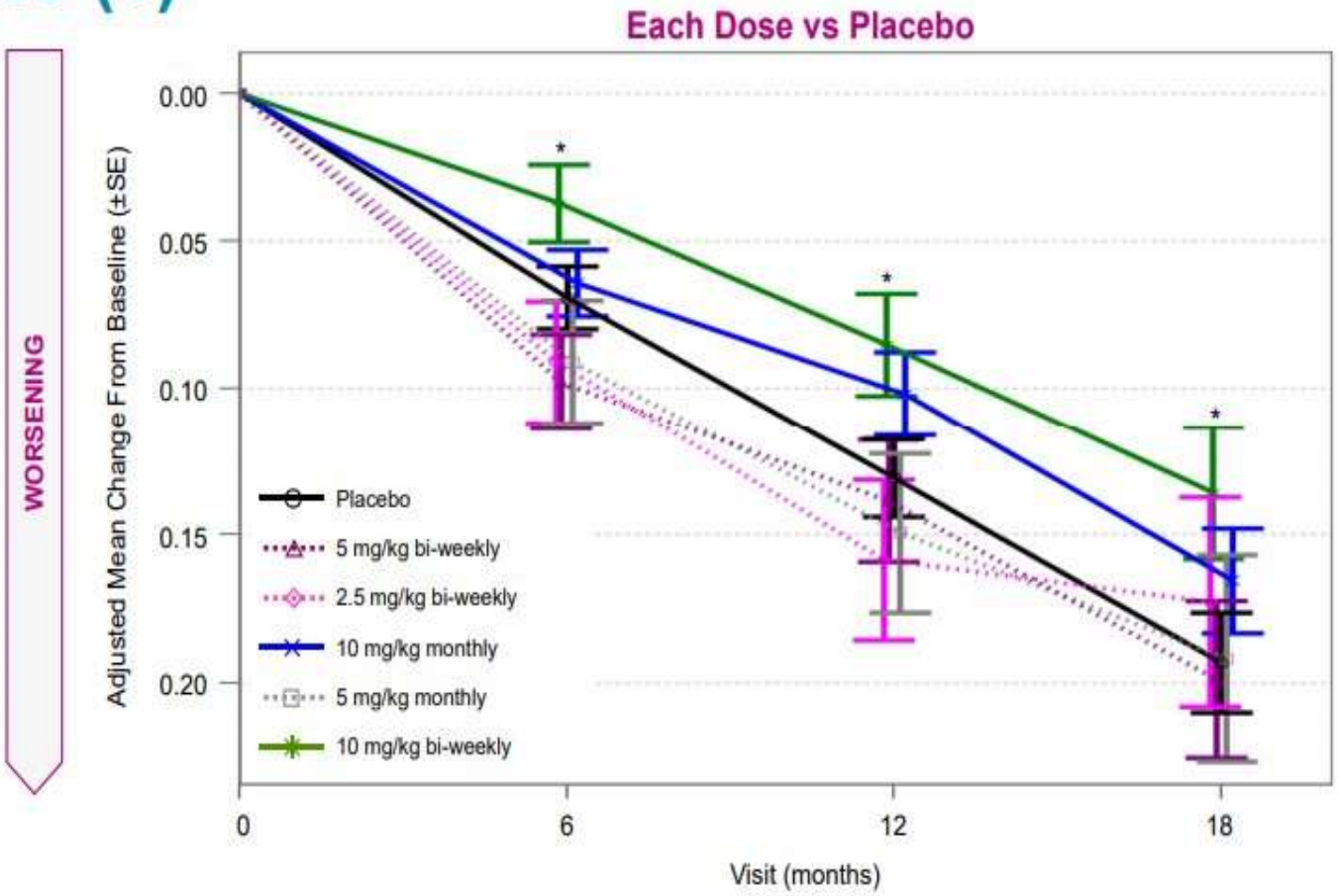


*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001

Baseline images were read at time of inclusion; longitudinal 12 and 18 month reads were conducted after all subjects completed 18 months of treatment. Fisher's exact test was used to compare each dose vs placebo.

BAN2401 Slowed Cognitive Decline on ADCOMS Over 18 Months (1)

- Dose dependent reduction in decline on ADCOMS over time; starting at 6 months of treatment



*$P<0.05$.

The Mixed Model Repeated Measures (MMRM) uses treatment group, visit, clinical subgroup (MCI due to AD, Mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, treatment group-by-visit interaction as factors, and baseline value as covariate.

Drug Studies Ongoing

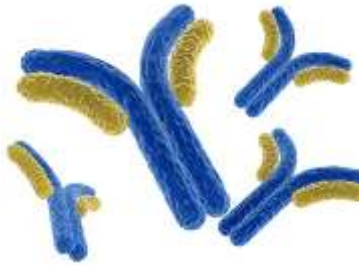
- Crenezumab
  - Binds to all types of amyloid (toxic fibrils and oligomers, but less to monomers)
  - Early studies disappointing, but larger Phase 3 study in early AD continues with higher dose
- Gantenerumab
  - Human antibody binds to all forms of amyloid
  - Prodromal AD study stopped for no effect
  - Phase 3 early AD ongoing with higher dose

Presymptomatic Treatment Trials: Stay Tuned

- ✓Alzheimer's Prevention Initiative (API) Autosomal Dominant Alzheimer's Disease Treatment Trial
- ✓Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4)
- ✓Dominantly Inherited Alzheimer Network Therapeutic Trial Unit (DIAN-TU)
- ✓Alzheimer's Prevention Initiative APOE4 Treatment Trial
- ✓TOMMORROW Study

Using Antibodies to stop Tau Spreading: Basic Laboratory Findings

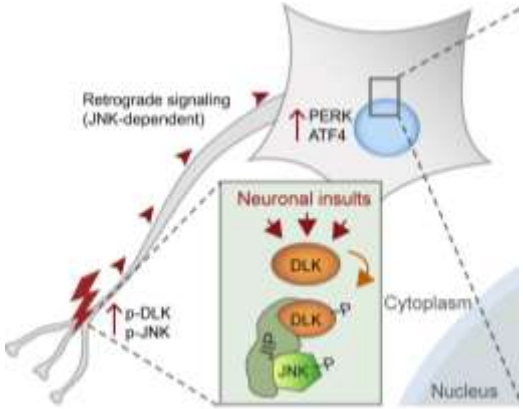
(Ayalon et al., AAIC, 2018)



- One possible way to stop tau from wreaking havoc across the brain is to catch it **while it's spreading**-- intercept tau in the **extracellular space** as it's travelling between neurons using **antibodies that specifically bind to tau--"Tau sponges"**
- It's important to not only select the right target, but also the right type of antibody, as some activate the immune system and others not
- Sometimes engaging the immune system is beneficial to more effectively attack a target (e.g., a cancer cell), while in other cases a more "passive" binding role is desired
- A so-called "effector-less" antibody that doesn't cause the immune system to respond was sufficient to slow the spread of tau tangles, and also indicated that full-effector tau antibodies may induce indirect toxicity in preclinical experiments.

Understanding Neurodegeneration

- Neurodegeneration occurs naturally – removing unnecessary projections commonly created early in life and helping to create precise connections in the brain
- Damage to brain cells creates a signal that triggers neurodegeneration and Dual Leucine Zipper Kinase (DLK) is a protein that plays an integral role in creating and amplifying the signal
- Removing DLK might protect neurons from neurodegeneration
- Scientists are just engineering the first DLK-specific inhibitors



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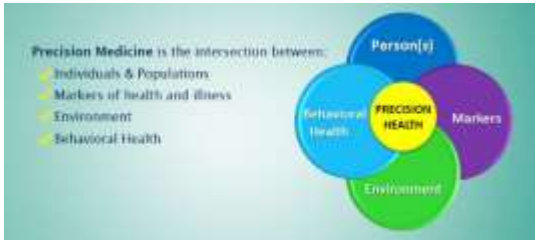
New Approaches: Precision Medicine

- Medical care designed to optimize efficiency or therapeutic benefit for particular groups of patients, especially by using genetic or molecular profiling
- ANAVEX®2-73, a selective sigma-1 receptor agonist, was studied in a Phase 2a trial with moderate AD patients for 57 weeks
- Systematic analysis identified several genetic variants impacting the response (if these persons were excluded (about 20% of study participants), then results show noticeable improvement
- Development of ANAVEX®2-73 utilizing genetic biomarkers could lead to a pre-specified population, who demonstrated a confirmed response with ANAVEX®2-73
- First full genomic analysis of an AD drug resulting in the identification of actionable genetic variants



