Early Detection of Dementia and Current Treatments: An Evolving Landscape

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Financial Disclosures

The following CME planners do not have relevant financial relationships with ineligible companies in the past 24 months:

- Leilanie Mercurio, Provider Continuing Education (PCE) Program Manager, L.A. Care Health Plan, CME Planner.
- Jennifer Schlesinger, MPH, CHES, Vice President, Healthcare Services & Professional Training, Alzheimer's Los Angeles, CME Planner.

The following ineligible company has relevant financial relationship with CME Presenter Zaldy Tan, MD, MPH, FACP, Director, Cedars-Sinai Health System / Memory & Healthy Aging Program.

- BioVie Pharma. Dr. Zaldy Tan is on the Advisory Board of BioVie Pharma.

All relevant financial relationship of Dr. Zaldy Tan, CME Presenter, with ineligible company BioVie Pharma has been mitigated.

An ineligible company is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Commercial support was not received for this CME activity.

Learning Objectives

At the completion of the activity, learners can:

1. **Identify the timeline and list three (3) stages of Alzheimer's disease. (Slide28)**
2. **Summarize three (3) risk factors that lead to Alzheimer's disease. (Slides 88, 89)**
3. **Specify at least two (2) current treatments for Alzheimer's disease. (Slides 53, 54)**
4. **Identify three (3) barriers to early detection and diagnosis of Alzheimer's disease. (Slide 43)**

AGENDA

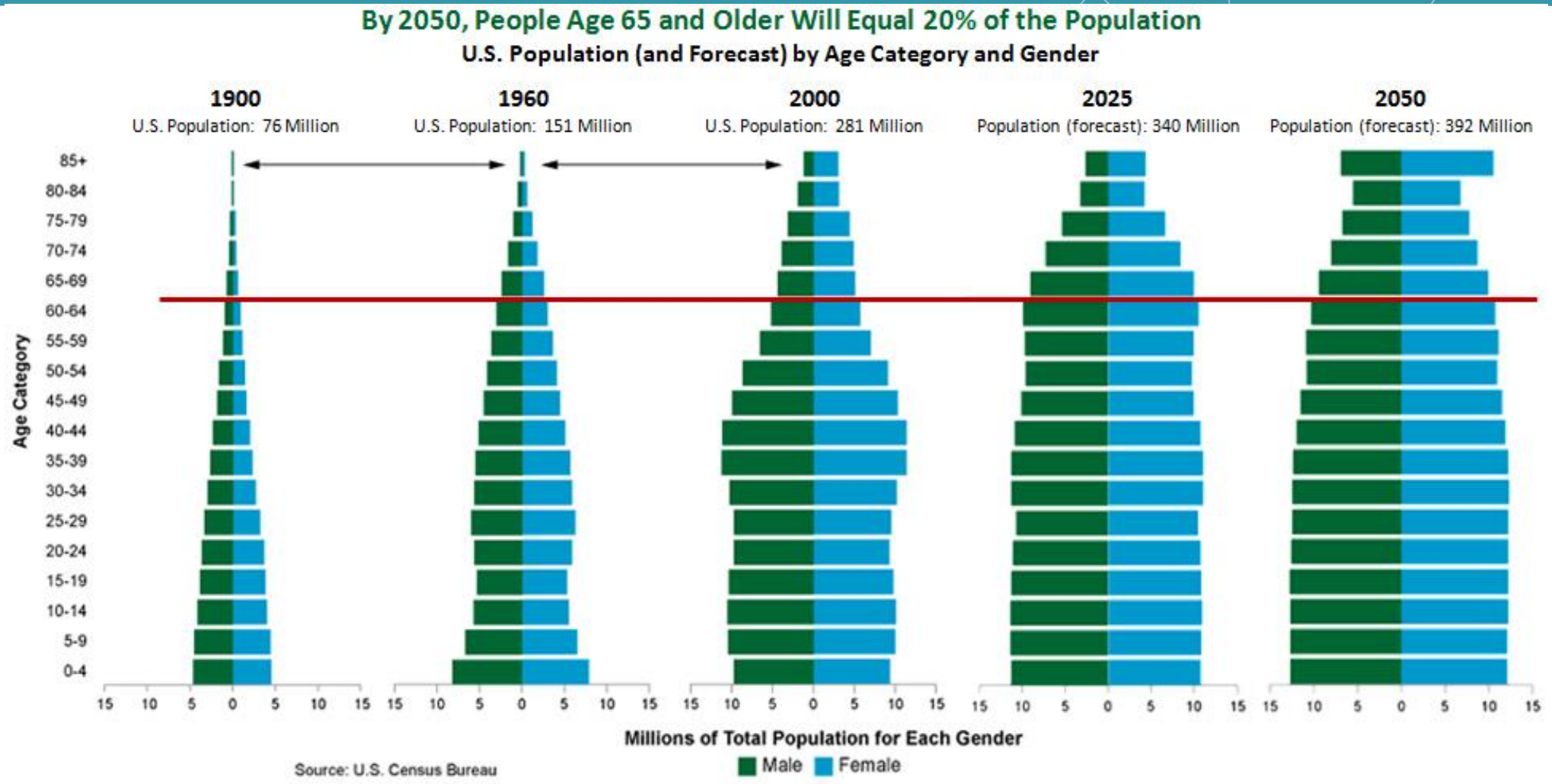
- **Prevalence of Alzheimer's Disease and Related Dementias (ADRD)**
  - Age, Gender and Racial Disparities
  - Risk factors
  - Disease Stages

- **Diagnosis and diagnostic biomarkers for Alzheimer's disease**
  - Types of dementia
  - Pathophysiology of Alzheimer's disease
  - Diagnosis of Alzheimer's disease
    - Cognitive testing
    - Laboratory tests
    - Neuroimaging

AGENDA

- **New and emerging therapies for Alzheimer's disease**
  - FDA-approved medications
  - New and emerging therapies
- **Behavioral Management**
  - Common behavioral challenges
  - Non-pharmacologic approaches
  - Pitfalls of pharmacologic treatments
- **Prevention / Risk reduction for ADRD**

The Silver Tsunami



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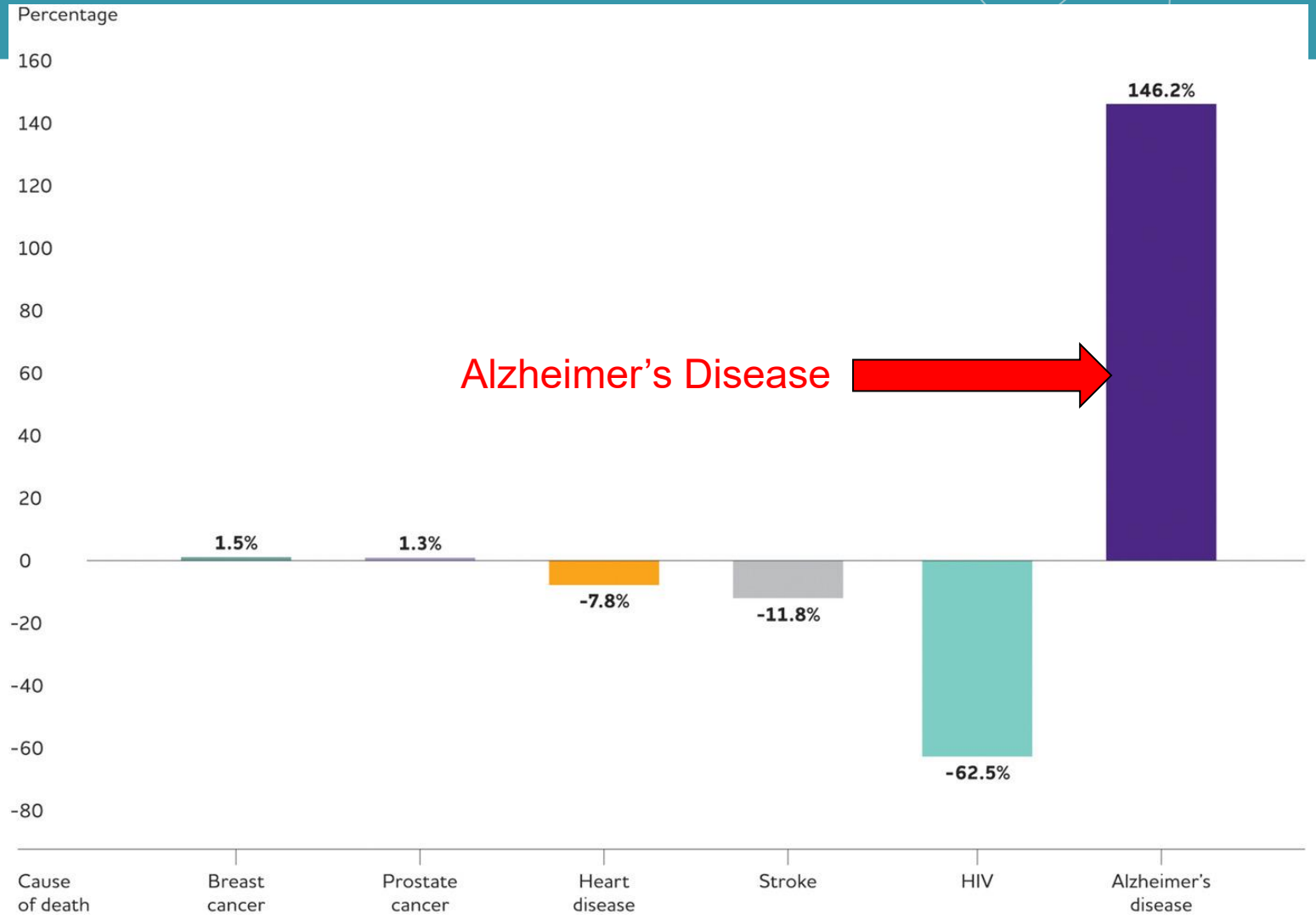
Percent Change in Causes of Death 2000-2018



