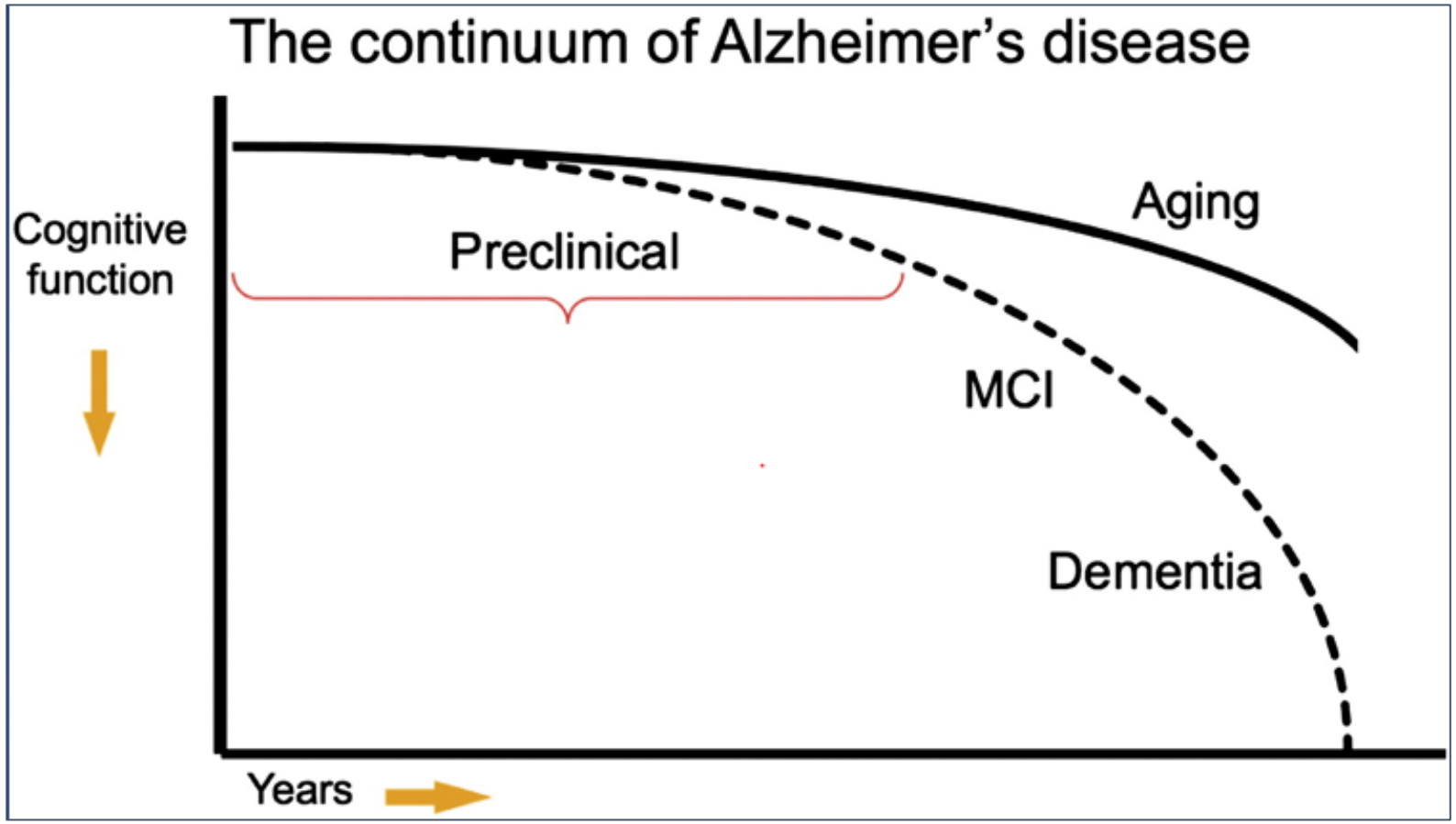
Updates on Alzheimer's disease

Ganesh Gopalakrishna M.D., M.H.A.



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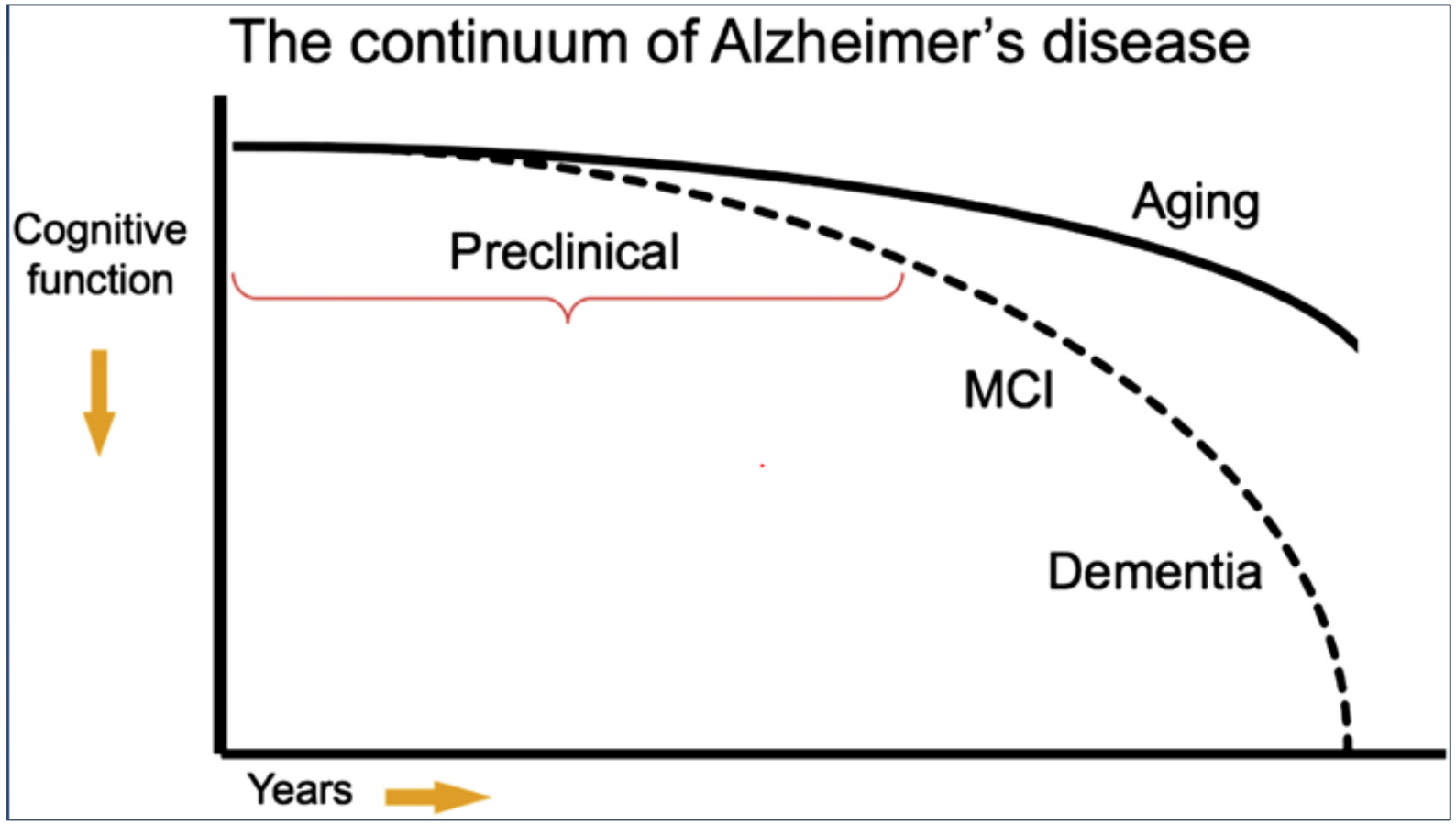
Age-Associated Cognitive Impairment

- Mild changes in memory with minimal progression over time
  - Slow decrease in rate of learning new information but not in retention (occasional "information overload")
- More difficulty with multi-tasking (divided attention)
  - Toasting a bagel while showering is not multi-tasking
  - Listening to the radio while driving *is*
- Mild word finding difficulty (especially words and names)
- "Sometimer's", e.g., slow retrieval of where car is parked
- Age "catching up with" longstanding ADD, depression (longstanding compensatory strategies harder to implement)
- The occasional lapses do not keep a person from functioning!