Other Avenues for Treatment & Understanding

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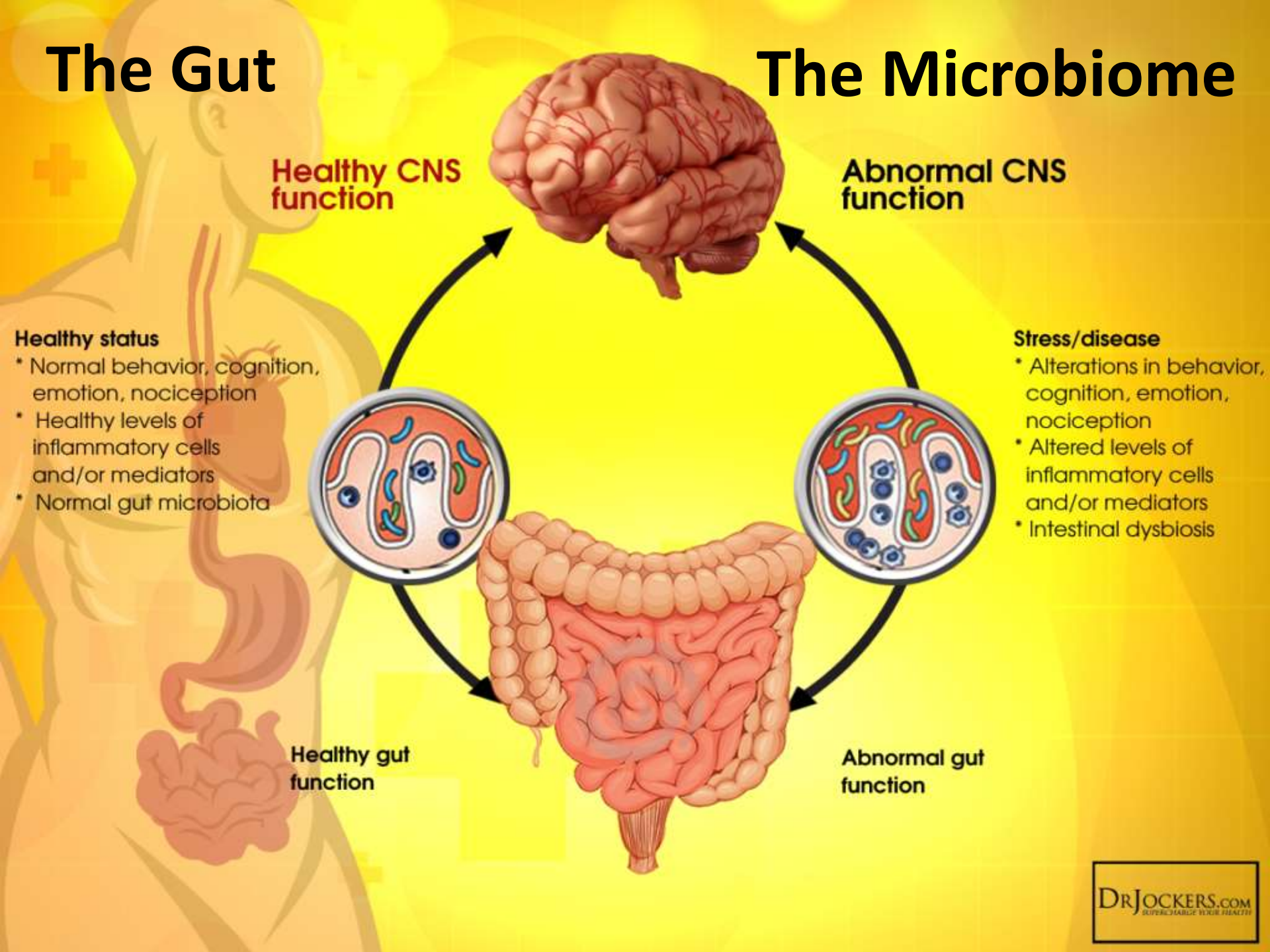
SPRINT MIND

- SPRINT Memory and Cognition IN Decreased Hypertension
- Randomized **clinical trial** comparing two strategies for managing high blood pressure (hypertension):
  - Intensive Strategy: Systolic blood pressure goal < 120 mm Hg
  - Standard Care: Systolic blood pressure < 140 mm Hg.
- Will a lower blood pressure target reduce risk of developing MCI or dementia (and reduce the total volume of white matter lesions in the brain)?
- N = 9,361 hypertensive older adults with increased cardiovascular risk but without diagnosed diabetes, dementia, or prior stroke

SPRINT MIND: 2019 Findings

- Significant reductions in the risk of MCI and MCI/Dementia in the Intensive Strategy group as compared to Standard Care group
- First trial to demonstrate a reduction in new cases of MCI and MCI/Dementia
- Strongest evidence to date about reducing risk of MCI and dementia through the treatment of high blood pressure
- The future of reducing MCI and dementia could be in treating the whole person with a combination of drugs and modifiable risk factor interventions

The Gut The Microbiome

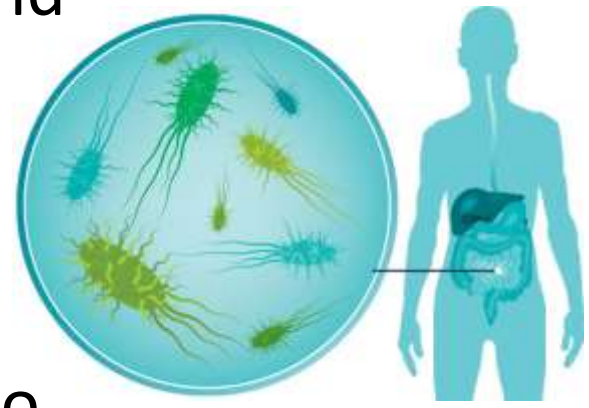


Key Terms for All This Fun

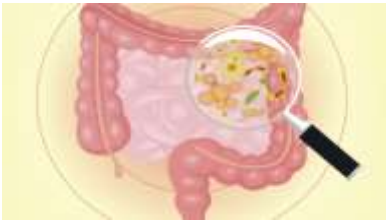
- The Gut
  - The stomach
- The Microbiome
  - Microbes in the gut that that protect us against germs, and break down food to release energy and produce vitamins
- Lipids
  - Fats (including cholesterol and triglycerides)—Important parts of living cells that together with carbohydrates and proteins
  - Several of the genes associated with Alzheimer's, including APOE-e4, are involved in lipid transport or metabolism
  - Blood flow supplies lipids to the brain, and a majority of circulating lipids are synthesized in the liver and gut
  - Lipids make up most of the brain's mass, so changes in the production or transport of lipids may have a significant effect on brain structure and function

Ties to the Gut

- **Gut-Liver-Brain Axis in Alzheimer's Disease**
- New studies investigated how the digestive system, including gut and liver functions, may be related to changes in the brain and AD
- Diet changes the gut bacteria (microbiome) and this can impact brain health
- Certain changes in gut bacteria are tied to inflammatory and autoimmune conditions, which are associated with AD
- NIH M2OVE-AD consortium: Studying liver/brain connections looking for new new targets for treatment and prevention



Four Key Studies



- **Plasmalogens** (Kaddurah-Daouk and ADNI Study Group, 2018)
  - Reduced levels of **plasmalogens**, a class of lipids that are integral to cell membranes, may increase risk of AD by reducing key lipids that the brain needs and this finding correlated with CSF tau levels
- **Bile Acids** (Nho, AAIC, 2018)
  - High levels of primary bile acids (synthesized from cholesterol in the liver) are correlated with ↑ CSF p-tau and CSF t-tau values, ↓ hippocampal volume and ↓ brain glucose metabolism
- **Lipid Metabolism** (Barapul et al., ADNI GROUP, AAIC, 2018)
  - AD associated with failure properly absorb key unsaturated fatty acids (e.g., EPA, DHA [fish oils]), especially in obese males
- **Genetics** (Ahmad, et al., AAIC, 2018)
  - Key AD genes (APOE-e4, SORL1, ABI3, TREM2, MS4A6A, ABCA7) tied to decreased levels of cholesterol components important for the health and repair of brain cell membranes
- **So?**
  - Could we use gut indicators as accurate markers of AD for non-invasive screening tool from blood?
  - Do they act as a cause, trigger or risk/protective factors?