Alzheimer's & Dementia 2020

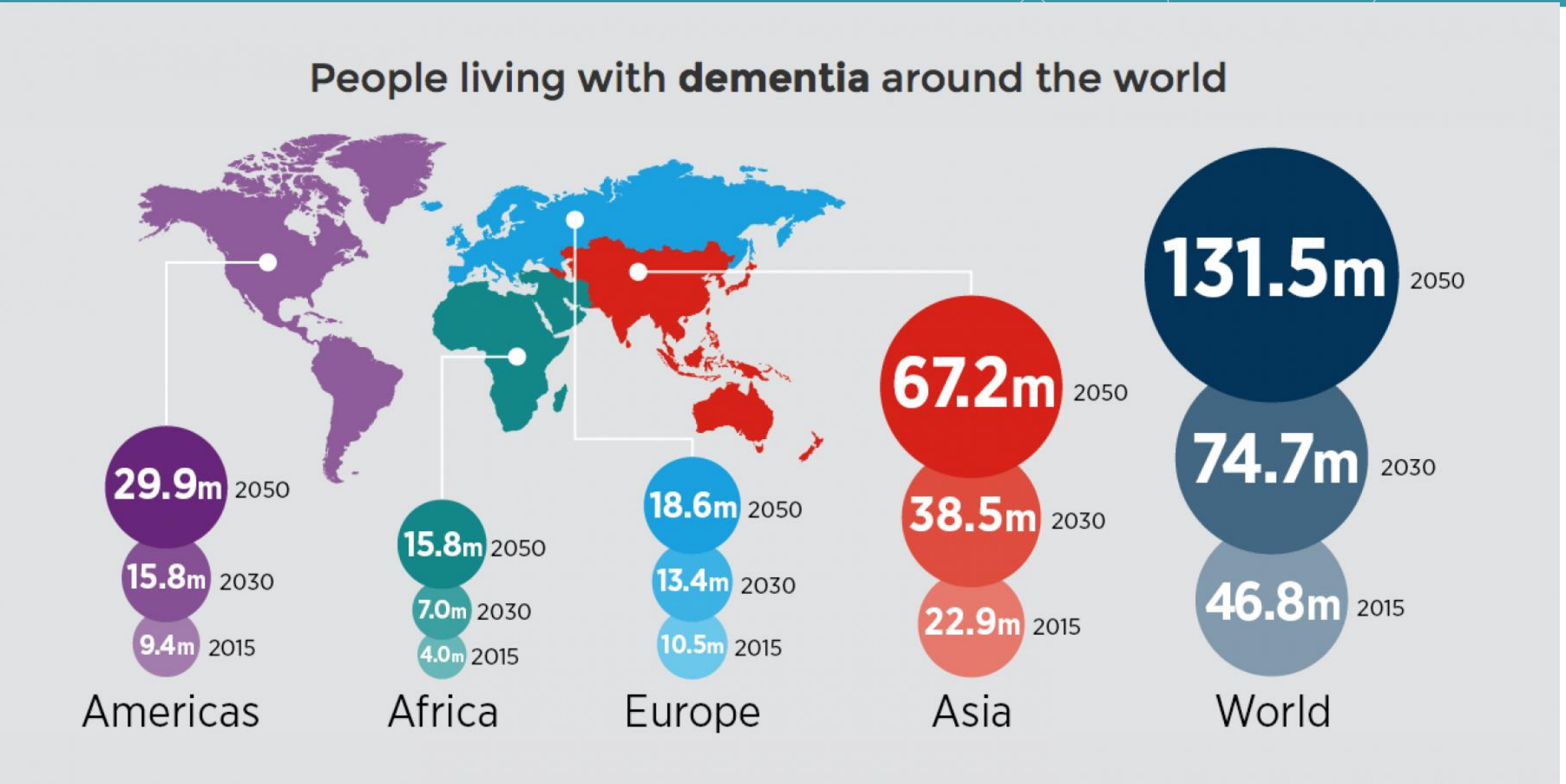
Alzheimer's Disease & Related Dementias (ADRD)

- 6.2 million Americans over age 65
  - Two-thirds are women
  - 200,000 under age 65
  - 11% of people > age 65
  - 32% of people > age 85
  - A third of all seniors who die have dementia

- $321 billion in 2022
  - Costs in last 5 years of life (2010)
    - Heart disease: $175,000
    - Cancer: $173,000
    - Dementia: $287,000

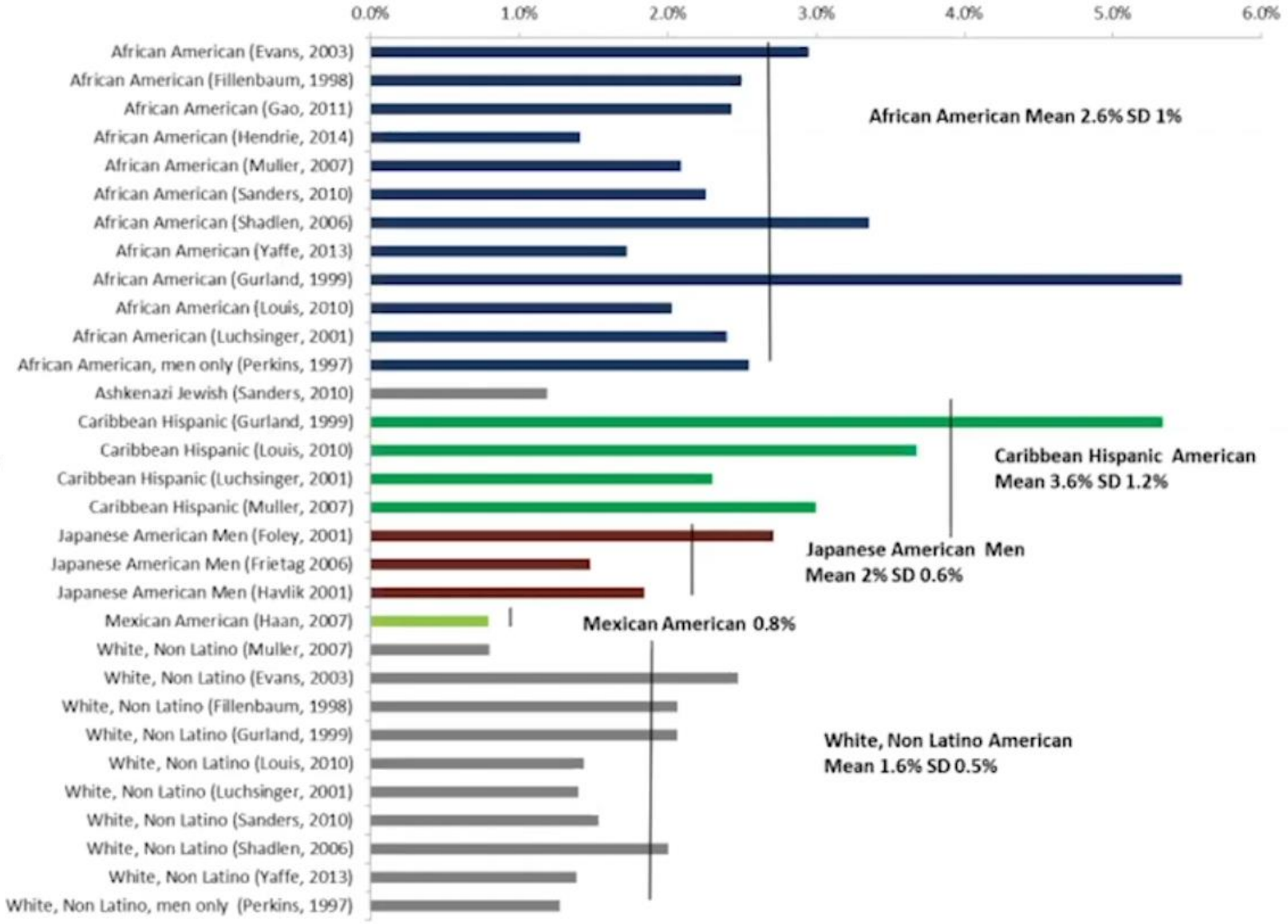
Alzheimer's disease Facts & Figures 2022
https://www.alz.org/alzheimers-dementia/facts-figures