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Mild Cognitive Impairment (Albert MS et al. Alz & Dem 2011; 7: 270-279)

- Concept emerged in late 1980's: A borderland or "grey zone" transition state, before functional decline (Petersen et al; 1999 Mar;56(3):303-8. doi: 10.1001/archneur.56.3.303.)
  - Initial focus was just on identifying early AD, but gradual recognition that there are multiple subtypes
- Estimated 8-10 million Americans affected
- Impairment in one or more cognitive domains
- Change in cognition in comparison with the person's previous level, noticed by patient, family and care partners, or his or her physician.
  - "Concern" is a core criterion
- Performance on objective memory tests > 1.5 SD below norms for age & education

Mild Cognitive Impairment – Cont'd

- Functional capacity largely unimpaired
- Functional assessment is critical, clinical judgment is needed
- Complex tasks may be done more slowly, less efficiently, more prone to errors, but external assistance is minimal
- About 15% progress to dementia each year
  - But not all progress: ~15% do not
- Rare reversion to cognitively unimpaired
- Hard to prognosticate at an individual level
  - Give broad picture
  - Emphasize benefit of monitoring over time

Mild Cognitive Impairment – Why Bother?

- Helpful to detect, describe, and consider etiologic diagnosis
  - Make sense of confusing early signs and symptoms
  - Understand prognosis
  - Participate in future care plan
  - Education and support for care partner and patient
    - Reduced burden over long haul
  - Educate *re* lifestyle factors
    - Diet, exercise, social/intellectual stimulation: more to follow in another session
  - Optimize future medical care
    - With focus on treatable/modifiable disease and risk factors
- Consider treatment

What is "Dementia?"

- Syndromal term, not a diagnosis
  - Like saying "cancer"
  - Does not say what lies ahead or how to treat
- Progressive loss of memory and/or other thinking ability*
  - Beyond what is seen in normal aging
- Eventual inability to function on a daily basis
- Almost always results in changes in emotions and personality
- Eventually causes neurological dysfunction
  - Examples: incontinence, swallowing problems, balance and walking problems
- There are many causes of this syndrome, not just Alzheimer's
  - But Alzheimer's is the most common cause

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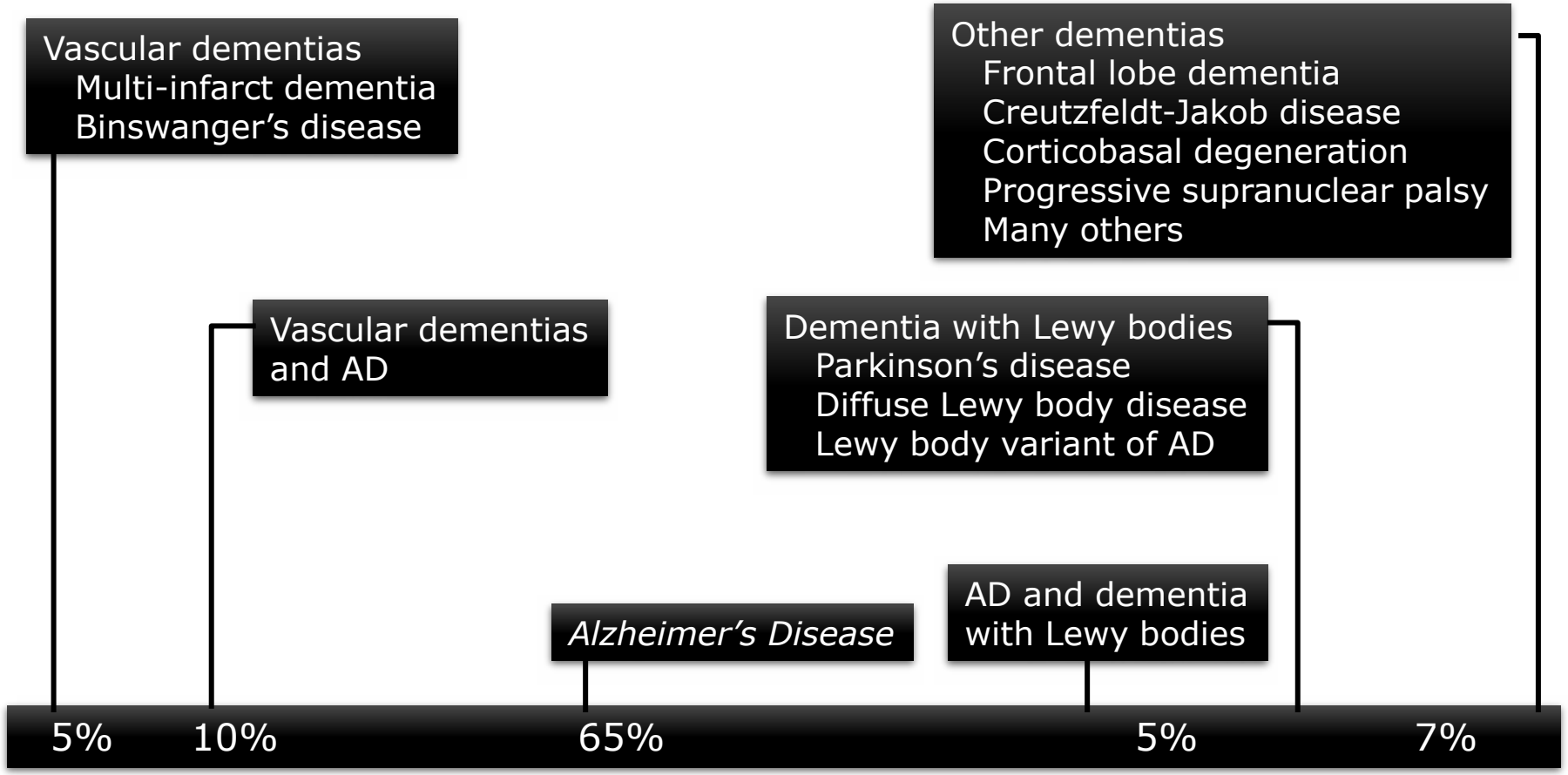
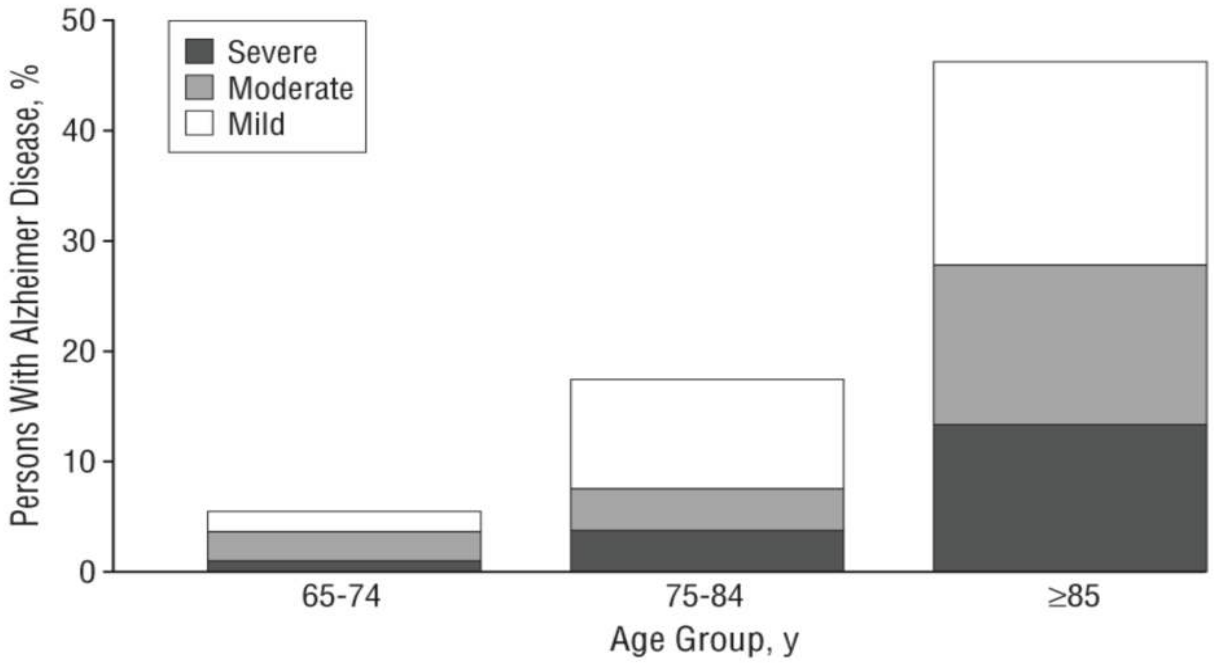
Differential Etiological Diagnosis of Dementia