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New Insights into Women and AD Risk

New Alzheimer's Association Supported Studies

- Almost 2/3 of Americans with Alzheimer's disease are women
- Why are women at higher risk?
- Belief: Women live longer than men and older age is biggest AD risk
- New research suggests higher risk could due to biological or genetic factors, different life experiences, (e.g., education, occupation), rates of heart disease, or even sex-based standards for cognitive tests

Four Key Studies

- **Reproductive History** (Gilsanz et al., AAIC, 2018)
  - Three or more children, fewer miscarriages, menstrual periods at a younger age, later age of menaupause all related to lower dementia risk

- **Pregnancy** (FOX ET AL., AAIC, 2018)
  - More months in pregnancy = lower dementia risk
  - Not simply estrogen exposure, but better nutrition, reducing or stopping smoking and drinking, also may be that having more kids increases cognitive reserve through cognitive challenge
- **Hormone Therapy** (Gleason et al., AAIC, 2018)
  - No negative effect on cognition in women who initiated hormone therapy between ages 50-54, but those who initiated ages 65-79 had lower global cognition
- **Better Verbal Memory**
- Advantage in verbal memory mask early AD, so we may need sex-specific test "cut points" to improve early detection in women
- Results may guide women's healthcare during and after the menopausal transition and help women make <u>personalized</u> and informed decisions

Special Populations: LGBT Seniors

(Fazio et al., AAIC, 2018)

- 2.7 million LGBT people over age 50, with that number doubling over next 15 years
- 200,000 LGBT individuals with dementia in the US, but almost nothing was known about the prevalence of dementia among people without HIV/AIDS dementia
- LGBT community faces similar health concerns as the general public, but LGBT with dementia face uniquely challenges
  - Even with recent advances in LGBT rights, LGBT older adults often marginalized and face discrimination
  - 2X as likely to age without a spouse or partner, 2X as likely to live alone, and 3-4X times less likely to have children –limiting their support
  - 40% of LGBT older people in their 60s and 70s say their healthcare providers don‘t know their sexual orientation
- Pressing health issues for LGBT people:
  - Lower rates of accessing care (up to 30%)
  - Increased rates of depression
  - Higher rates of obesity in the lesbian population
  - Higher rates of alcohol and tobacco use for LGBT persons
  - Higher risk factors of cardiovascular disease for lesbians

Special Populations: Oldest Old

(Leung et al., AAIC, 2018)

- "Conventional wisdom:" If you reach age 90+ without dementia, you are very unlikely to get it
- Studied 4,100 persons aged 95-110 in 11 countries
  1. Prevalence increased with age in all countries
  2. Risk of dementia and cognitive/functional decline varied significantly between countries (i.e., cultural and lifestyle factors play a role in remaining physically and cognitively healthy)
  3. Persons with higher levels of education had lower prevalence of dementia and cognitive impairment
  4. Women in this age group had a higher risk of dementia and cognitive impairment

Special Populations: Younger Onset AD

(Rhodius-Meester et al., AAIC, 2018)

- Studies of survival times in persons with dementia have varied considerably (3 - 12 years)
- 4,495 early-onset dementia patients in a memory clinic with any type of dementia, MCI, or subjective cognitive decline
- The median survival time across all groups was **6 years**, but varied by dementia type:
  - 6.4 years in FTD
  - 6.2 years in AD
  - 5.7 years in VAD
  - 5.1 years LBD
  - 3.6 years for rarer causes of dementia

- Survival time hardly differed when comparing younger patients (age 65 or younger) to those older than 65
  - Despite being younger and perhaps physically ‘healthier’

Special Populations: Caregivers, the "Second Patient"

Many Studies, AAIC, 2018

- Negative effects
  - High levels of stress
  - Physical health suffers
    - e.g., ↓immunity, ↑mortality
  - Social isolation
  - Financial hardship
- Positive effects
  - Increased reciprocity
  - Increased altruism

Good Practices for Clinical Evaluation of AD

(Atri et al., AAIC, 2018)

- In 2017, the Alzheimer's Association convened a Diagnostic Evaluation Clinical Practice Guideline workgroup (AADx-CPG) to review timely and accurate diagnosis and disclosure
- Currently no U.S. consensus for best clinical practice guidelines for integrated multispecialty clinical evaluation of cognitive impairment and suspected AD/ADRD
- At their core, the recommendations include guidance that:
  - All middle-aged or older individuals who self-report or whose care partner or clinician report cognitive, behavioral or functional changes should undergo a timely evaluation
  - Concerns should not be dismissed as "normal aging"
  - Evaluation should involve not only the patient and clinician, but also a care partner

FDA Guidelines for Treatment of Behavioral Symptoms

- Behavioral symptoms of dementia often cause the greatest caregiving challenges and leading causes for placement in assisted living or a nursing home
  - Agitation, anxiety, insomnia, depression, wandering, incontinence, disinhibition

- No approved drug treatments are available
- Psychotropic medications may need to be considered when behaviors have not responded to non-pharmacologic approaches, especially if causing physical or emotional harm to the person with dementia or caregiver
- Must be used with extreme care and must be regularly evaluated to determine the appropriate time to stop
- Using antipsychotics to treat these behaviors was associated with increased mortality
- Need for new research on new medication (e.g., Nuedexta, Mibrampator, Nabilone)

Possible Treatment of Non-Cognitive Symptoms

(Lanctôt ET AL., AAIC, 2018)

- Nabilone is a synthetic form of THC, the psychoactive element in marijuana
- 39 participants with average age of 87 received Nabilone
- Agitation improved significantly compared to placebo.
  - But, more people in the study experienced sedation on nabilone (45%) compared to placebo (16%)
- Marijuana is, essentially, an untested drug in Alzheimer's and yet no clinical trial data supporting the use

Treatment of Non-Cognitive Symptoms: Sleep

(Figueiro et al., AAIC, 2018)

- AD/ADRD leads to changes in sleep, patterns, insomnia, and daytime sleepiness
- Light/dark patterns are typically experienced by people living in residential care facilities & may underlie sleep pattern disturbances
- Circadian Stimulus Metric (Lighting Research Center)
  - How well does a light source stimulate the circadian system (i.e., suppressing the body's production of the hormone melatonin, well-established marker of the circadian system) after a 1-hour exposure
- Short term study of 43 people in 10 nursing homes
  - Participants who had high-circadian stimulus showed significant decrease in sleep disturbance, depression and agitation
  - Ongoing long-term study

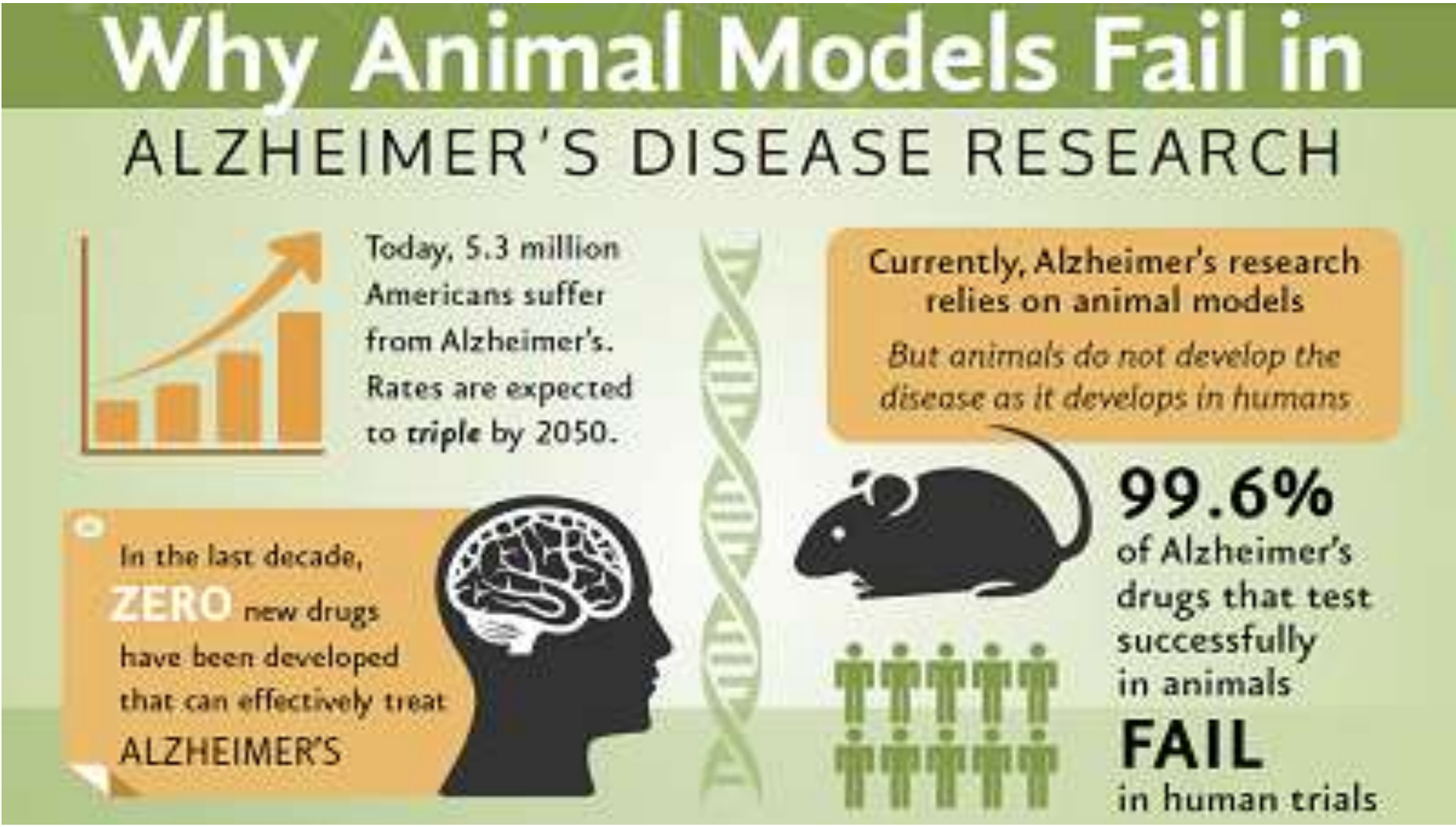
Treatment of Non-Cognitive Symptoms: Sleep