Global Dementia Prevalence

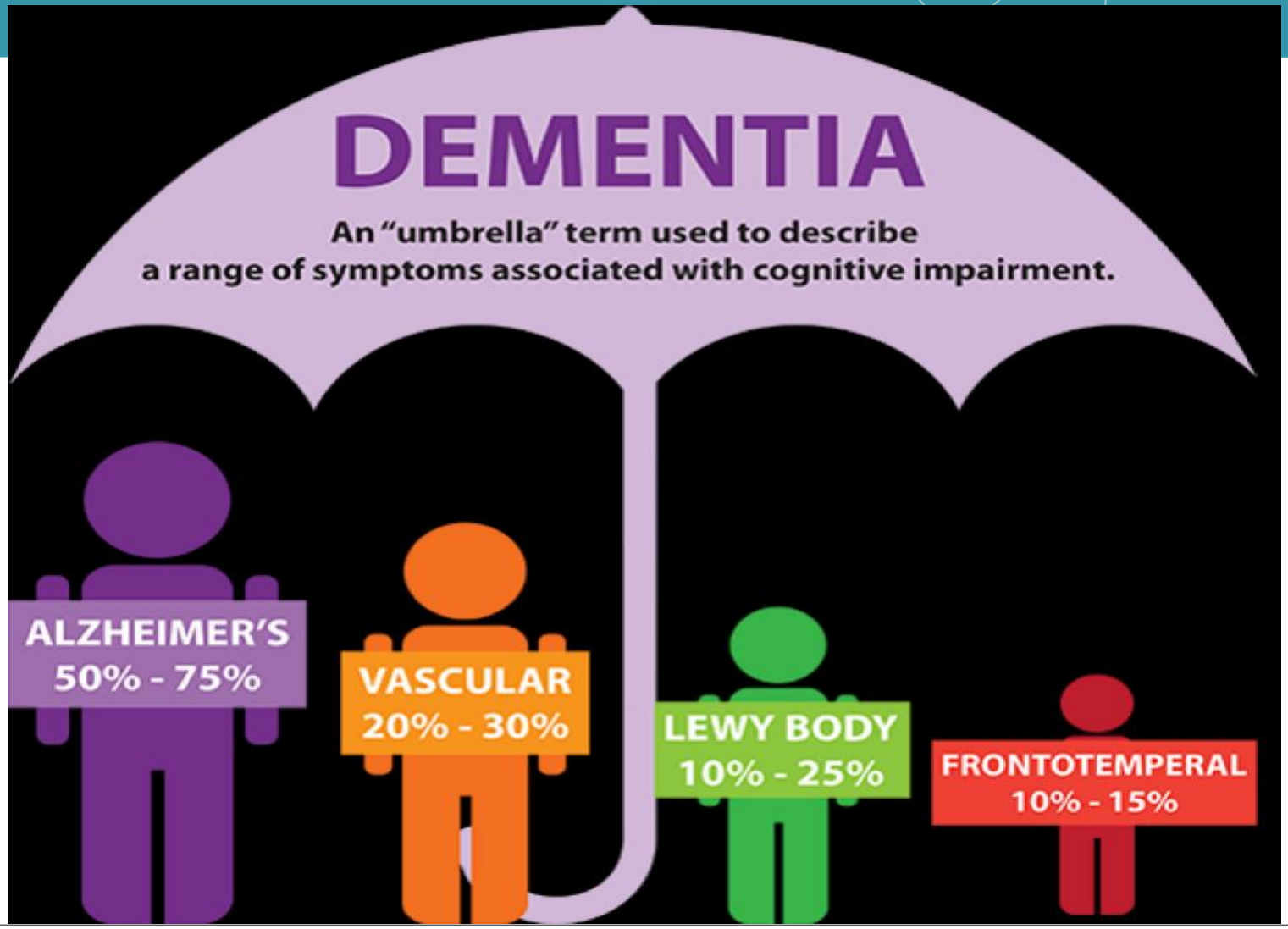


Meta-Analysis: Dementia Incidence by Race

Racial disparities in dementia incidence, prevalence, diagnosis, and survival



Mehta et al, *Alzheimers Dement*, 2017.

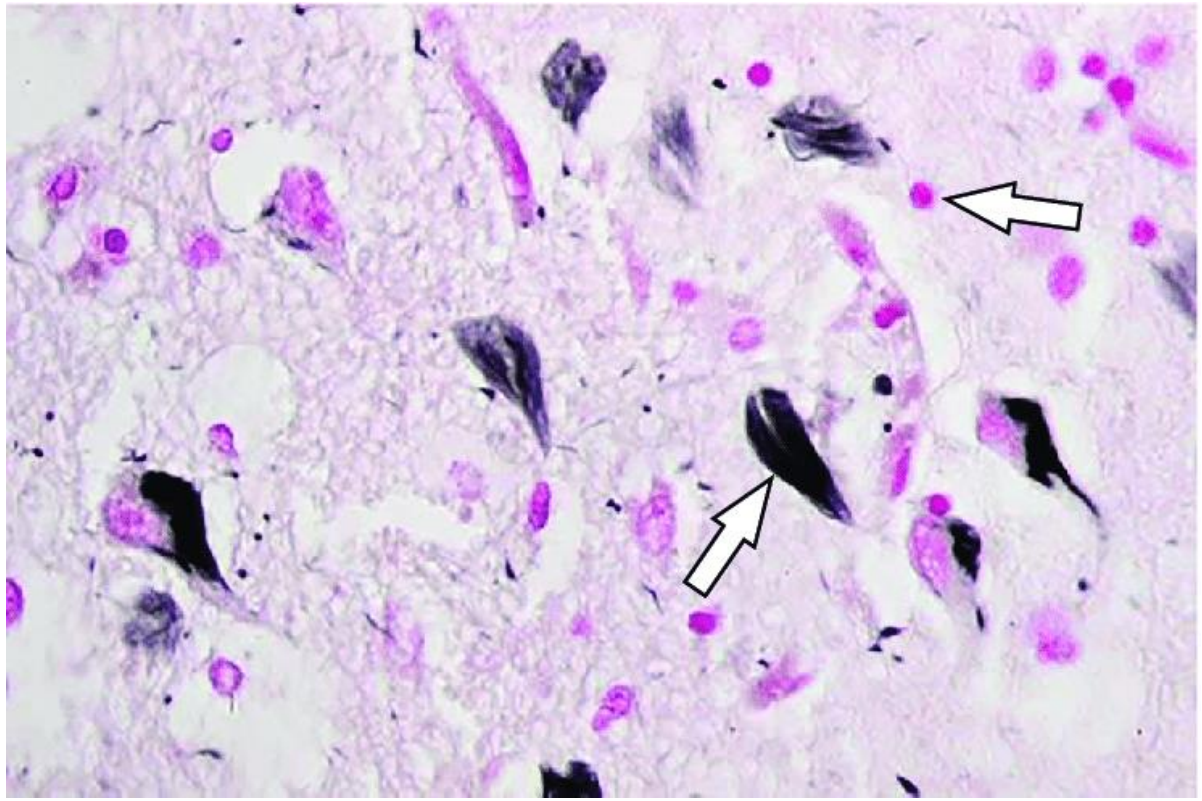

DEMENTIA
An "umbrella" term used to describe
a range of symptoms associated with cognitive impairment.
ALZHEIMER'S
50% - 75%
VASCULAR
20% - 30%
LEWY BODY
10% - 25%
FRONTOTEMPERAL
10% - 15%

Alzheimer's Disease

Accounts for 60-80% of all dementias.

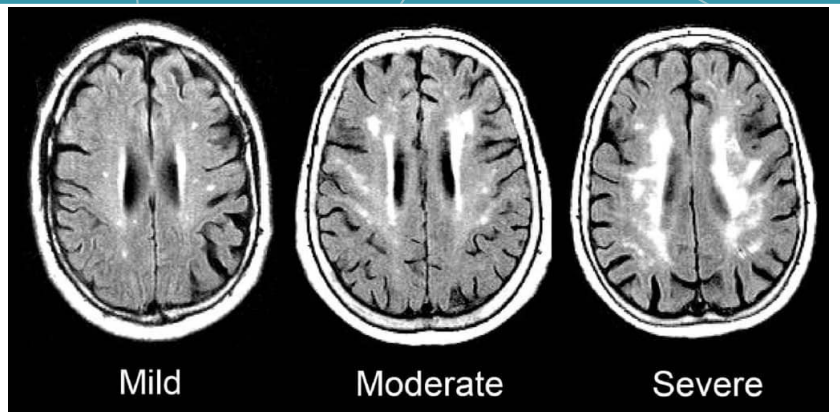
Pathologic neuron loss and decrease in synaptic density.

Amyloid plaques and neurofibrillary tangles are pathologic hallmarks.



Zafeiris D, Rutella S, Ball GR. 2018

Vascular Dementia (VaD)



Accounts for 10-30% of dementia patients.

3rd most common cause of dementia after AD and DLB.

Very common after stroke.

Half of all VaD patients may have mixed VaD and AD pathology.

Risk factors: hypertension, hyperlipidemia, diabetes, cardiac disease, prior strokes, advancing age, ApoE4, smoking.

Obrien DM, Thomas A. Lancet 2015

Lewy Body Dementia (LBD)

Parkinsonian symptoms.

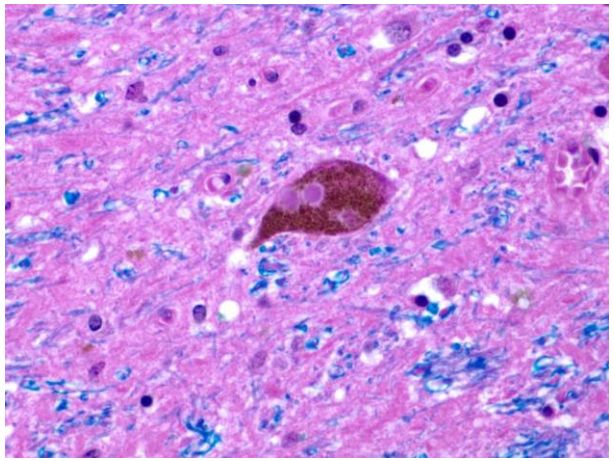
Visual hallucinations (also delusions, auditory hallucinations, depression).