Small GW, et al. *JAMA.*1997;278:1363-1371. American Psychiatric Association. *Am J Psychiatry*. 1997;154(suppl):1-39. Morris JC. *Clin Geriatr Med*. 1994;10:257-276.

From: Alzheimer Disease in the US Population: Prevalence Estimates Using the 2000 Census

Arch Neurol. 2003;60(8):1119-1122. doi:10.1001/archneur.60.8.1119



Prevalence of severe (Mini-Mental State Examination score, ≤9), moderate (Mini-Mental State Examination score, 10-17), and mild (Mini-Mental State Examination score, ≥18) Alzheimer disease, in each of 3 age groups, in the community population providing data for these estimates.

Risks: Late Onset Alzheimer's

- Genetics
  - APOE genes ("alleles")
  - 1 copy from mother and 1 from father
  - Three versions: APOE 2,3,4
    - ***Increased risk associated with one or two E4 alleles***
  - APOE2 alleles associated with decreased risk
  - Note: A rare mutation of a different gene that blocks amyloid also reduces risk ("Icelandic mutation")
- Most late onset Alzheimer's result from genetic factors (APOE) **and** lifestyle and environmental risk factors

Possibly Protective Lifestyle and Environmental Factors

- Mental Activity
- Mid-life smoking cessation
- Aerobic exercise
- Diet low in animal fat
- Fish consumption
- Moderate wine intake
- Limited refined carbs
  - "Mediterranean diet"
- Avoid head trauma
- Control blood pressure, cholesterol, diabetes

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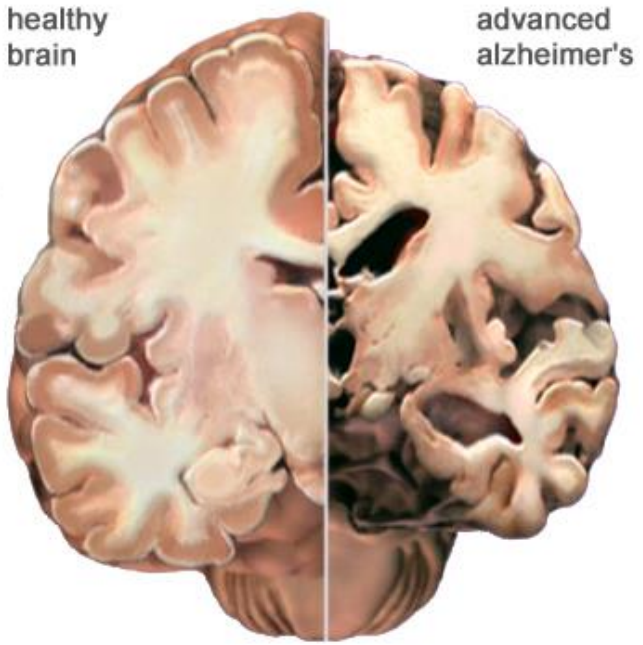
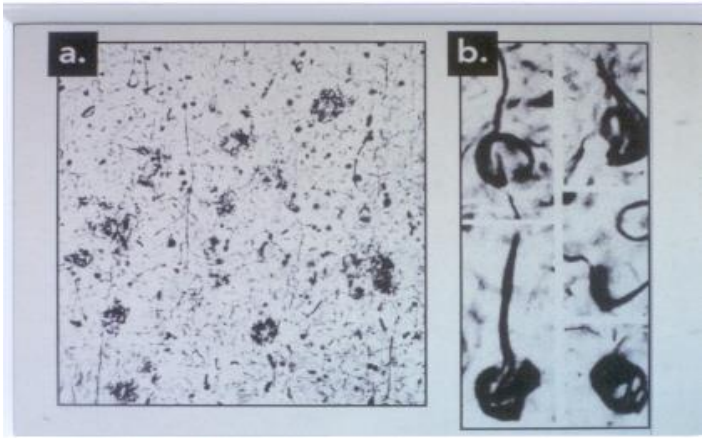
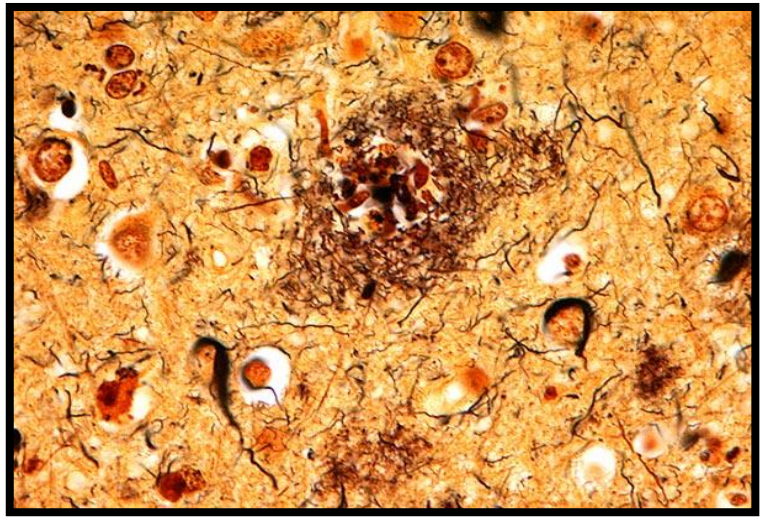
The Main Changes in the Brain in Alzheimer's Disease

- Amyloid plaques
- Neurofibrillary tangles (tau)
- Inflammation
- Shrinkage of the brain (atrophy)