(Fox et al., AAIC 2018)

- Non-benzodiazepine hypnotic "Z-drugs," (e.g., zolpidem, zopiclone and zaleplon) often prescribed to help treat insomnia
- Analyzed existing data from the UK Clinical Practice Research for persons newly prescribed Z-drugs vs persons not prescribed

- Use of Z-drugs was associated with a 40% increased risk of any type of fracture (dose dependent)
- Z-drugs also associated with a greater risk of hip fractures, but not falls, infections, or stroke
- Consider non-pharmacological alternatives, and when Z-drugs are prescribed, care should be given to reduce or prevent falls

Why Research Participants Are So Crucial



National Strategy for AD Clinical Trial Recruitment

- Increasing numbers of potential therapeutic targets moving to clinical trials, **BUT** volunteer numbers have not kept pace
- Growing global AD epidemic and the recent string of negative clinical trialss makes this a critical problem for all of us
- The **National Strategy for Recruitment and Participation in Alzheimer's Disease Clinical Research** is an outgrowth of the National Plan to Address Alzheimer's Disease (NAPA) and focuses on the fact that all recruitment and participation is local and a **shared responsibility** with **shared benefits, we must**
  - Increase awareness and engagement
  - Engage local communities
  - Build and Improve infrastructure for recruiting
  - Develop a science of recruitment to develop and test innovative strategies

Whoa…Lots of Info….Lots of Facts

- AD/ADRD is a critical problem facing all of us……..
  - We must train new clinicians and we have some new ways
- We know what happens, now, even more clearly
  - Cascade….Cascade…..Cascade
- Why can't we prevent/fix it?
  - New meds are in the pipeline and things looking hopeful
  - Precision Medicine….Precision Medicine…..
  - Lifestyle still clearly important
  - Gut…Microbiome….Gut…….Microbiome……
  - How do we increase our research participant pool?
- We know so much more about risk factors
  - Health, gender, genetic, race, pregnancy
- We know more about special populations
  - New possibilities to help caregivers/care partners
  - More info about LGBT community and special age issues
  - What can we to help caregivers/care partners?

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Local research opportunities

How does work we are doing fit into the big picture?

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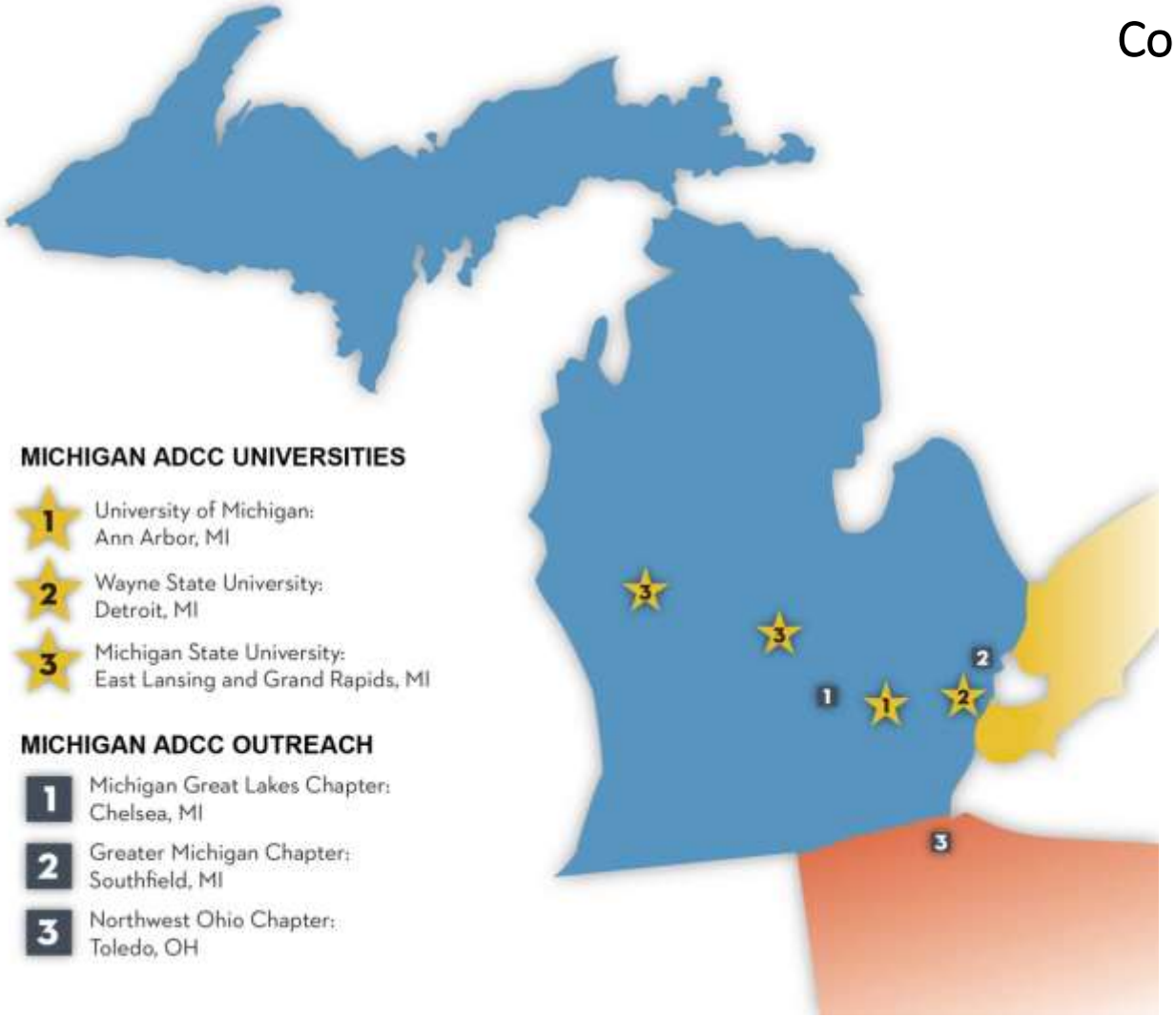
What's new at the Michigan Alzheimer's Disease Center