Fluctuating cognition

Memory problems precede motor symptoms.

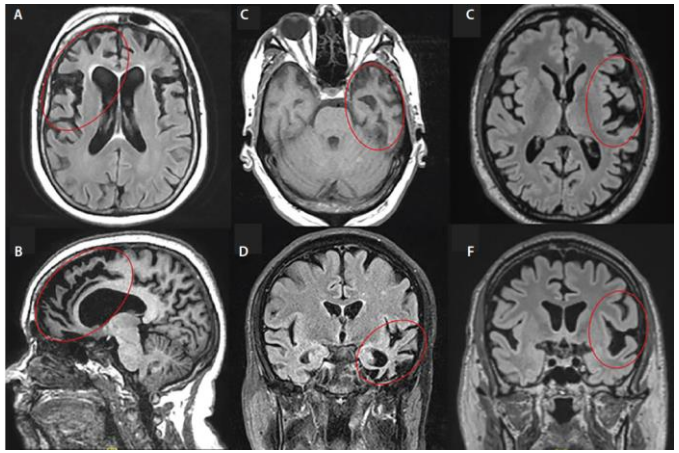
2 to 3-fold increased mortality w/ neuroleptics.

Extensive cholinergic neurotransmission.



Sanford AM. Clin Geriatr Med 2018

Fronto-temporal Dementia (FTD)



Typical age presentation 45-65 yr old.

3rd most common dementia.

Positive family history found in up to 40% of cases.

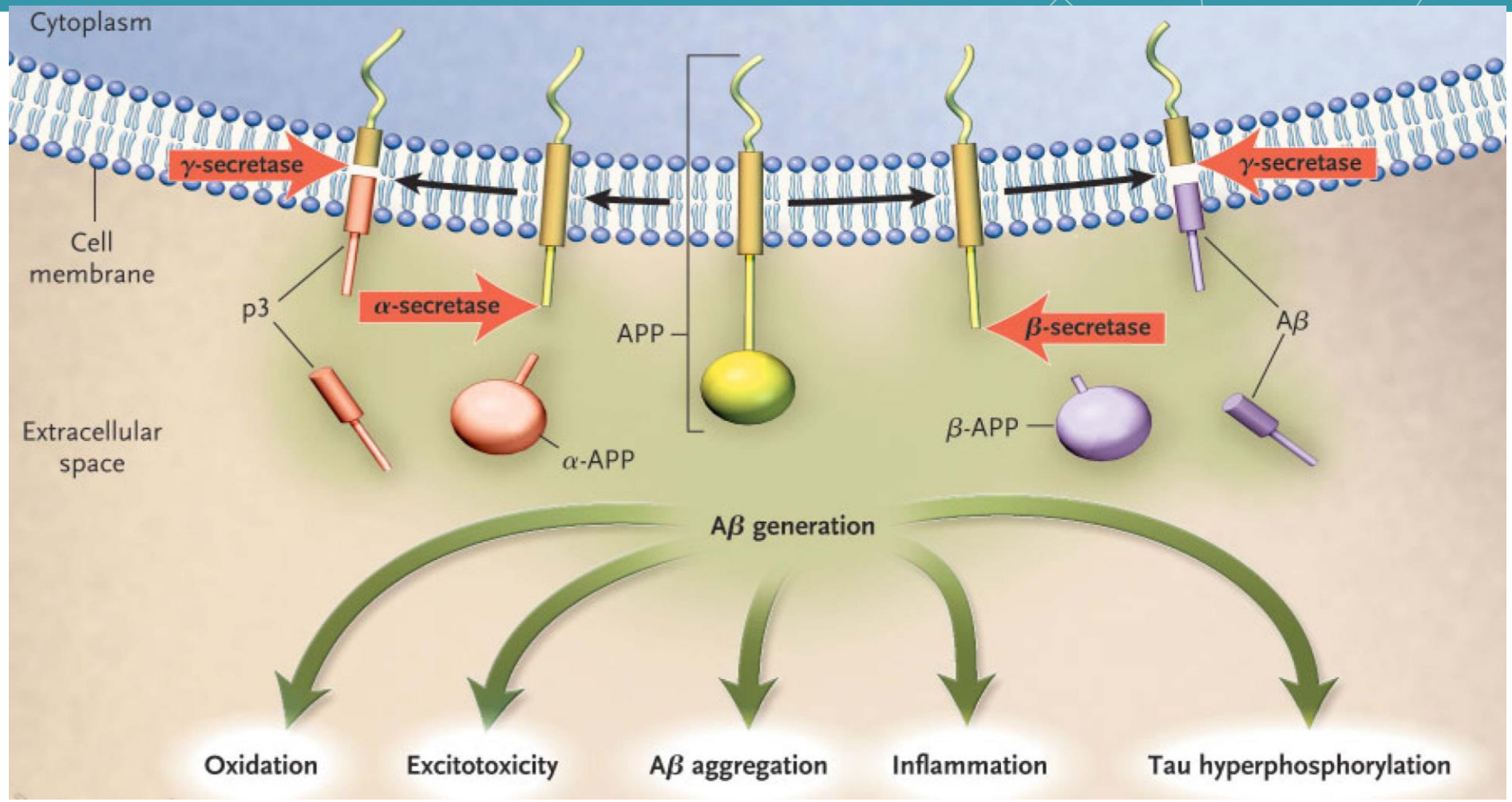
Disinhibition and personality changes.

Hypometabolism of the frontal and temporal lobes on FDG-PET scan.

No benefit from acetylcholinesterase inhibitors.