Plaques Tangles



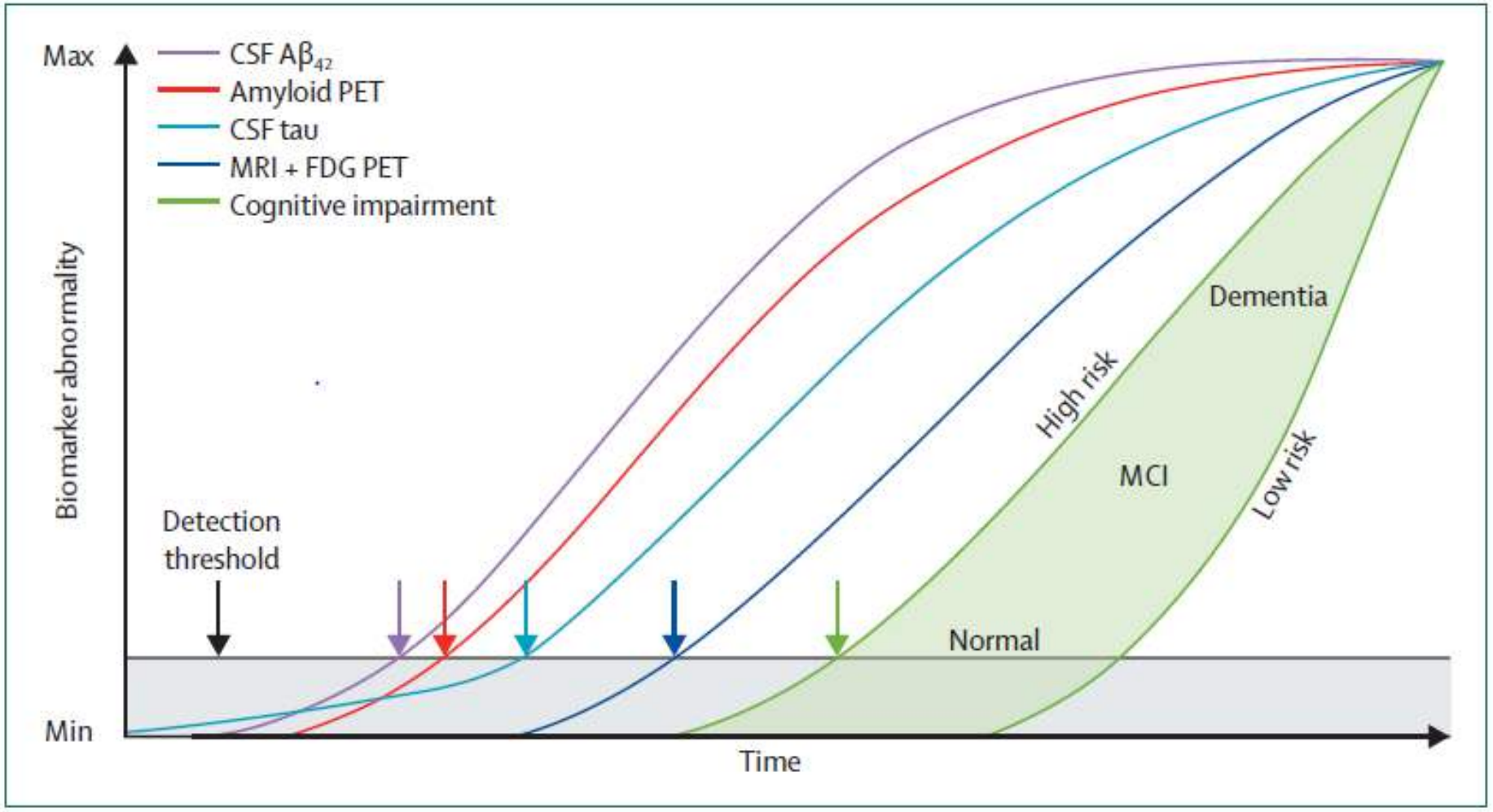


Figure 6: Model integrating Alzheimer's disease immunohistology and biomarkers

(Jack, C., et al., Lancet Neurol. 2013 Feb;12(2):207-16. doi: 10.1016/S1474-4422(12)70291-0.)

Dementia

Cognitive impairment+ functional decline

MCI

Cognitive impairment- functional decline

Preclinical AD

No cognitive impairment. No functional decline. Positive AD biomarkers

Observations on the patient/family journey that may influence what/how you communicate

- Importance of “phases” in their experience
- Early on:
  - *What is going on?!*
  - Is it my imagination? Never mind, it’s probably nothing
  - It can’t be!
  - Why is she/he acting this way? What is the meaning or purpose of this change?
  - She’s never done that before!
  - Inchoate data
  - I don’t want to open Pandora’s Box
- This phase could last months to years

Observations on the patient/family journey: tipping point

- Or eye-opener
  - Except for the rare folks with the ability to discern the changes clearly and act accordingly
- Examples of problem areas
  - Work
  - Driving
  - Financial management
  - New technology ("It started the day we got the new car!")
  - Incontrovertible emotional changes
  - Safety
  - Social lapses
- Holy cow #1: we need help!
- Appointment is arranged

The Clinical Evaluation 1: *Always* Perform

- History
- Neurological Exam: esp. focal findings, parkinsonism, abnormal tone, saccadic eye pursuit, frontal release signs, abnormal gait
- Mental Status Exam
- Office neuropsychological testing
- Labs: CBC w diff, CMP, B12, TSH
- CT/MRI: looking for stroke, mass, NPH, inflammation, cortical/hippocampal atrophy

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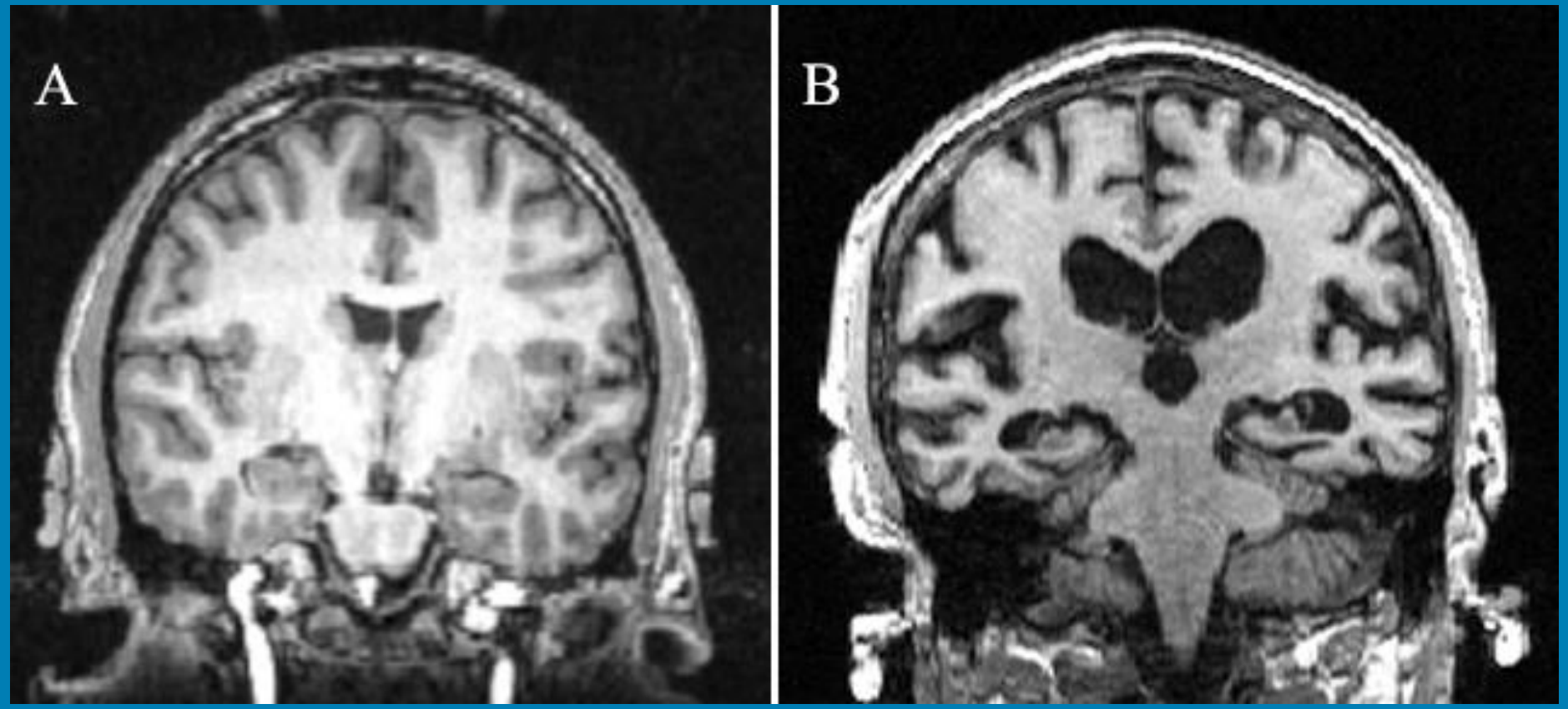
MRI Brain: Normal vs. AD