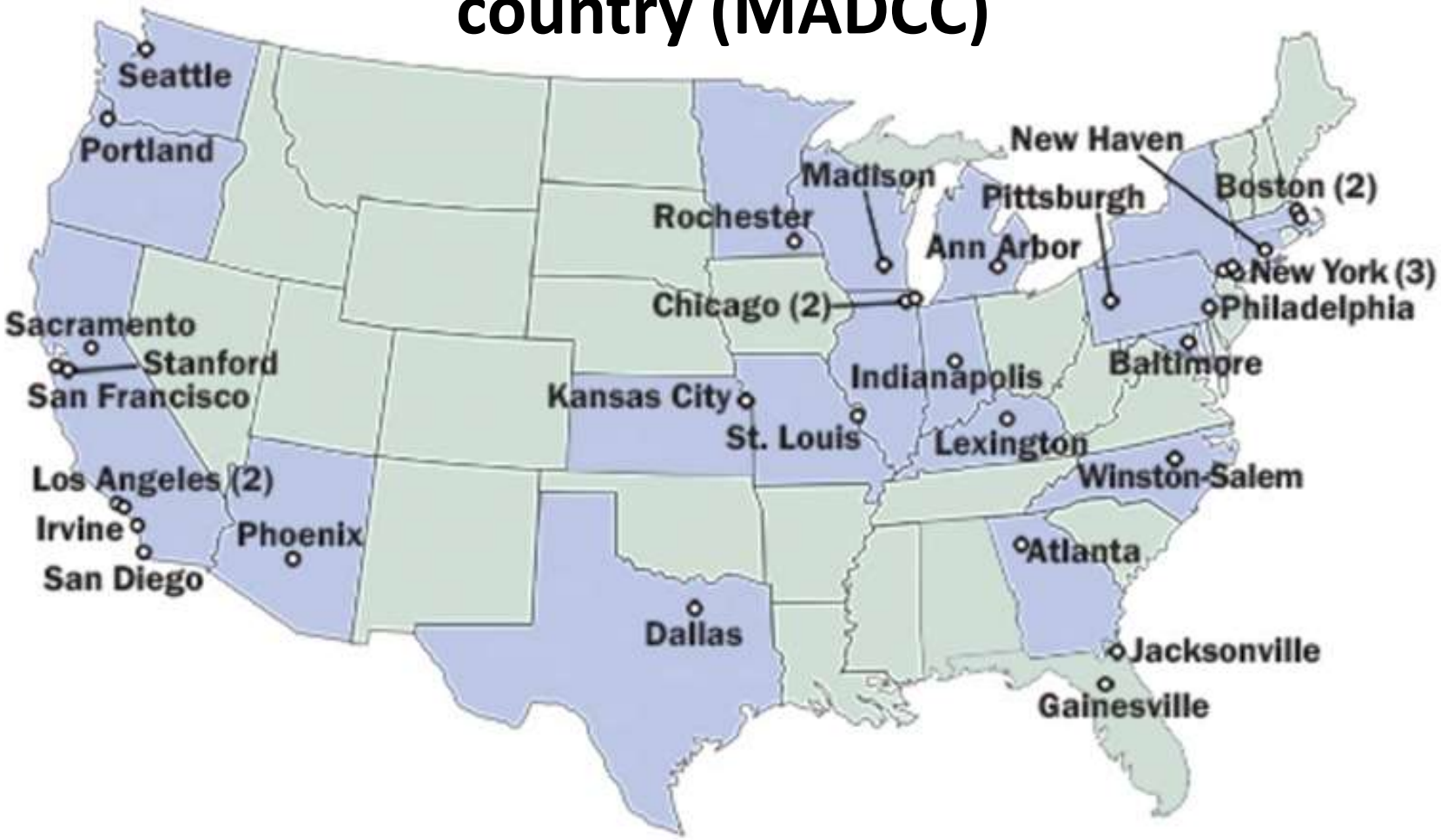
Connecting across the region…



UNIVERSITY OF MICHIGAN

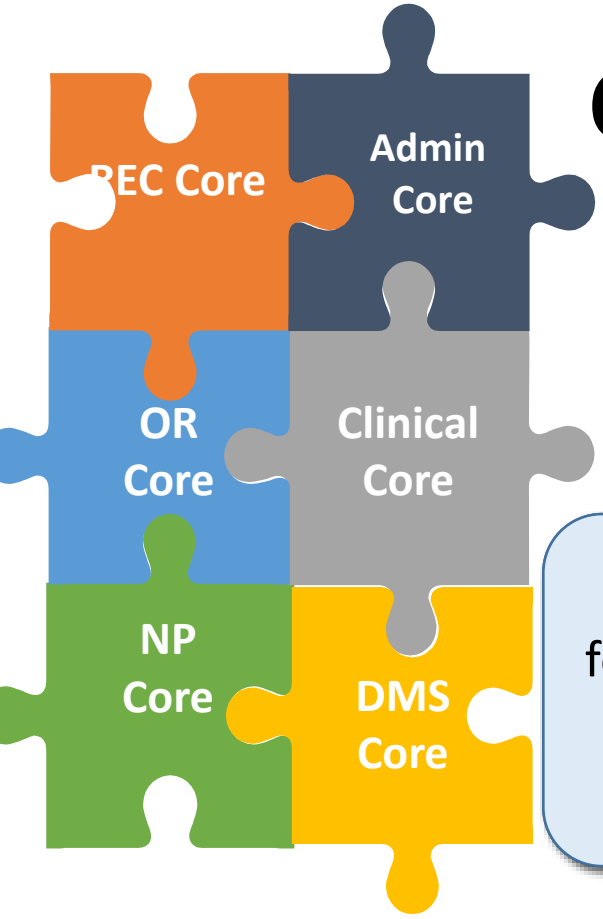
WAYNE STATE

A component of the MADC is one of 31 NIH/NIA funded Alzheimer's Disease Core Centers in the country (MADCC)



https://www.nia.nih.gov/research/dn/national-alzheimers-coordinating-center-nacc

Core Components



Primary Partners

Udall Center for Parkinson's Disease Research

Claude D. Pepper Older Americans Independence Center

Michigan ADCC

Protein Folding Diseases Initiative

MCUAAAR
(Michigan Center for Urban African American Aging Research)

HBEC
(Healthier Black Elders Center)

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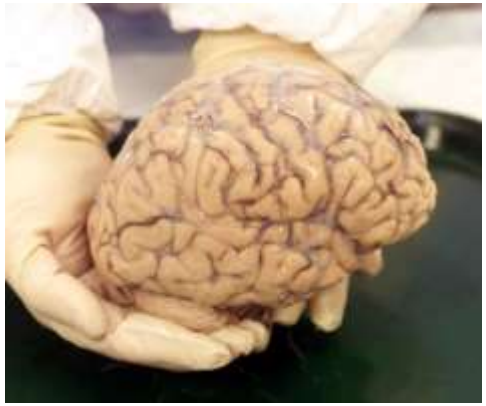
Who makes the MADCC go? The staff!

Brain Donation with the MICHIGAN BRAIN BANK

(Learning more about basic mechanisms)



Matthew Perkins, BS
Michigan Brain Bank Coordinator

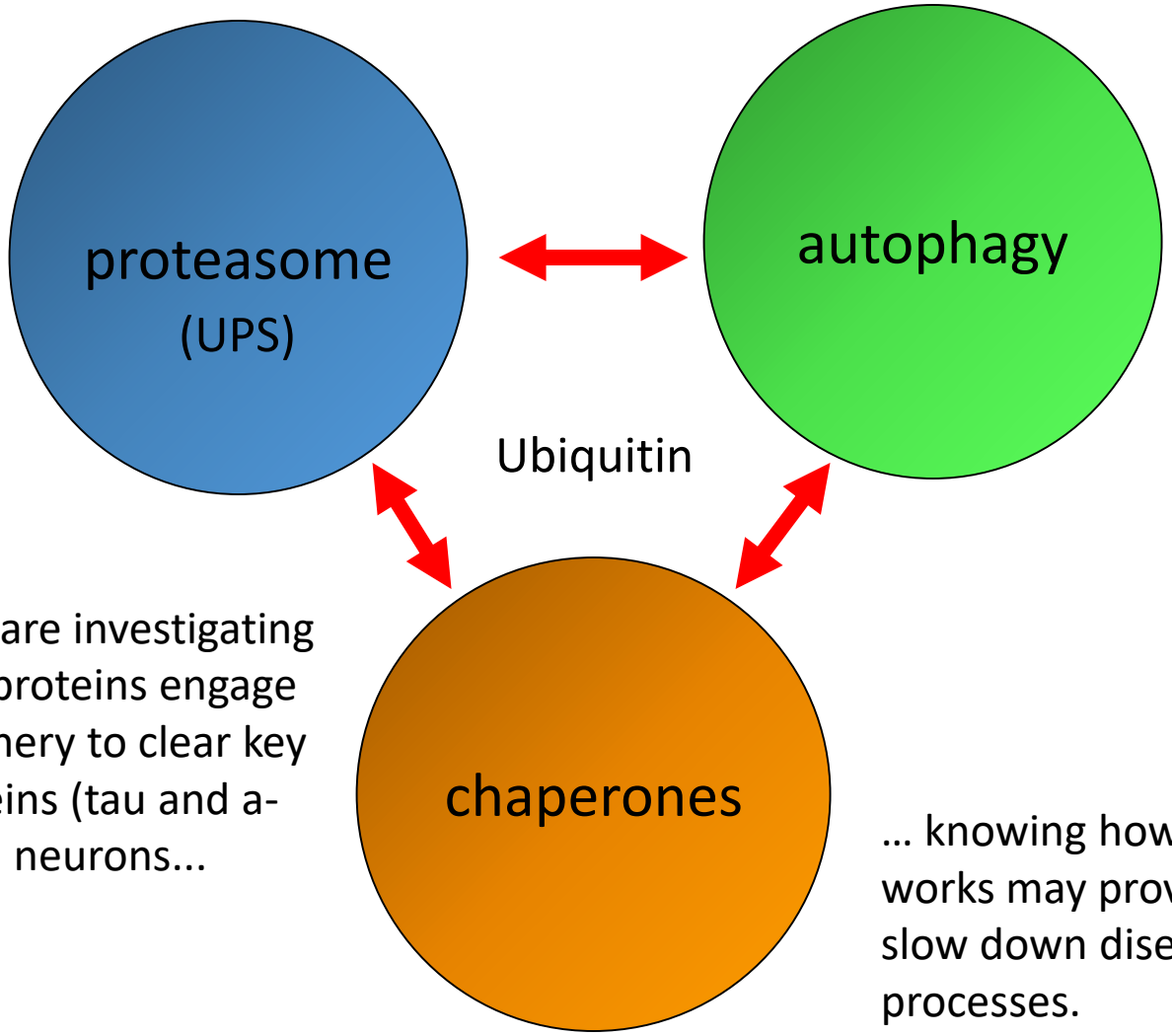
Paulson Laboratory

Reagan	Gehrig	Ali	Guthrie
AD	ALS/FTD	PD	HD
Ab, Tau	many proteins	synuclein	polyglutamine

Degenerative brain diseases share important feature: Specific proteins accumulate and aggregate and brain cells must cope with aggregated protein to continue their vital functions

For years, Paulson studies how cell's "protein quality control" machinery counters toxic disease proteins

Hank Paulson, MD, PhD
Director, Michigan Alzheimer's Disease Center
University of Michigan



Currently, they are investigating how Ubiquitin proteins engage the PQC machinery to clear key dementia proteins (tau and a-synuclein) from neurons...

… knowing how this process works may provide clues to slow down disease processes.

University of Michigan Memory & Aging Project (UM-MAP)

(Longitudinal follow-up for health and lifestyle factors)

- The information gathered will help researchers develop new strategies to prevent neurological disorders
- The UM-MAP study helps researchers learn more about normal memory changes and about specific diseases that cause dementia

We need you!