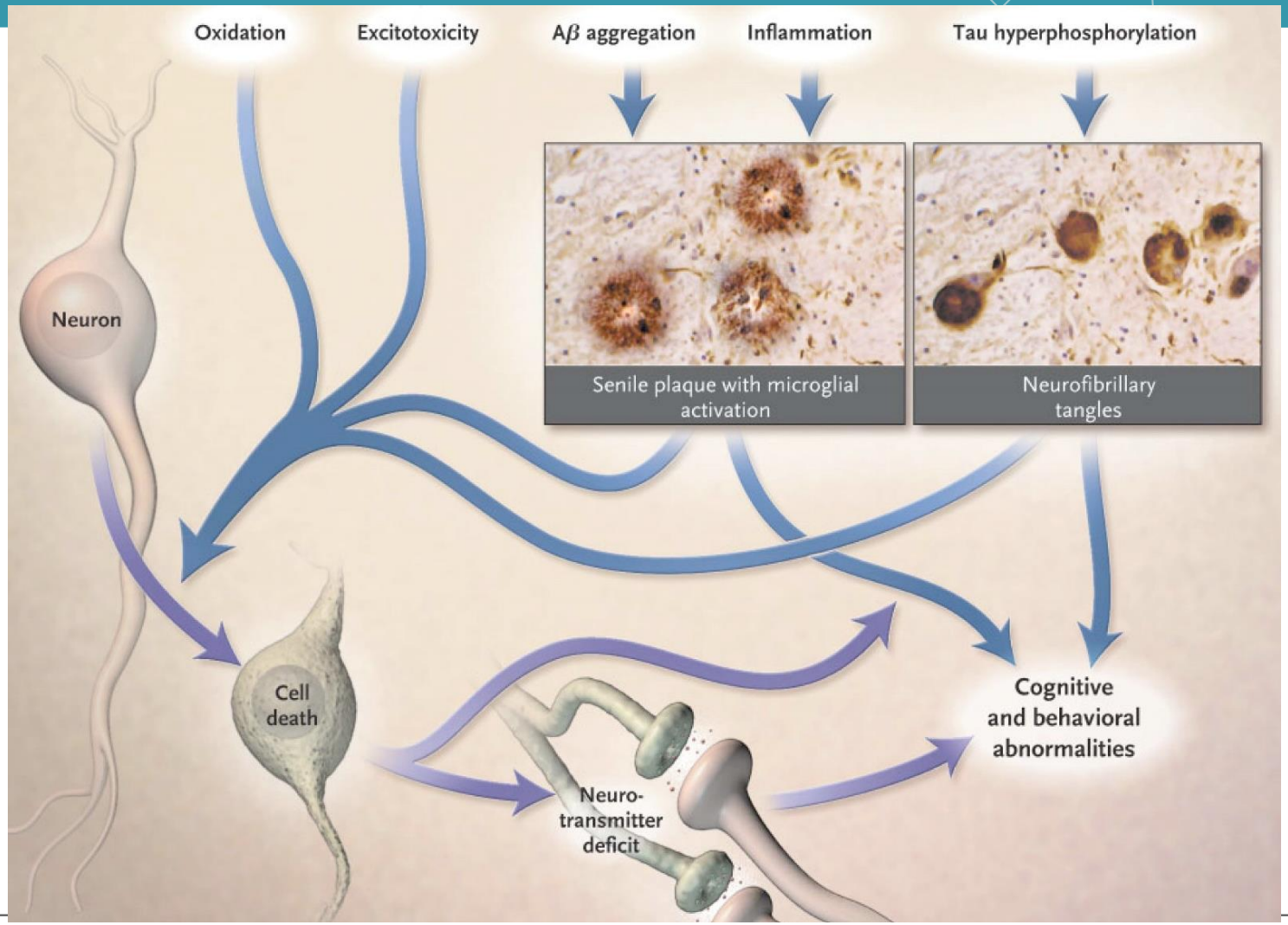
Ban J, Spina S, Miller BL . Lancet 2015

AD Pathophysiology: Amyloid Hypothesis



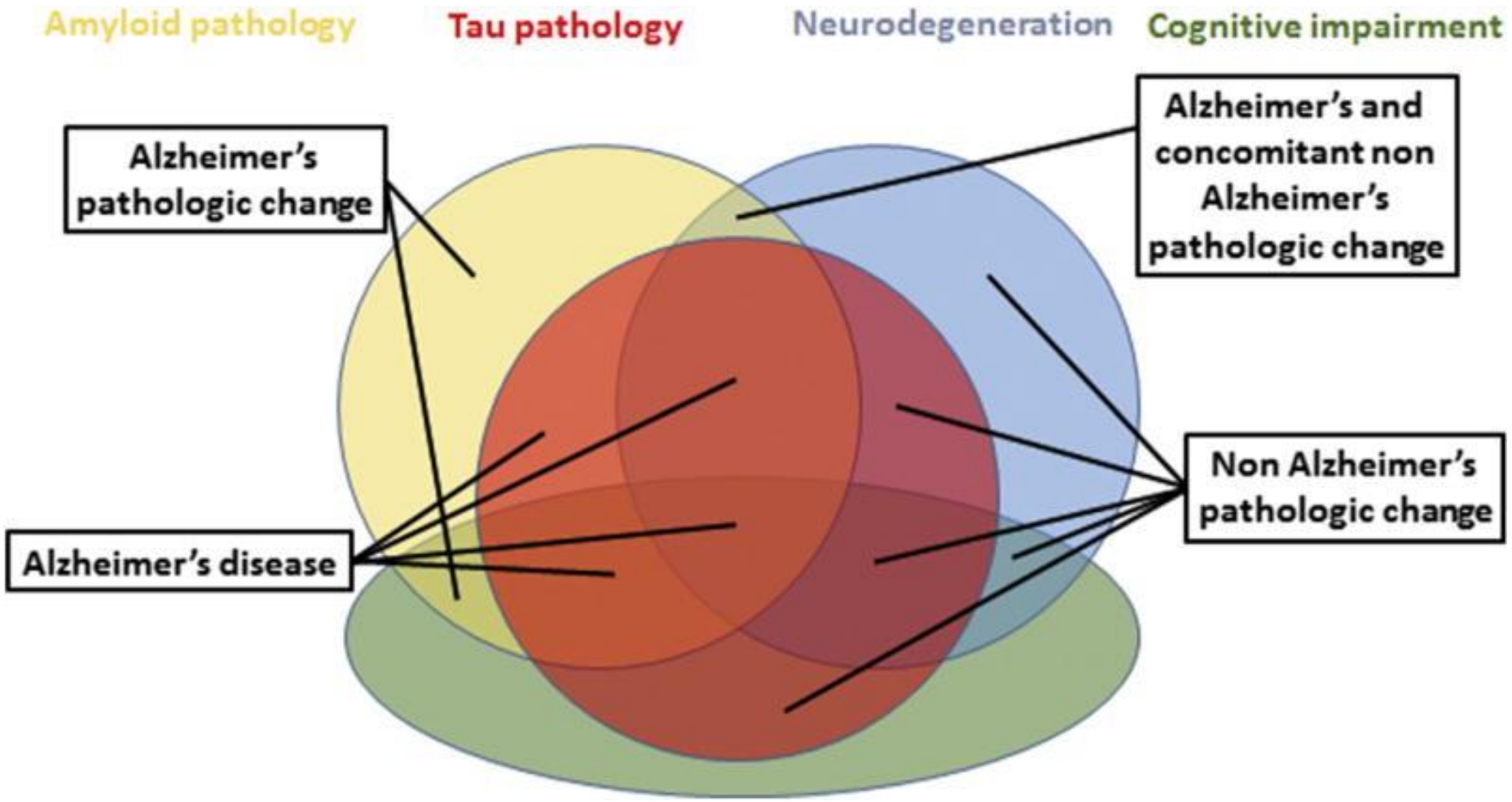
Cummings, 2004

AD Pathophysiology



Cummings, 2004

A-T-N Classification System



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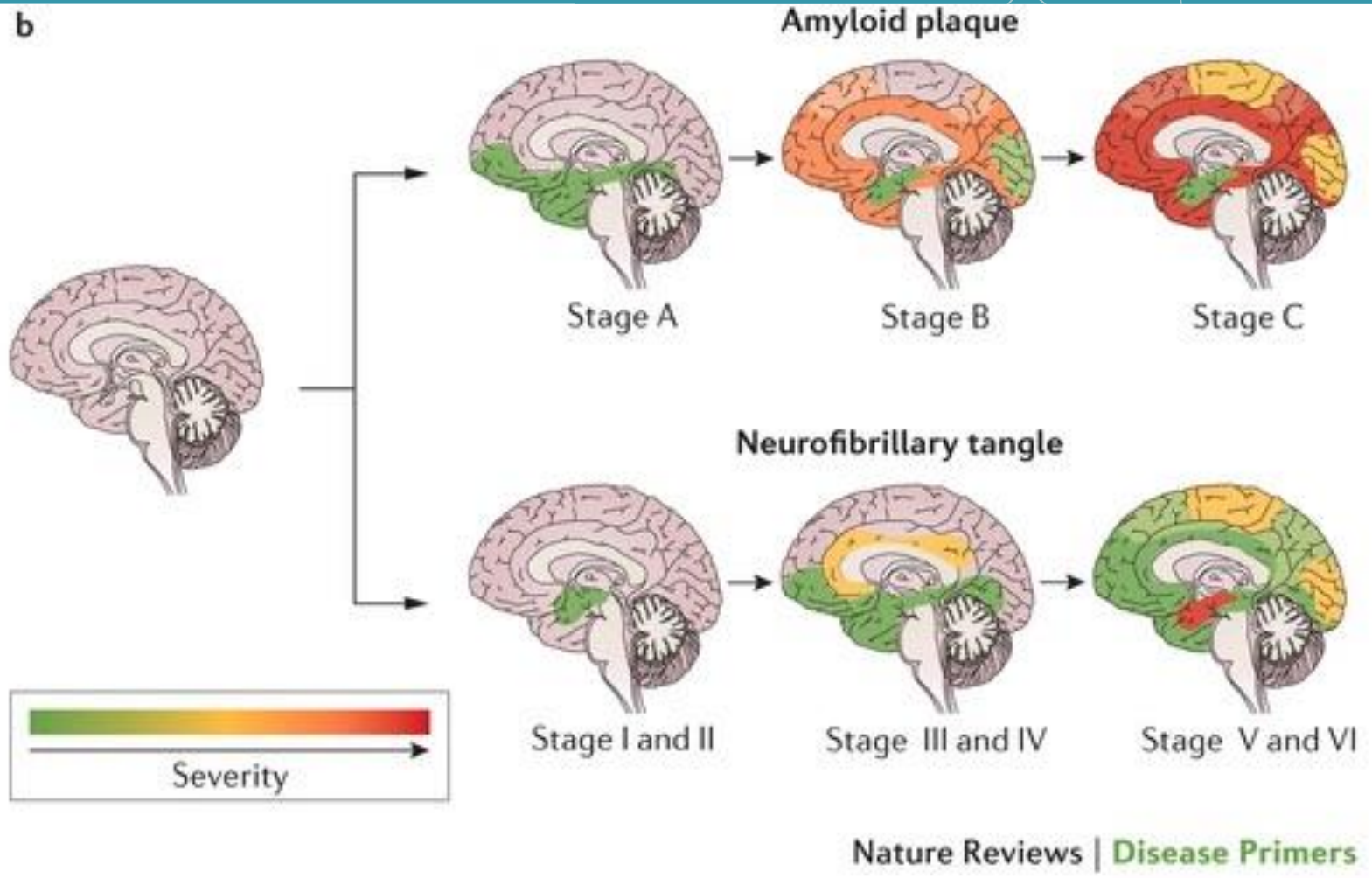
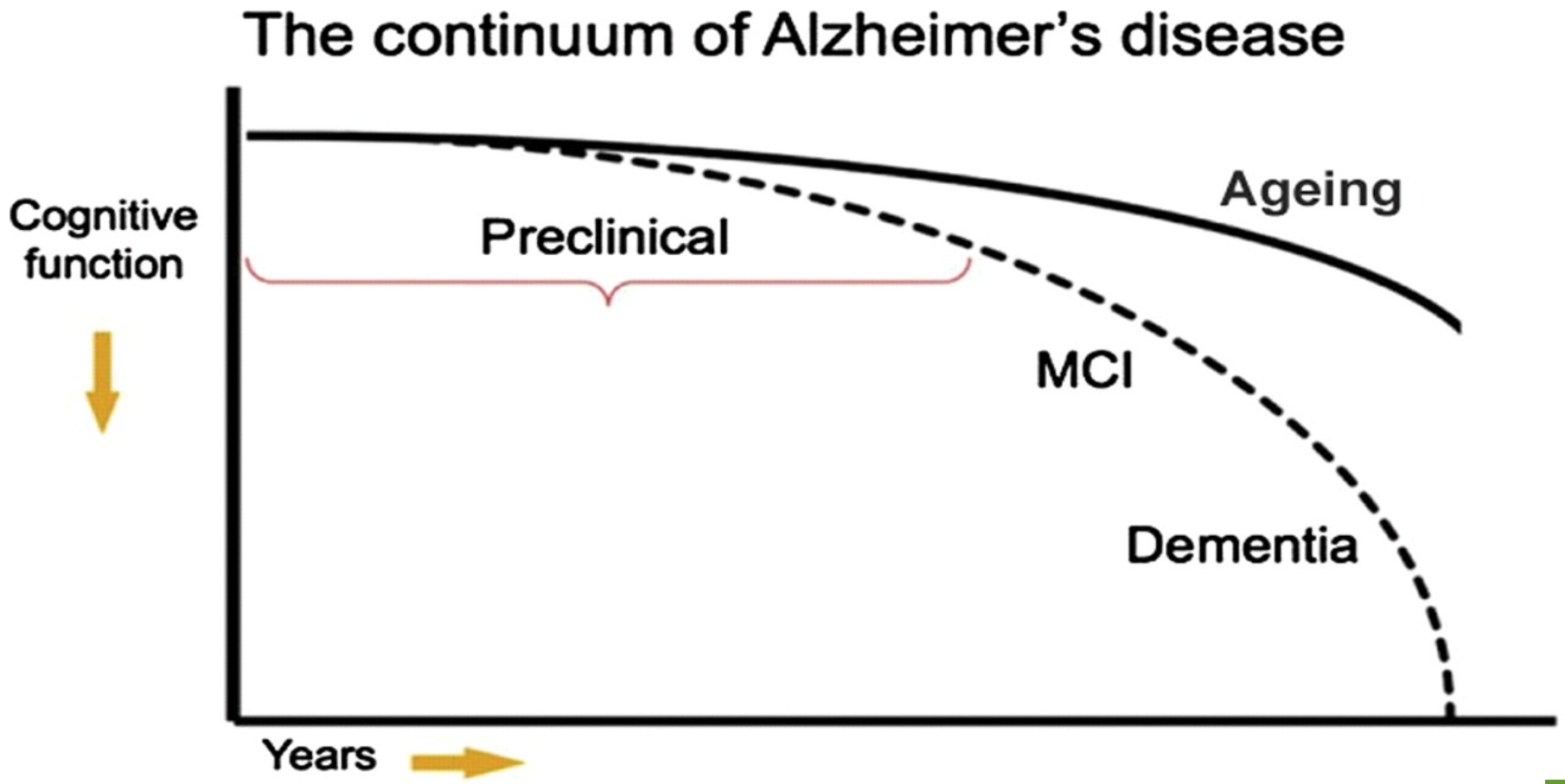
Jack CR Jr, et al. Alzheimers Dement. 2018;14:535-562.

