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Controversy and Update on Dementia and Dementia-Causing Disease

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August 20, 2021

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Outline

- Review basic “ground rules” of what dementia is and what it is not
- Update recent findings in dementia and dementia-causing diseases
- Explore ethical and other challenges

Disclosures

- Last 5 years
  - Board member, Alzheimer Association
  - Research support (NIH, IDEAS trial)
  - Consultant fees (R3 Continuum)
  - Independent medical witness in legal cases
  - Speaker bureau (Biogen, *pending*)
- More than 5 years ago
  - Research support (NIMH, AAN Foundation, Novartis)
  - Consultant fees (Teva, Hines & Associates, BMI)
  - Speaker bureau (Eisai-Pfizer, Novartis)
  - Independent medical expert witness in legal cases

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Some basic ground rules

Cognitive concerns

- Episodic memory
- Attention
- Semantics
- Language
- Higher motor function
- Higher sensory/perceptual function
- Executive function
- Social cognition.

- Random forgetting
- Age-appropriate forgetting
- Physiologic forgetting
- Task effect
- Impairment
  - Brain as victim ("performance effect")
  - ***Brain as perpetrator***.

Selected neurobehavioral deficits

- Amnesia
- Aphasia
- Alexia
- Agraphia
- Anosognosia
- Alexythymia
- Confabulation
- Delusional misidentification
- Acalculia
- Apraxia
- Agnosia
- Pure word deafness
- Simultanagnosia
- Prosopagnosia
- Hemineglect
- Hemi-asomatognosia
- Aprosodia

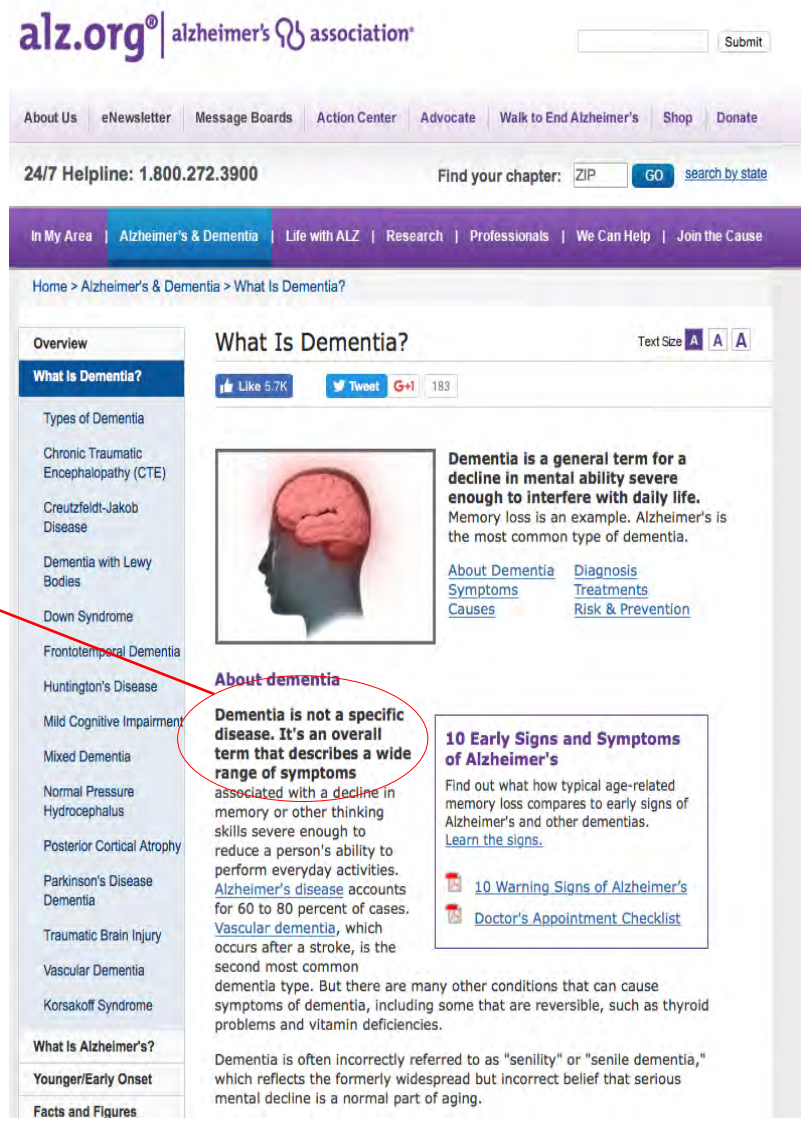
Dementia

DSM-5 “Major Neurocognitive Disorder”

A clinical *state*

1. Abnormal
2. Acquired
3. Multiple areas of
4. true cognitive impairment
5. Due to brain damage
6. Lasts a while
7. ~~Functional impairment~~

“Dementia is not a specific disease. It’s an overall term that describes a wide array of symptoms.”