✓ Over 55 years old
✓ Volunteers with and without memory concerns are important

ADNI3: Brain Aging Study

Judy Heidebrink, MD, MS
Director, Cognitive Disorders Program
University of Michigan

Normal Aging

MCI

Mild

Moderate

Severe

Clinical AD

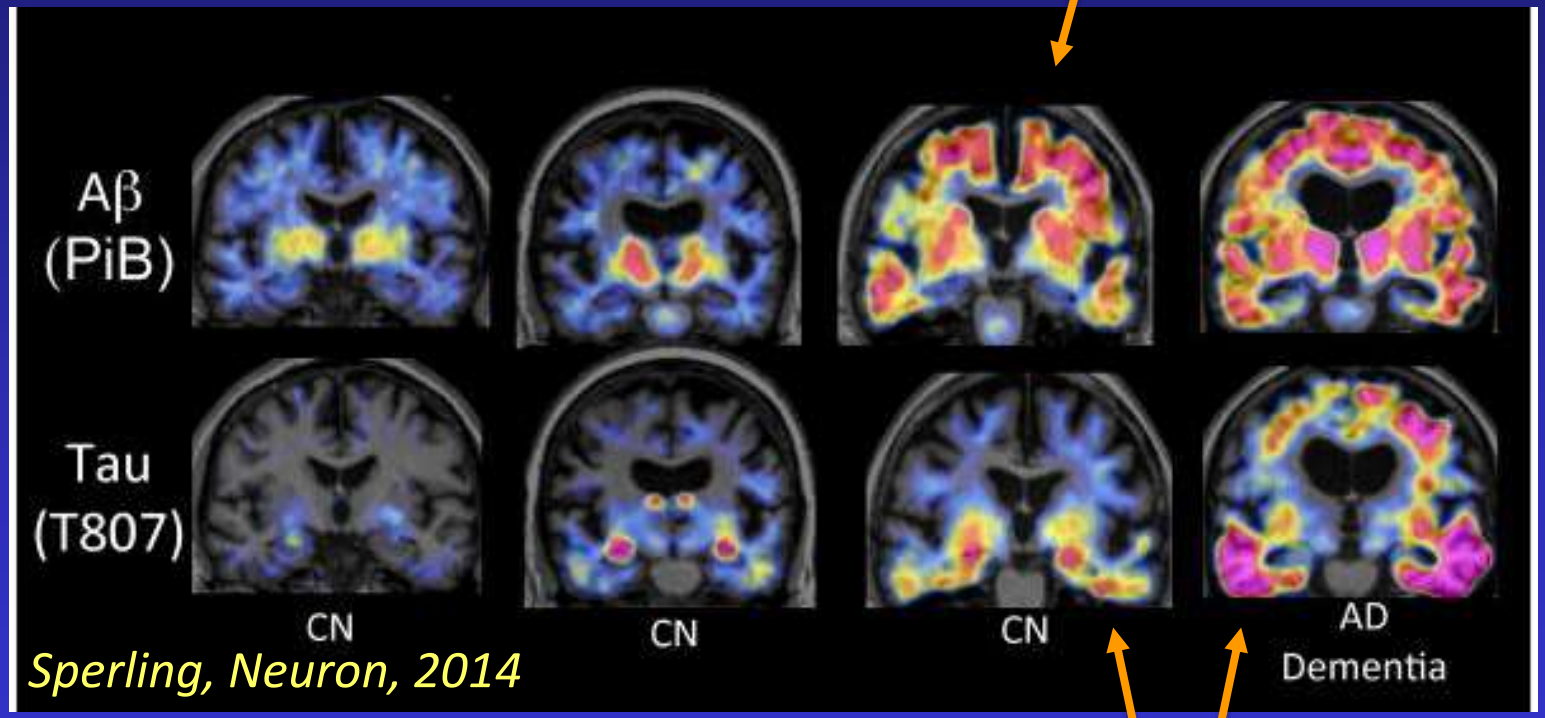
What biomarkers predict the onset and progression of AD?

Cognitive Decline

Time (Years)

PET Amyloid and Tau Imaging

Prior ADNI studies: You can have elevated brain amyloid and normal cognition



ADNI 3: Does brain tau predict cognitive decline?

New Approaches to Computer-Based Testing

- ARMADA Study to validate tablet-based Toolbox
- Comparison Studies of test properties and sensitivity / specificity of different computer-based measures

Bruno Giordani

Tanisha Hill-Jarrett

Voyko Kavcic

Hiroko Dodge

Sarah Shair

Arijit Bhaumik

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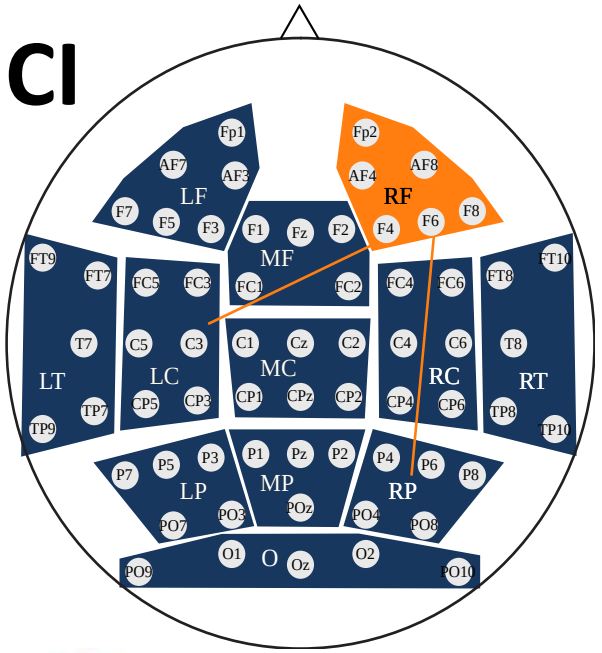
New Methodology to Identify MCI



Accuracy of MCI vs. Controls: 88%

Feature Selection for MCI vs. Control

Features	Frequency
regional PLI between RF and LC	1
One Card Learning	0.83
degree divergence	0.76
Dimensional Card Sorting	0.74
Picture Sequence Memory	0.55
regional PLI between RF and RP	0.21
regional average PLI for RF	0.19
leaf fraction	0.05
maximum vertex degree	0.02
Pattern Comparison	0.02
One Back-Working Memory	0.02

COGSTATE

NIH TOOLBOX® Motor Emotion Sensation Cognition

Voyko Kavcic, PhD
Wayne State University

Bruno Giordani, PhD
University of Michigan

Frontotemporal Dementia Research

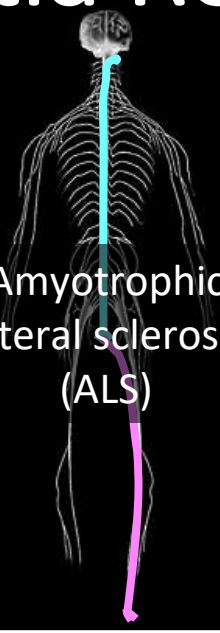
(New options for treatment)

Personality change

Word-finding difficulties

Lack of motivation

Frontotemporal dementia (FTD)



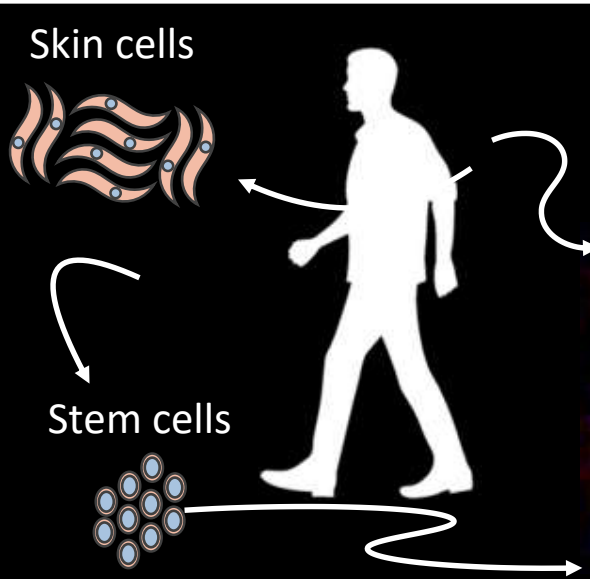
Amyotrophic lateral sclerosis (ALS)