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Neuropsychiatric Features of Dementia

Prevalence

- **Community**
- 65% have at least 1 disruptive behavior
- 40% have at least 3 disruptive behaviors
- **Nursing Homes**
- 90% have at least 1 disruptive behaviors
- 45% have at least 4 disruptive behaviors

Greater impairment in activities of daily living

Worse quality of life

Earlier institutionalization

Major source of caregiver burden

> $10,000/year additional total direct care costs per patient

Accelerated mortality

Tampi et al, 2011; Lykestos et al, 2011

Supplements as Cognitive Enhancers

- Limited evidence that any vitamin or mineral supplementation benefit:
  - Cognitively healthy adults in mid or late life regarding effect on cognitive decline or dementia[1]
  - Improving dementia related outcomes[2]
- COSMOS-Web study showed benefit of multivitamin to improve memory among older adults.
- In 2019, the FDA warned 17 companies to stop advertising their dietary supplements as treatments for AD

Recent updates

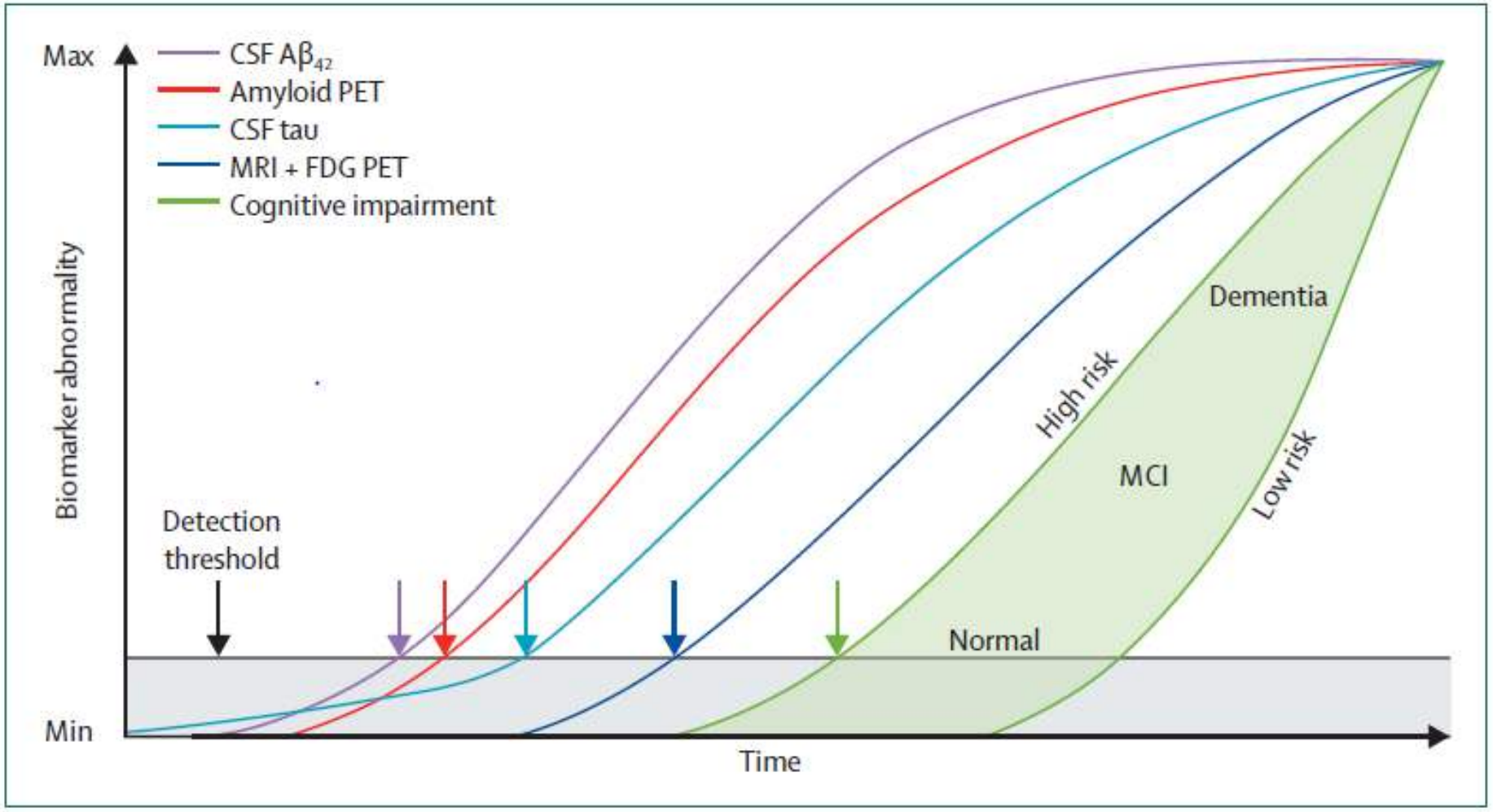

Figure 6: Model integrating Alzheimer's disease immunohistology and biomarkers

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Emerging fluid biomarkers: tau, amyloid and neurodegeneration

- p-tau217 in blood collected during life accurately predicted tau brain changes seen in post-mortem brain tissue in AD patients
  - Increasing blood tau levels detected up to 20 years before average age of onset AD symptoms.
- Two companies have the FDA breakthrough device designation
- Could become the "cholesterol" of Alzheimer's disease.
- Also: Blood beta amyloid 40/42 ratio predicts *amyloid* PET results; NfL (neurofilament light) shows extent of *neurodegeneration.*

(Palmqvist et al JAMA 2020; Barthelmy et al Front.Aging Neurosci.2020)

Emerging fluid biomarkers: tau, amyloid and neurodegeneration

- Jan 2023: FDA approved first in vitro diagnostic test for early detection of amyloid plaques associated with Alzheimer's disease
- July 2020: newly validated, blood test for p-tau217 accurately distinguishes Alzheimer's from other neurodegenerative disorders.
- Aug 2023: Quest AD-Detect test is a blood test based on amyloid-beta 42/40 ratio. Direct to consumer.