Pathological Disease Progression



Masters et al., 2015

Model of the clinical course of Alzheimer's disease and mild cognitive impairment.



Budson A E , and Solomon P R Pract Neurol 2012;12:88-96

PN

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The 3 **Stages** of Dementia

Early-stage	Middle-stage	Late-stage
Experience short term memory loss, e.g. cannot figure out what has just happened	Distorted reality with preserved long term memories, e.g. running to school to pick up her grown-up child	Loss of memory, including the significant persons and events
Difficult to express and understand abstract terms	Difficult to find the right words	Loss of language ability
Able to manage daily living activities with assistance	Need assistance in self-care	Depend on self-care including feeding and continence
---	Confusion with date, time and place, and may get lose in the familiar place	Unable to understand date, time and place
Experience unusual emotions, having unusual behaviors, and being suspicious	Having fluctuating emotions, significantly changing personalities and problematic behaviors	Personality and behavioral changes and being passive
Normal physical ability	---	Bed-ridden or wheelchair bound

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DSM V: Major Neurocognitive Disorder

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:

Learning and memory

Language

Executive function

Complex attention

Perceptual-motor

Social cognition

B. The cognitive deficits interfere with independence in everyday activities

C. The cognitive deficits do not occur exclusively in the context of a delirium

D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)

The Dementia Syndrome: “Chief Complaint”

Memory deficit is the main feature

Other cognitive deficits

Attention	- Abstract thinking
Executive function	- Calculation

Personality disturbances *(‘Combative’; ‘Irritable’*)

Behavioral disorders *(‘AMS’; ‘Agitation’; ‘Delirium’)*

Neurologic deficits *(‘Fall’; ‘Dysphagia’; ‘Parkinsonism’)*

Geriatric Depression Scale

Depression assessment

Are you basically satisfied with your life?	☐ Yes	☐ No
Have you dropped many of your activities and interests?	☐ Yes	☐ No
Do you feel that your life is empty?	☐ Yes	☐ No
Do you often get bored?	☐ Yes	☐ No
Are you in good spirits most of the time?	☐ Yes	☐ No
Are you afraid that something bad is going to happen to you?	☐ Yes	☐ No
Do you feel happy most of the time?	☐ Yes	☐ No
Do you often feel helpless?	☐ Yes	☐ No
Do you prefer to stay at home, rather than going out and doing new things?	☐ Yes	☐ No
Do you feel you have more problems with memory than most?	☐ Yes	☐ No
Do you think it is wonderful to be alive now?	☐ Yes	☐ No
Do you feel pretty worthless the way you are now?	☐ Yes	☐ No
Do you feel full of energy?	☐ Yes	☐ No
Do you feel that your situation is hopeless?	☐ Yes	☐ No
Do you think that most people are better off than you are?	☐ Yes	☐ No

Previous results | Print questionnaire | Finish | Cancel

Confusion Assessment Method

1a. **Acute onset**: Is there evidence of an acute change in mental status from the patient's baseline?

OR

1b. **Fluctuating course**: Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity?

AND

2. **Inattention**: Did the patient have difficulty focusing attention, for example being easily distractible, or having difficulty keeping track of what was being said?

AND

3. **Disorganised thinking**: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

OR

4. **Altered level of consciousness**: Overall, how would you rate this patient's level of consciousness? Any answer other than 'alert' indicates an abnormal level of consciousness.

4AT

(label)

Patient name:

Date of birth:

Patient number:

Assessment test for delirium & cognitive impairment

Date: Time:

Tester:

CIRCLE

[1] ALERTNESS

This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	**0**
Mild sleepiness for <10 seconds after waking, then normal	**0**
Clearly abnormal	**4**

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	**0**
1 mistake	**1**
2 or more mistakes/untestable	**2**

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December."
To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 months or more correctly	**0**
	Starts but scores <7 months / refuses to start	**1**
	Untestable (cannot start because unwell, drowsy, inattentive)	**2**

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	**0**
Yes	**4**

4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE ☐

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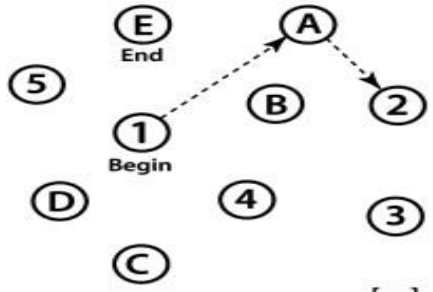
MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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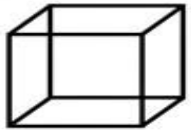


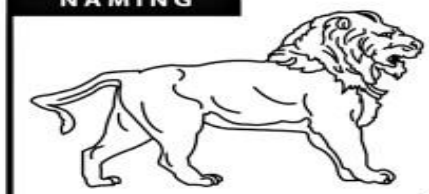
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING



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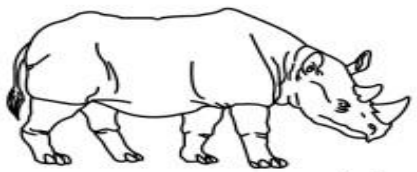

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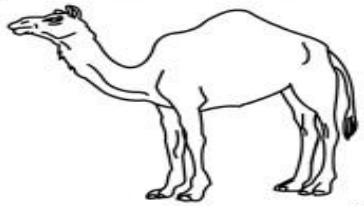

[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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Routine Labs