Muscle weakness

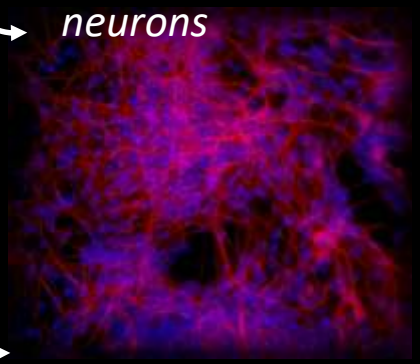
Overactive reflexes

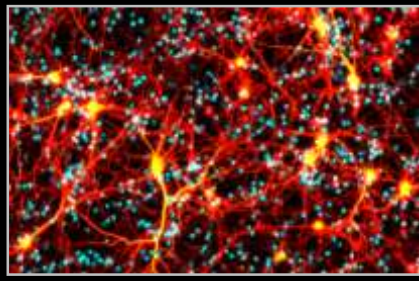
Loss of muscle

Sami Barmada, MD, PhD
University of Michigan



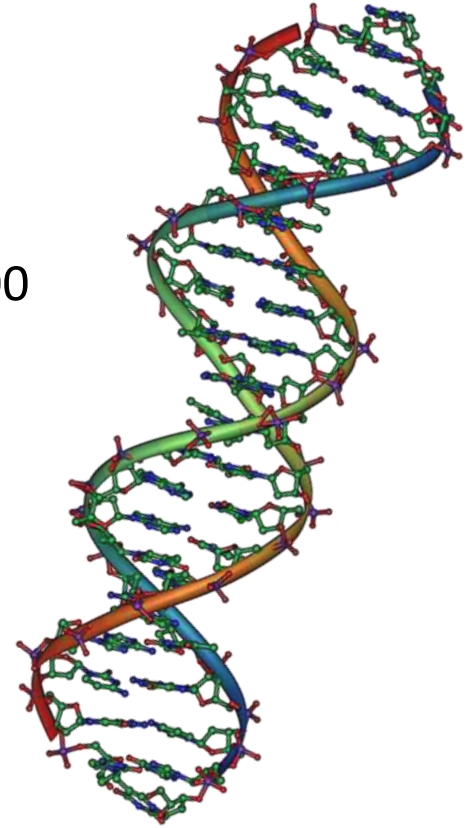
Human neurons





“Big Data” Projects and AD

(Putting all the information together)



Global Alzheimer's Association Interactive (GAAIN)

Massive data network of genome sequencing data, neuroimaging, and neuropsychological data on over 800 participants

By being open access, *GAAIN will transform how neuroscience data* is shared and accessed by scientists throughout the world and thereby accelerate investigation and discovery

Hiroko Dodge, PhD
University of Michigan

Ivo Dinov, PhD
University of Michigan

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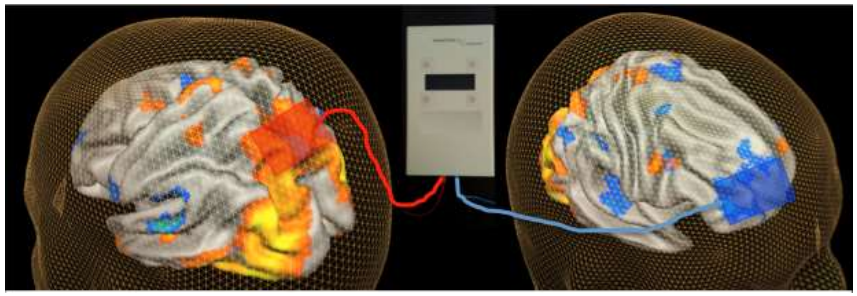
Memory Rehabilitation Studies

Benjamin Hampstead, PhD
University of Michigan



- **Transcranial Direct Current Stimulation (tDCS) is** a form of neurostimulation (neuromodulation) where very low levels of constant current are delivered to targeted areas of the brain
- tDCS can increase cognitive performance on a variety of tasks, depending on the area of the brain being stimulated

Contact Julia Laing
734-764-4709

Newly Funded NIA R01 AG058724

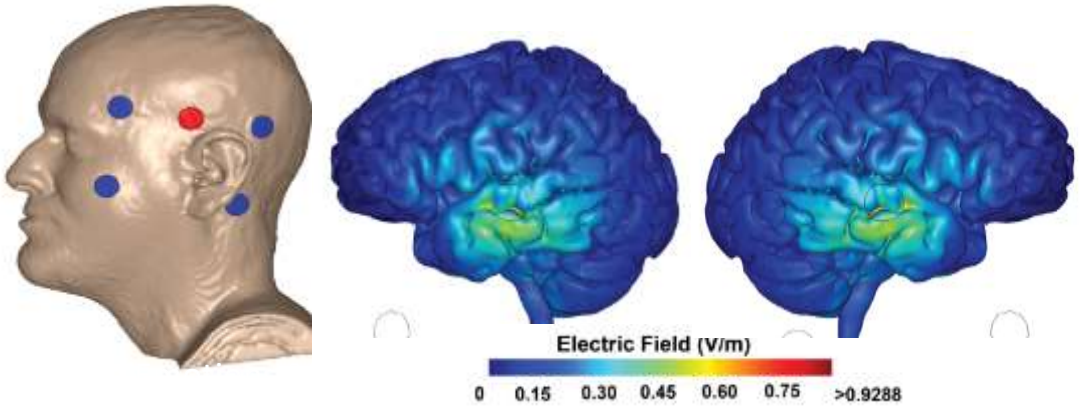
Treating mild cognitive impairment with High Definition transcranial direct current stimulation

Study 1. Double-blind randomized controlled study (RCT) combining memory strategy training and HD-tDCS over the brain's left prefrontal cortex (PFC)

Study 2. What level of current is necessary?

- Double blind RCT comparing sham, 1mA, 2mA, 3mA HD-tDCS for 5 sessions

Contact Julia Laing
734-764-4709



Driving Studies

- Fatigue Mitigation in Older and Younger Drivers
  - Developing safe and user-friendly methods to assist drivers in longer-distance driving
- Personalized System to Assist Aging Drivers
  - Investigates driving behaviors and environmental and personal factors that might influence driving safety
- Enhancing Safe Mobility Among Older Drivers
  - How do older drivers change driving behavior over time and what influences such changes


Bruno Giordani, PhD


Carol Persad, PhD


Yi Murphey, PhD


David Eby, PhD


Lisa Molnar, PhD

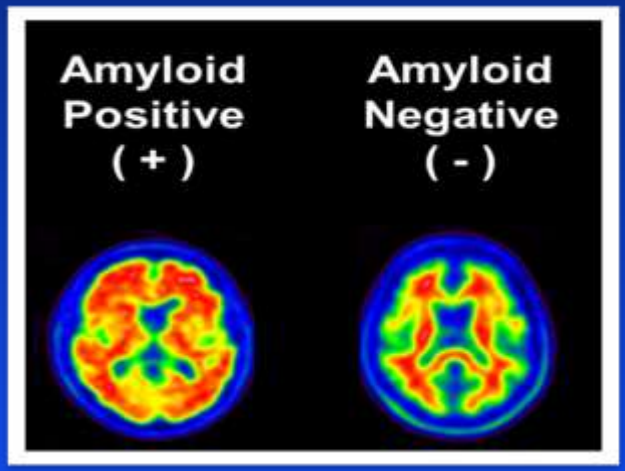
Amyloid Imaging

(Increasing the sample pool)

REVEAL-SCAN
RISK EVALUATION & EDUCATION FOR ALZHEIMER'S DISEASE
The Study of Communicating Amyloid Neuroimaging

Scott Roberts, PhD
University of Michigan

- Multisite RCT now underway
- Cognitively normal older adults offered opportunity to learn their amyloid status
- Followed for 6 months to assess impact of disclosing scan results
- Evaluations include cognitive, psychological, and behavioral impact



Training the next generation of clinicians

- Medical school courses: family doctoring and family medicine
- UM School of Social Work online advanced dementia certificate program

Nan Barbas, MD, MSW

Bruno Giordani, PhD

Judy Heidebrink, MD, MS

Scott Roberts, PhD

Ben Hampstead, PhD

Dementia Caregiver Studies

- Tele-Savvy Online Education Program
  - Online group education for caregivers adapted from an established in-person program
- Characterizing Dementia Caregiver Styles
  - How caregiver styles impact their mental & physical health, use of health services
- Adaptive Coping Engagement (ACE) survey-based project for African-American caregivers
  - Help develop culturally tailored programs
- Burden and Service Utilization Among African American and White Caregivers: Similar or Different Patterns?
  - Studying community services needed by caregivers