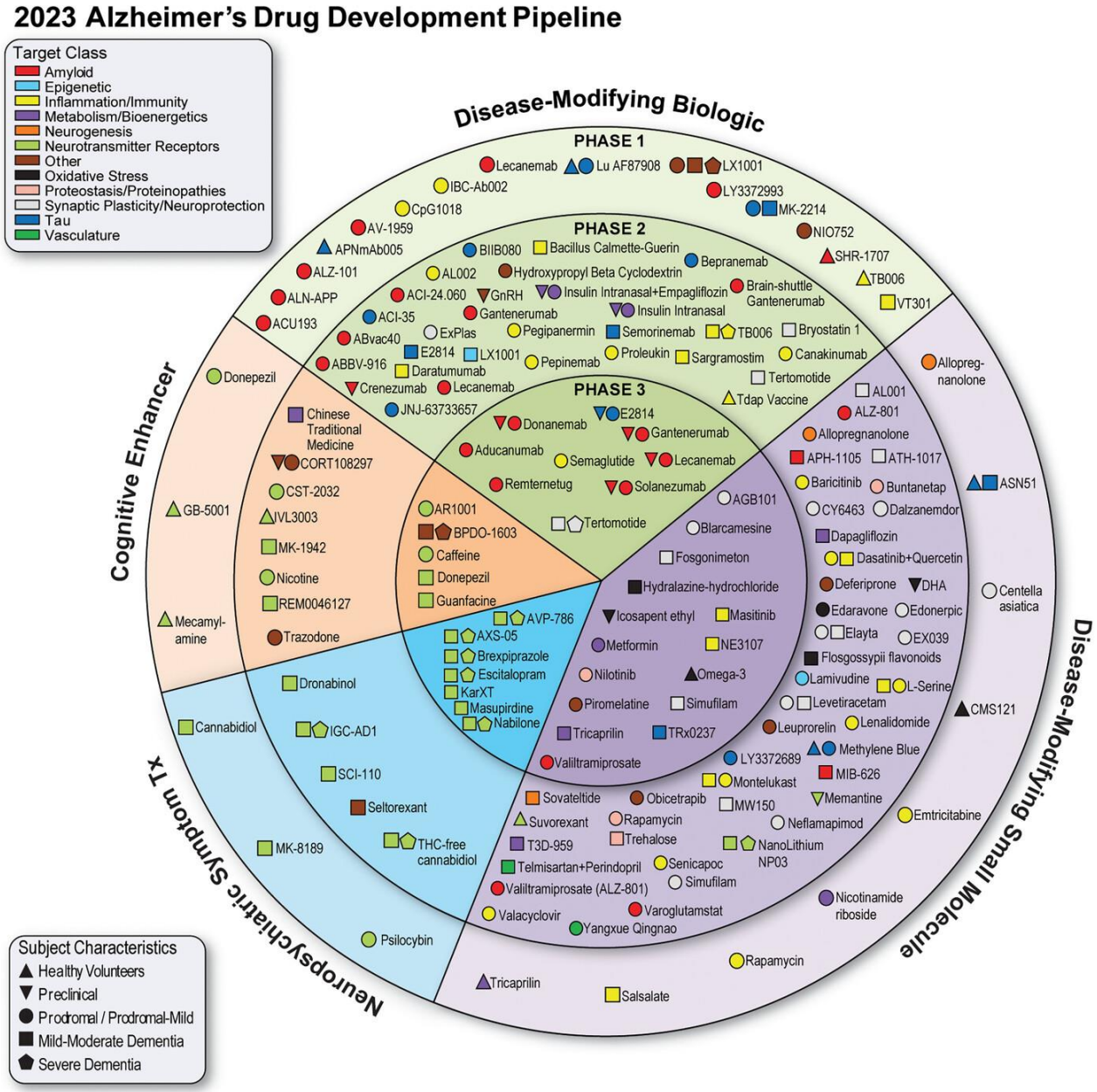
(Palmqvist et al JAMA 2020; Barthelmy et al Front.Aging Neurosci.2020)

Types of Interventions

- "Symptomatic" therapy:
  - Interventions that improve cognition, defer functional decline, or ameliorate behavioral symptoms without altering the underlying disease processes that comprise AD pathogenesis and without producing enduring changes that persist when the treatment is withdrawn.
- Disease modifying therapy:
  - Interventions that produce an enduring change in the clinical progression of AD by interfering in the underlying pathophysiological mechanisms of the disease process that lead to cell death as demonstrated by biomarkers