- **CBC**
- **Comprehensive Metabolic Panel**
- **VB12, folate**
- **TSH**

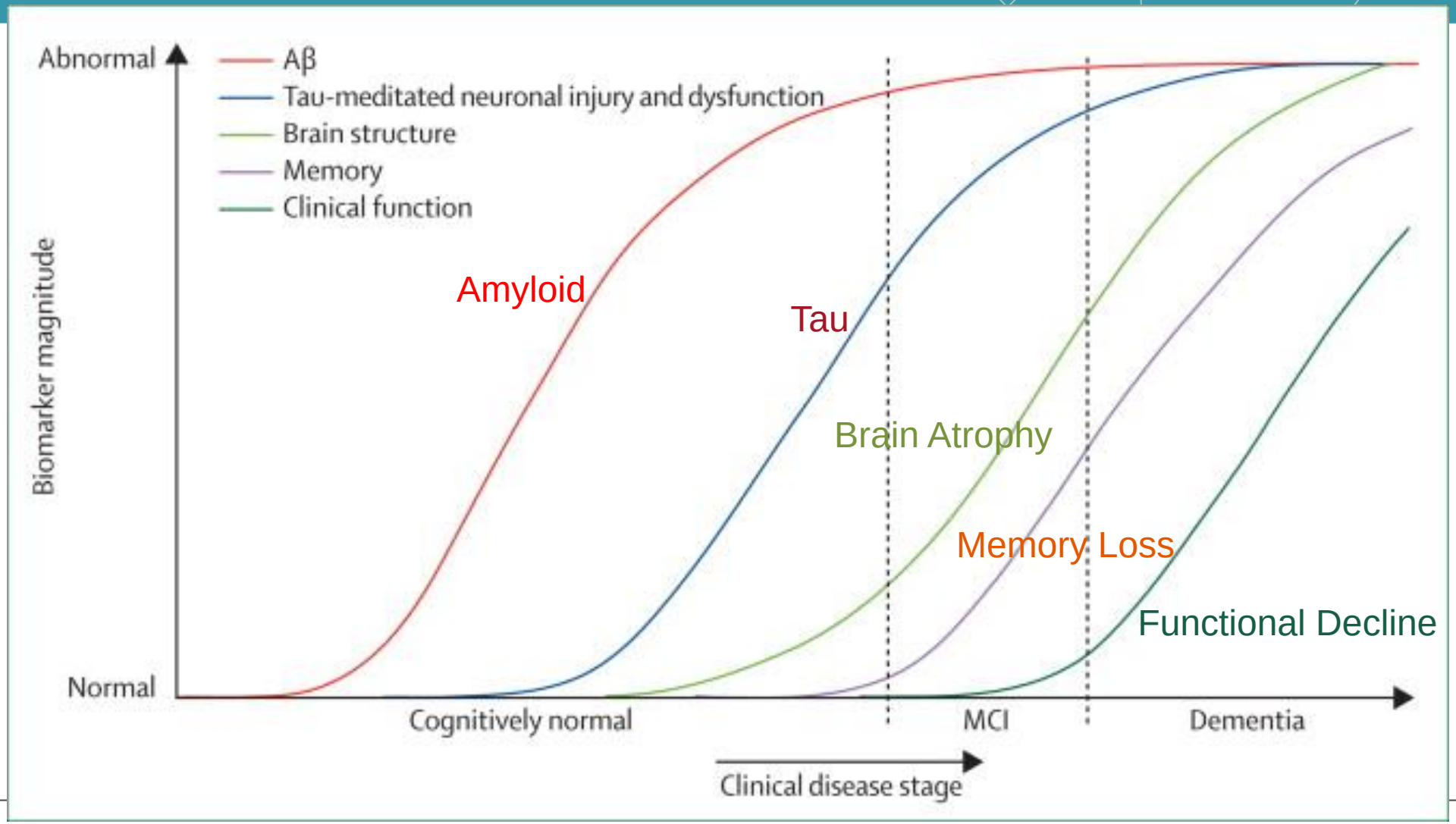
- **For older typical onset, the above might be enough.**
- **For younger or atypical onset, will probably need to do more.**

Brain Imaging

- **Always do a structural brain scan**
  - Brain MRI preferred over Brain CT

- **To get more information, sometimes we add:**
  - Functional scan
    - FDG-PET
  - Biological scan
    - Amyloid PET
    - Dopa PET

Clinical Stages of Alzheimer's Disease



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Jack et al., 2010

3 Barriers to Early Diagnosis of Dementia

- **Ageism**
  - **"All old people get forgetful"**
- **Denial**
  - **"It's probably just normal aging"**
- **Fatalism**
  - **"There's no cure, so what's the point?"**

Why Early Diagnosis of Dementia?

Patient safety and public health

Treatment planning

Goal-setting

- Advance directives
- Physician Order for Life Sustaining Treatment
- Financial matters