Mild cognitive impairment (MCI)

DSM-5 “Minor Neurocognitive Disorder”

A clinical *state*

1. Abnormal
2. Acquired
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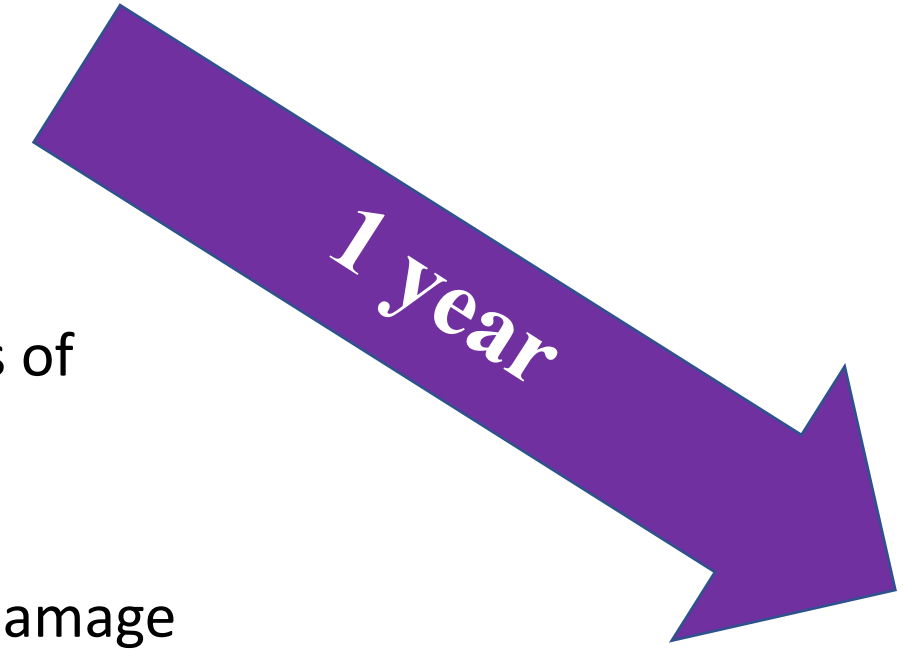


Dementia (13.7%)

Tifratene et al., 2015, *Neurology, 85*: 331-8.