Cummings, NEJM, 2004

2023 Alzheimer's Drug Development Pipeline



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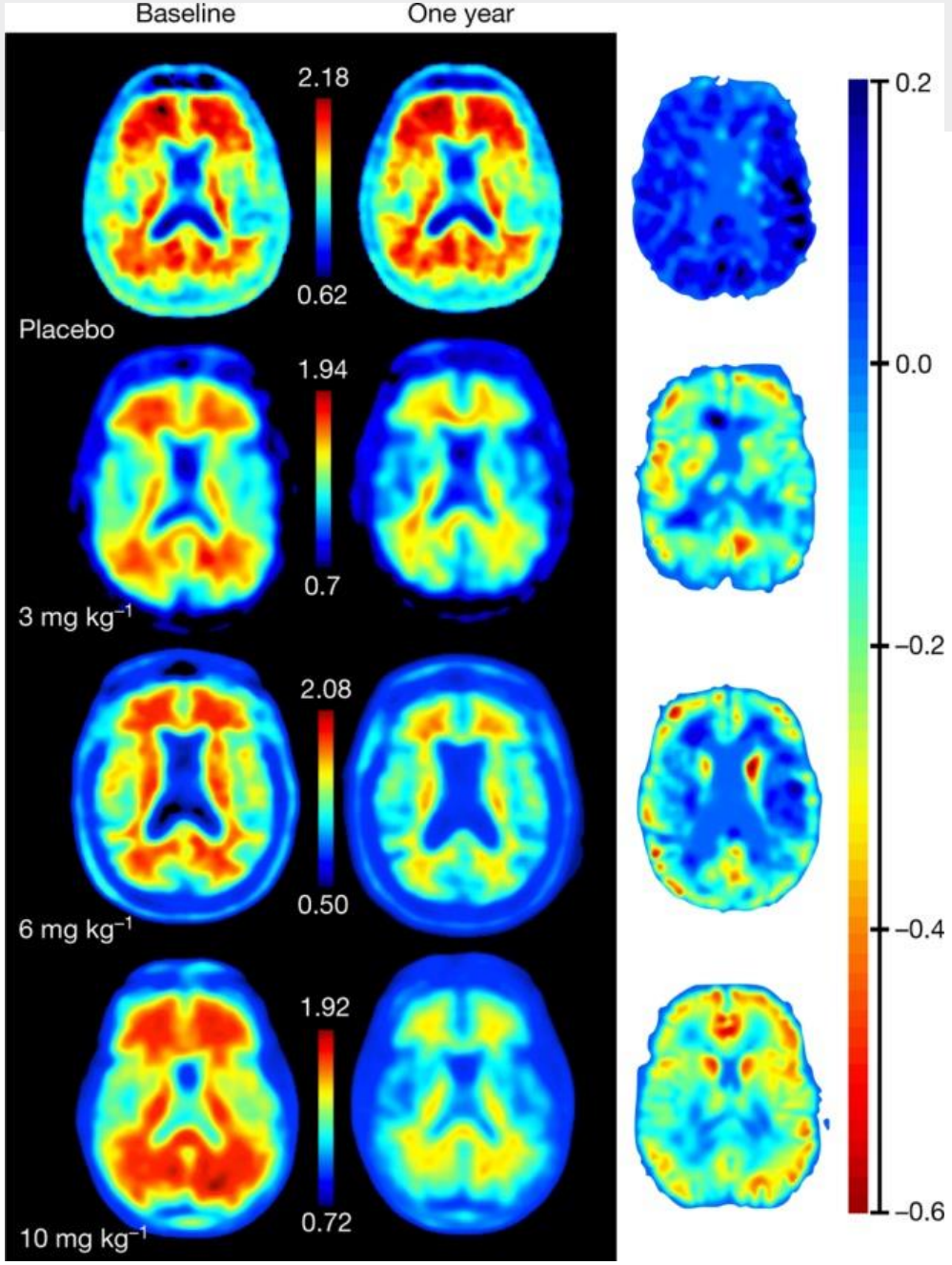
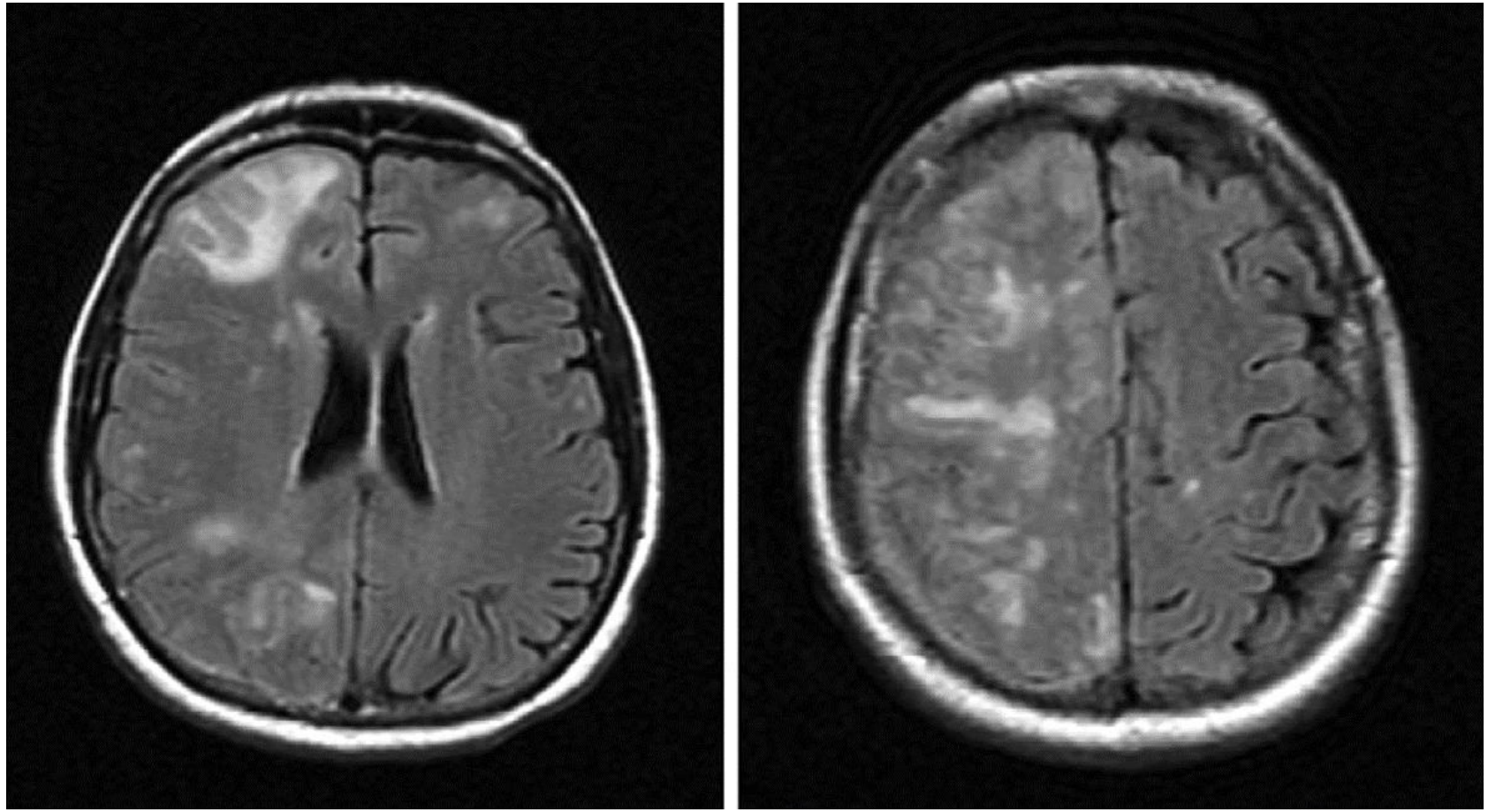
Aducanumab Phase 1b: Reduced brain amyloid after 1 year



nature

J Sevigny *et al. Nature* **546**, 564 (2017) doi:10.1038/nature22089

ARIA-E: Vasogenic Edema

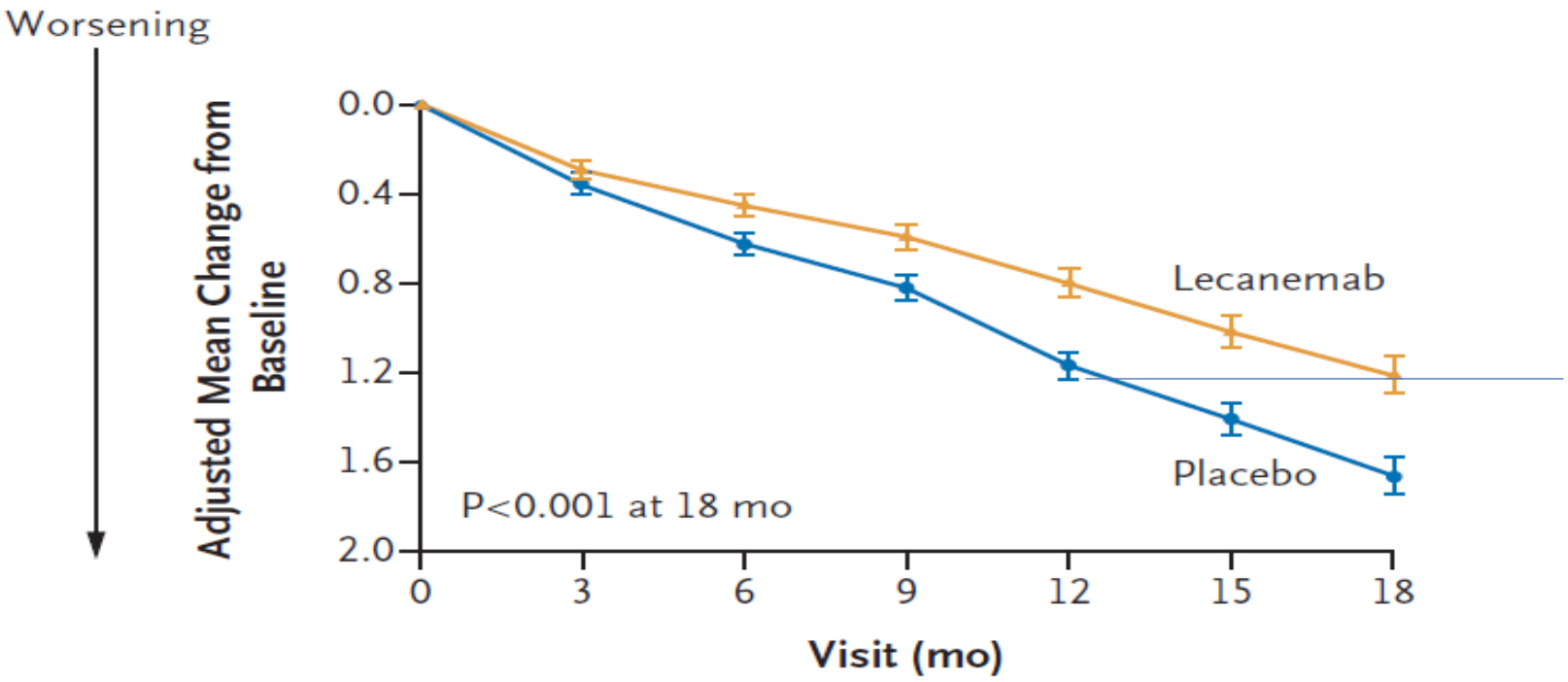


- Reprinted from Alzheimer's & Dementia, 7/4, Sperling RA, Jack CR Jr, Black SE, Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup, 367-385, copyright 2011, with permission from Elsevier