Educate and support family / caregivers

Access to clinical research trials

Population health

Dementia Diagnosis: Biomarkers

Structural MRI/CT

Atrophy of medial temporal lobe, anterior temporal and parietal cortex

CSF Aβ, p-tau, total tau

Decreased Aβ, increased p-tau/total tau

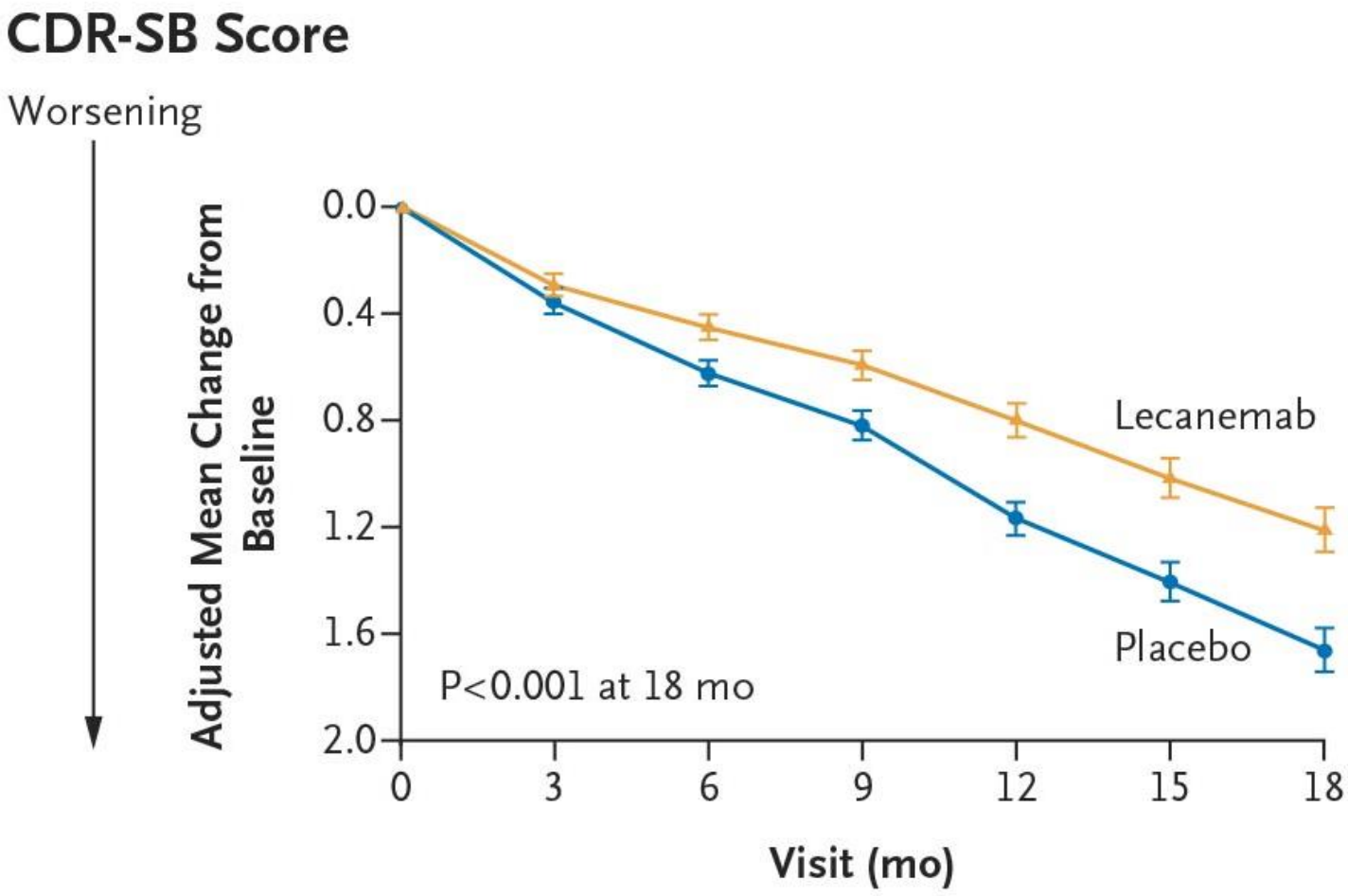
FDG-PET

Decreased metabolism in temporal and parietal lobes

Lecanemab

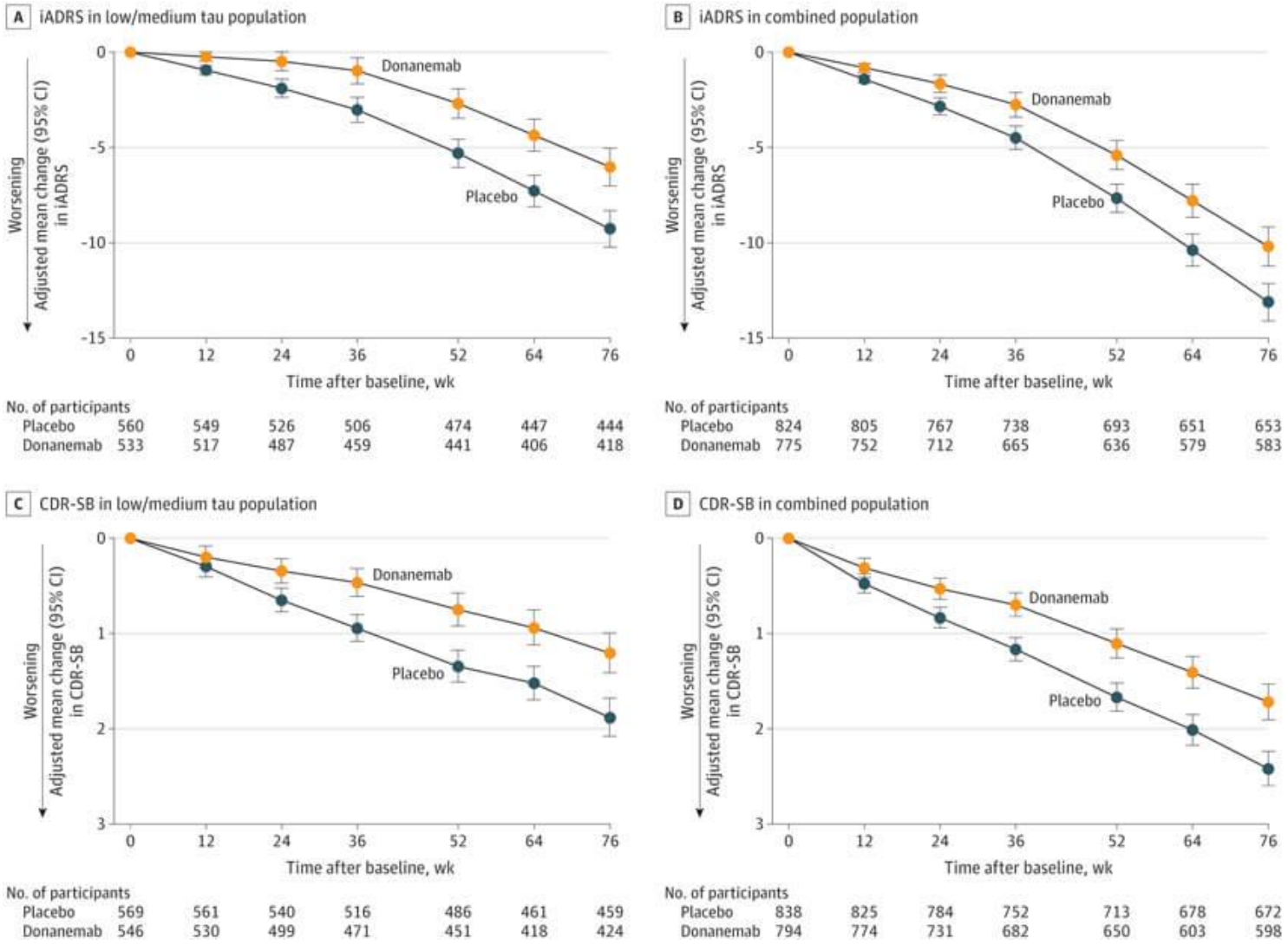
- Disease-modifying treatment for AD approved by the FDA in 2023.
- Monoclonal antibody that clear fibrillar and deposited amyloid.
- Bi-monthly (2x/month) IV infusions.
- Statistically significant slowing of cognitive and functional decline.

Lecanemab Phase 3 – Primary Cognitive Outcome



Van dyck et al. NEJM 2022

Donanemab



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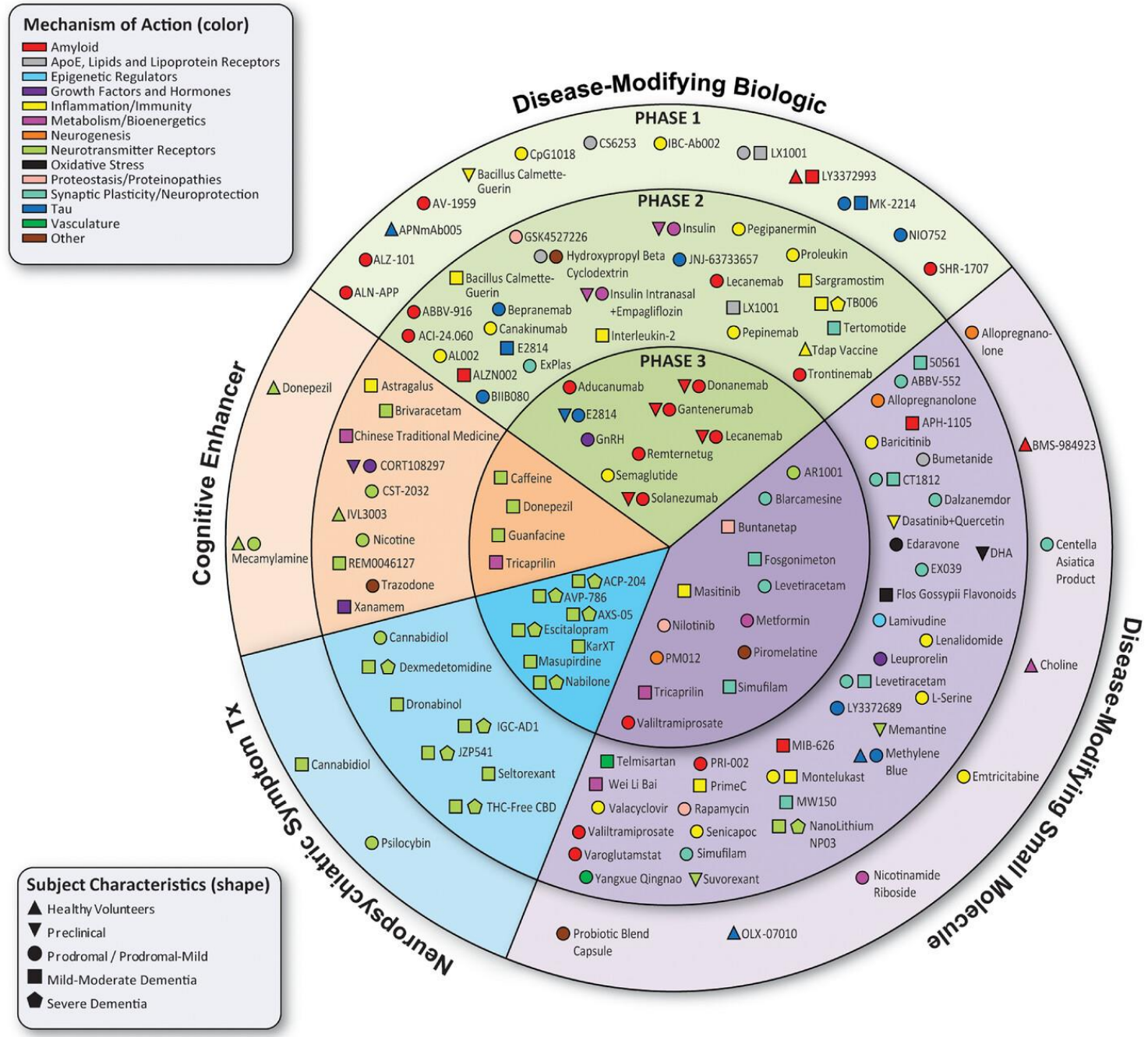
Sims JR et al. JAMA 2023

Concerns for Prescribing Clinician

- **Efficacy**
  - Uncertain clinical significance.
- **Side effects**
  - Risk-benefit analysis given potentially serious side-effects (including death).
- **Cost & Resources**
  - Drug
  - Amyloid PET scans
  - Genetic testing (ApoE4) required to help guide dosing/safety monitoring
  - MRI scans (at least 3 within 1 year, possibly more)
  - Infusion center (space, nursing time)
  - Neurology check ups
  - Time (bi-monthly infusions….for how long?)
  - No coverage currently by any insurance to cover amyloid PET scans or drug -->will this change?
- **Patient Access**
- **Baseline for future standard-of-care medications**

2024 Alzheimer's Drug Development Pipeline



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Cummings et al 2024

Talk Summary

- ADRD prevalence will rise in parallel with population aging and increasing life expectancy
- Alzheimer's disease is now recognized to be a heterogenous neurodegenerative disease (A-T-N Classification)
- New and emerging diagnostic biomarkers will make early / accurate ADRD diagnosis possible
- Disease modifying therapies (DMTs) for AD have received FDA-approval
- Non-pharmacologic measures are first-line interventions for behavioral symptoms
- Risk reduction / Prevention of ADRD will be part of a multi-modal approach to reducing population disease burden

Resources

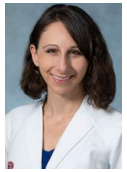
- **Alzheimer's Los Angeles https://www.alzheimersla.org/**
- **Alzheimer's Association https://www.alz.org/**
- **Cedars-Sinai Memory & Healthy Aging https://www.cedars-sinai.org/programs/neurology-neurosurgery/specialties/memory-disorders/healthy-aging.html**
- **CMS GUIDE Model https://www.cms.gov/priorities/innovation/innovation-models/guide**
- **Caregiver Corner https://caregivercorner.org/**

Cedars-Sinai Neurology / Memory Programs

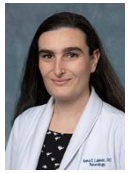
Physicians

Zaldy Tan, MD, MPH

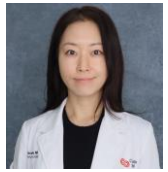
Sarah Kremen, MD



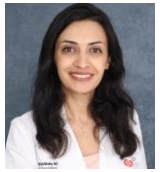
Jessica Besbris, MD



Ilana Lasner, DO



Sarah Kim, MD



Golnaz Yadollahikhales, MD

Nurse Practitioners

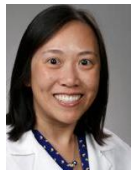
Deana Rhinehart, NP, DNP

Dyane Gatmaitan, NP

Christina Quach, NP

Stephanie Bray, NP

Fellows



Melissa Quan, DO

Michael Sonson, MD

Social Work

Veronica Romo, LCSW

Neuropsychology

Mitzi Gonzales, PhD

Genetic Counselling

Tara Jones, MS, LCGC

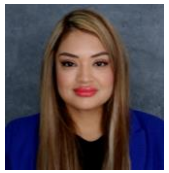
Administration

Erica Spivack, MHA

Qunesha Dale, MHA

James Ma

Medical Assistants



Gabriela Torres

Kassandra Herrera

Research

Nabeel Qureshi, PhD

Andrew Hirsch

Languages: English, Spanish, Korean, Farsi, Filipino, Japanese, French

Cedars Sinai

Thank you for your attention!

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