Hiroko Dodge PhD

Lenette Jones, PhD

Tanisha Hill-Jarrett, PhD

Salli Bollin, PhD

Bruno Giordani, PhD

Edna Rose, PhD

Sheria Robinson-Lane, PhD

Improving Health Outcomes of Black Caregivers of Older Adults with Dementia

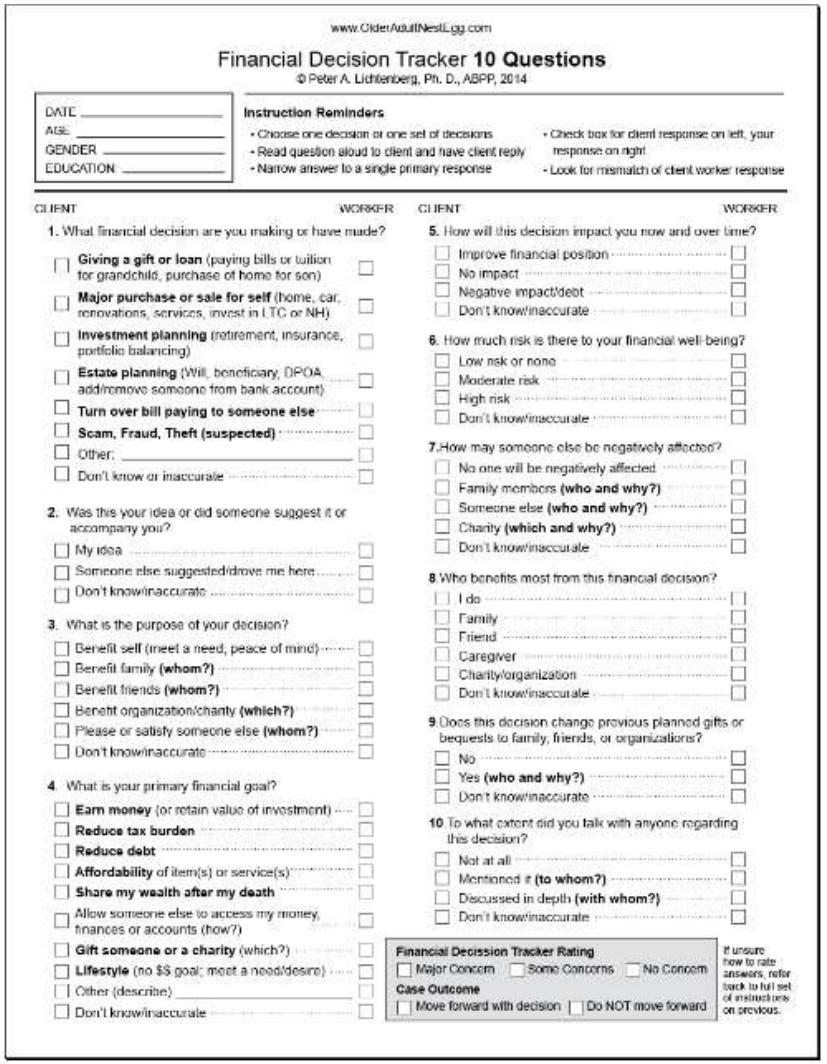
- Family caregivers have multiple risk factors for new onset dementia and few interventions are designed to assist
- The shared values, beliefs, and customs that create communities extend to ways of coping.
- Identifying and reinforcing the adaptive coping strategies communities prefer to use, strengthens both the community and the individual
  - Evaluate the effects of physical function, social supports, coping, caregiving self-efficacy, self-efficacy in managing personal health, psychological distress, and positive aspects of caregiving for both African American and non-African American caregivers

Sheria Robinson-Lane, PhD, RN
School of Nursing
University of Michigan

A Person-Centered Approach to Financial Capacity Assessment

Peter Lichtenberg, PhD
Director, Institute of Gerontology
Wayne State University

Financial exploitation and decision-making capacity have become critical issues in caregiver and patient lives.



www.OlderAdultNestEgg.com

Financial Decision Tracker **10 Questions**

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DATE _____
AGE _____
GENDER _____
EDUCATION _____

Instruction Reminders

- Choose one decision or one set of decisions
- Read question aloud to client and have client reply
- Narrow answer to a single primary response
- Check box for client response on left, your response on right
- Look for mismatch of client worker response

CLIENT WORKER

1. What financial decision are you making or have made?
   - **Giving a gift or loan** (paying bills or tuition for grandchild, purchase of home for son)
   - **Major purchase or sale for self** (home, car, renovations, services, invest in LTC or NH)
   - **Investment planning** (retirement, insurance, portfolio balancing)
   - **Estate planning** (Will, beneficiary, DPOA, add/remove someone from bank account)
   - **Turn over bill paying to someone else**
   - **Scam, Fraud, Theft (suspected)**
   - Other: _____
   - Don't know or inaccurate

2. Was this your idea or did someone suggest it or accompany you?
   - My idea
   - Someone else suggested/drove me here
   - Don't know/inaccurate

3. What is the purpose of your decision?
   - Benefit self (meet a need, peace of mind)
   - Benefit family **(whom?)**
   - Benefit friends **(whom?)**
   - Benefit organization/charity **(which?)**
   - Please or satisfy someone else **(whom?)**
   - Don't know/inaccurate

4. What is your primary financial goal?
   - **Earn money** (or retain value of investment)
   - **Reduce tax burden**
   - **Reduce debt**
   - **Affordability** of item(s) or service(s)
   - **Share my wealth after my death**
   - Allow someone else to access my money, finances or accounts (how?)
   - **Gift someone or a charity** (which?)
   - **Lifestyle** (no $$ goal; meet a need/desire)
   - Other (describe) _____
   - Don't know/inaccurate

CLIENT WORKER

5. How will this decision impact you now and over time?
   - Improve financial position
   - No impact
   - Negative impact/debt
   - Don't know/inaccurate

6. How much risk is there to your financial well being?
   - Low risk or none
   - Moderate risk
   - High risk
   - Don't know/inaccurate

7. How may someone else be negatively affected?
   - No one will be negatively affected
   - Family members **(who and why?)**
   - Someone else **(who and why?)**
   - Charity **(which and why?)**
   - Don't know/inaccurate

8. Who benefits most from this financial decision?
   - I do
   - Family
   - Friend
   - Caregiver
   - Charity/organization
   - Don't know/inaccurate

9. Does this decision change previous planned gifts or bequests to family, friends, or organizations?
   - No
   - Yes **(who and why?)**
   - Don't know/inaccurate

10. To what extent did you talk with anyone regarding this decision?
    - Not at all
    - Mentioned it **(to whom?)**
    - Discussed in depth **(with whom?)**
    - Don't know/inaccurate

Financial Decission Tracker Rating
☐ Major Concern ☐ Some Concerns ☐ No Concern

Case Outcome
☐ Move forward with decision ☐ Do NOT move forward

If unsure how to rate answers, refer back to full set of instructions on previous.

Institute of Gerontology

Does Having MCI Influence Physician Thinking About Stroke Treatment?

Deborah Levine, MD, MPH
University of Michigan

Bruno Giordani, PhD
University of Michigan

Interview Theme	%	Example Quote
Physicians believe MCI patients are older or frailer than patients with normal cognition.	61%	• "So preventive medicines is an interesting concept, right, because a lot of things that are preventive in the patient in the 60s or 50s have never been proven to work in the elderly."
Physicians believe MCI patients are likely to progress to dementia.	50%	• "I would tell them upfront that there is risk of patients with MCI progressing into a condition with dementia"
Physicians believe that MCI patients do not understand treatment.	56%	• "Somebody who is readily confused, delirious at that point in time, I might not send you down for many or as lengthy tests."
Physicians believe that MCI patients do not comply with treatment	39%	• "If you don't think a patient is going to be able to comply with dual antiplatelet therapy there's actually a harm associated with putting a stent in their coronary arteries."
Physicians believe MCI patients want less treatment in general than patients with normal cognition.	22%	• "I certainly have seen examples where the primary team has, you know, taken patients with MCI statements maybe at face value"

Reasons Caregivers / Patients Think Their Neurologists Recommend Fewer Stroke Treatments

Factor	%	Example Quote
Doctors assume MCI patients have poor prognosis	45%	“Or are they just writing them off? ‘Well, they don’t have a future.’”
Doctors assume MCI patients can’t comply with treatment	31%	“Maybe they feel that the patient with mild memory problems might have more trouble remembering to take their medication.”
Doctors discriminate or assume MCI patients have no value	48%	"That, plus, are they discriminating because it’s a memory problem, they’re going to have dementia, Alzheimer’s, you know, they’re not going to have a future?"

Cardiovascular Health

Lenette M. Jones, PhD, RN, ACNS-BC
University of Michigan
School of Nursing

Reducing health disparities in cardiac-related illnesses

Self-management to improve blood pressure control in African American women

Health information behavior (seeking, sharing, and use) to support self-management

Neurobiological mechanisms – how brain activity predicts self-management behavior

Wellness Initiative

at the Michigan Alzheimer's Disease Center

(Putting Wellness into Practice for Care Partners)

Catching Your Breath

- Monthly stress-resilience program

Caregiver Wellness Day

- Half-day wellness retreat

Mindfulness-based Dementia Care

- 8-week course

Laura Rice- Oeschger, LMSW
Wellness Initiative Coordinator

We Need Your Help!

- Volunteer for Research
- Sign up for Trial Match
- Donate your time and support
- Volunteer for our Alz Board Committees
- Join or create a Walk team

Contact us at the MADC:

(734) 936-8803

alzheimers.med.umich.edu

Also, please **Register for Trial Match:**

Go to: www.alz.org/TrialMatch

Or Call: (800) 272-3900

MADCC
MICHIGAN ALZHEIMER'S DISEASE CORE CENTER

Questions?

Contact Us: (734) 936-8803

Ask-UM-MADC@med.umich.edu

alzheimers.med.umich.edu

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@umichalzheimers

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