Lecanemab (anti-amyloid antibody)

- Slowed clinical decline from baseline by 27% (p=0.00005) on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) compared to placebo at 18 months
- Met all key secondary endpoints
- ARIA-E was 12.5% in the lecanemab group and 1.7% in the placebo group
- Symptomatic ARIA-E was 2.8% in the lecanemab group and 0.0% in the placebo group
- FDA approved through accelerated pathway in January 2023
- On July 6, 2023, lecanemab received full FDA approval for MCI and mild dementia due to AD
- CMS has agreed to cover the cost of the infusion
    - 20% copay

Lecanemab Phase 3 Primary Outcome: CDR Sum of Boxes (Van Dyck et al NEJM 2022)



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Donanemab in Early Alzheimer's Disease

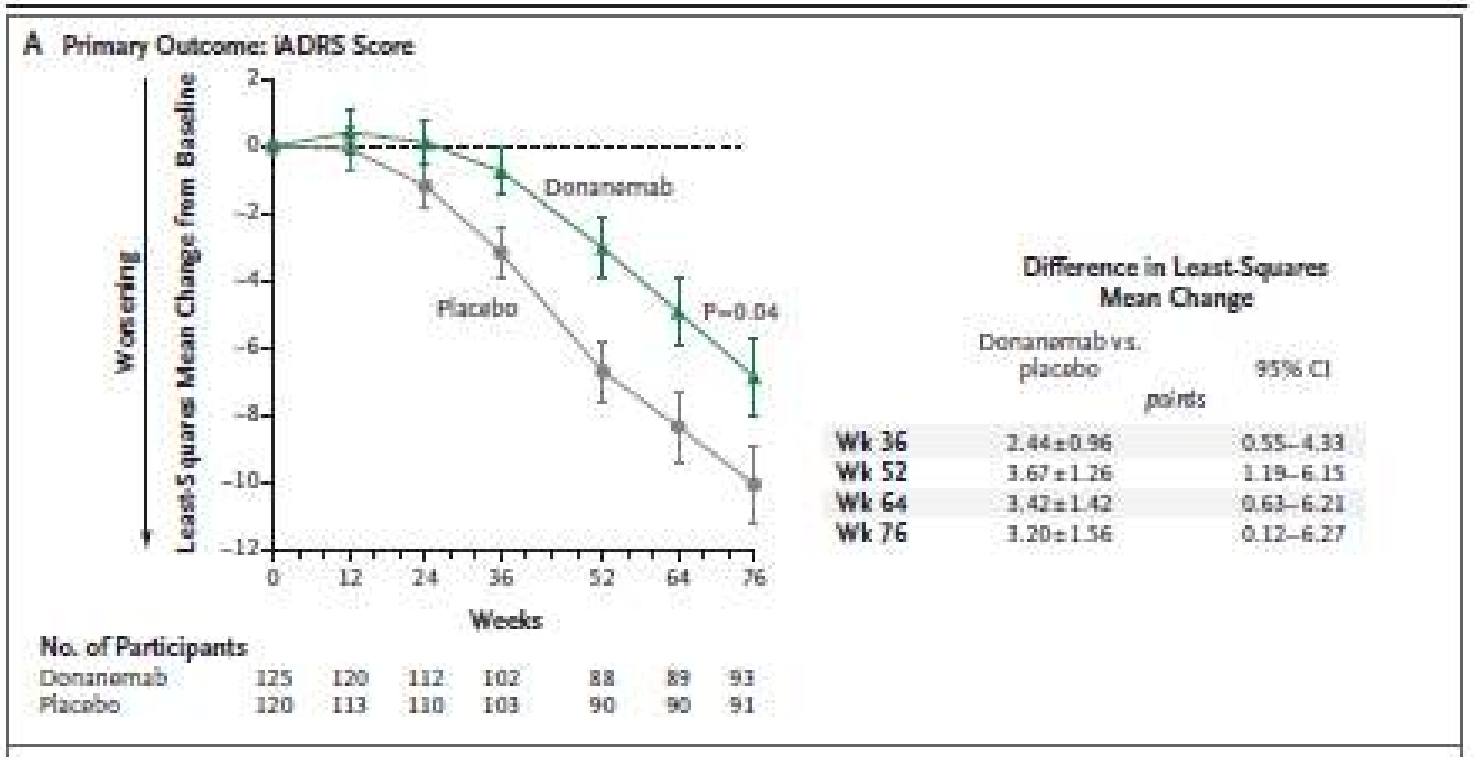
ORIGINAL ARTICLE

Donanemab in Early Alzheimer's Disease

Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway, M.D., and Daniel M. Skovronsky, M.D., Ph.D.

ABSTRACT

- Different anti-amyloid antibody
- First phase 2 trial to show a disease modifying effect
- Selected patients with medium level of tau tangles ("sweet spot")
- Rapid reduction of brain amyloid
- Larger Phase 3 trial recently read out



Difference in Least-Squares Mean Change

	Donanemab vs. placebo	95% CI
	points	
Wk 36	2.44±0.96	0.55–4.33
Wk 52	3.67±1.26	1.19–6.15
Wk 64	3.42±1.42	0.63–6.21
Wk 76	3.20±1.56	0.12–6.27

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Prevention Trials (active at BAI)

- A4 (solanezumab, negative study)
- AHEAD (A3-45, Lecanemab, age 55-80)
  - At risk for late onset AD because of positive amyloid brain scan
- Trailblazer 3-launched 2021
  - Donanemab
  - At risk for late onset AD: age 55-80 & plasma ptau-217
  - Normal telephone cognitive screen
  - Decentralized

SPRINT MIND Study (Williamson et al JAMA 2019)

- 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 lower blood pressure reduce risk of developing MCI or dementia?**
- N = 9,361 hypertensive older adults with increased cardiovascular risk but without diabetes, dementia, or prior stroke
- Primary analysis was negative
- Secondary analyses suggested reductions in the risk of MCI and MCI/Dementia in the Intensive Strategy group as compared to Standard Care group
- 1st trial to demonstrate a possible reduction in incident MCI and MCI/Dementia

Lifestyle modifications

- The FINGER trial is the first randomized controlled trial (RCT) showing that it is possible to prevent cognitive decline using a multidomain lifestyle intervention among older at-risk individuals.
- Interventions included:
  - nutritional guidance
  - physical exercise
  - cognitive training
  - social activities and
  - management of vascular and metabolic risk factors.
- After two years, cognition improved by approximately 25% more in the multidomain intervention group.

Dementia and schizophrenia

- Emil Kraepelin's characterization of "dementia praecox" as a psychotic illness with a progressively deteriorating disease course, the chronic cognitive and functional deficits of schizophrenia
- Key parallels to dementia and other neurodegenerative diseases
- Neurocognitive deficits are observed during the premorbid phase of schizophrenia
- 10- to 20-fold higher prevalence of dementia among patients with schizophrenia compared to the general population
- Some studies have shown faster decline in cognition after age 65 but others have not

Possible Mechanisms of Cognitive decline and Dementia

- Low cognitive reserve
- Accelerated cognitive aging
- Cerebrovascular disease
- Antipsychotic and other medications

Evaluations & CME Certificates

For more information, or to register, visit
www.BannerHealth.com/DementiaECHO
or
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