Subjective cognitive decline

NIA-AA classification system*

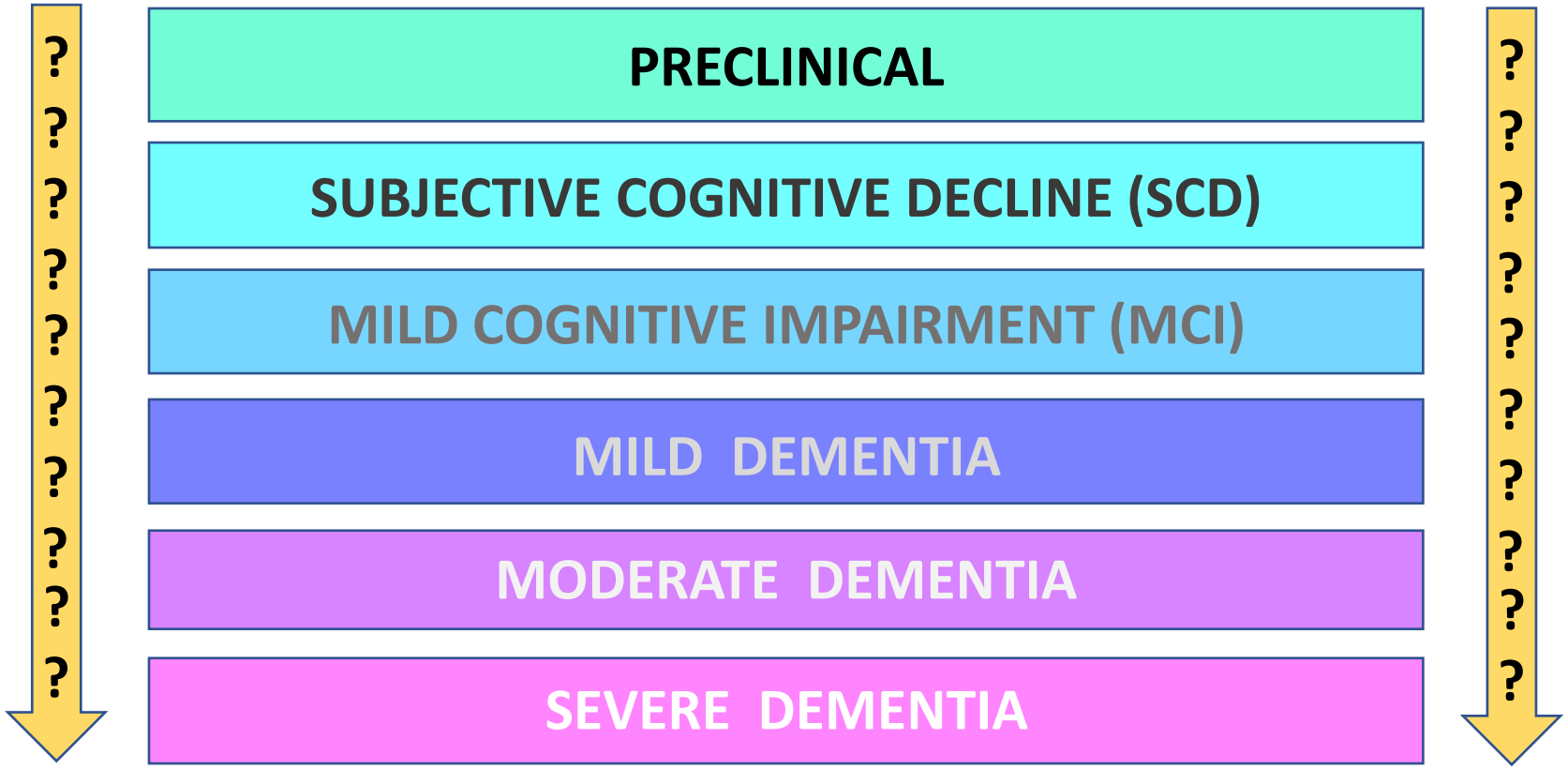
- *Self* observed *marked* ↓ mental ability (e.g. memory)
- Not explained
- OK on formal testing

- 28 studies
- 29,723 people
- Mean age 71.6
- Mean duration 4.8 y

- SCD ~ doubles risk MCI/dementia
- 24.4% MCI
- 10.9% → dementia

*Jack et al., 2018, *Alzheimer's Dementia, 14*:535

NIA-AA classification system



*Jack et al., 2018, *Alzheimer's Dementia, 14*:535

Lots of possible causes

alzheimer's association

Vascular Dementia

AFTD The Association for Frontotemporal Degeneration
Opening the gateway to help and a cure

Lewy Body Dementia Association, Inc.

Parkinson's Foundation

Hippocampal sclerosis of aging
Argyrophilic grain disease
Primary age-related tauopathy (PART)
Limbic age-related TDP-43 encephalopathy (LATE)

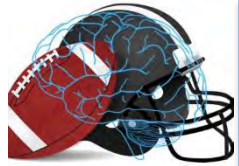
American Brain Tumor Association®

cure PSP

Brain Injury Association of America

Huntington's Disease Society of America

AUTOIMMUNE ENCEPHALITIS ALLIANCE



Meningitis Foundation of America Inc.

The Encephalitis Society
Support, Awareness & Research for Inflammation of the Brain

Hydrocephalus Association

NUTRITION

cid

FRAXA Finding a Cure for Fragile X

Lots of possible causes

Alzheimer Disease and Associated Disorders
Vol. 16, No. 4, pp. 203–212

Relative Frequencies of Alzheimer Disease, Lewy Body, Vascular and Frontotemporal Dementia, and Hippocampal Sclerosis in the State of Florida Brain Bank

*Warren W. Barker, *Cheryl A. Luis, *Alice Kashuba, *Mercy Luis, *Dylan G. Harwood, *§David Loewenstein, †Carol Waters, ‡Pat Jimison, †Eugene Shepherd, §Steven Sevush, ¶Neil Graff-Radford, **Douglas Newland, ††Murray Todd, ‡‡Bayard Miller, §§Michael Gold, ¶¶Kenneth Heilman, ¶¶Leilani Doty, ‡Ira Goodman, ***Bruce Robinson, ‡Gary Pearl, ¶Denn

Only 42% "purely" due to Alzheimer

Only 58% "purely" due to <u>any</u> etiology

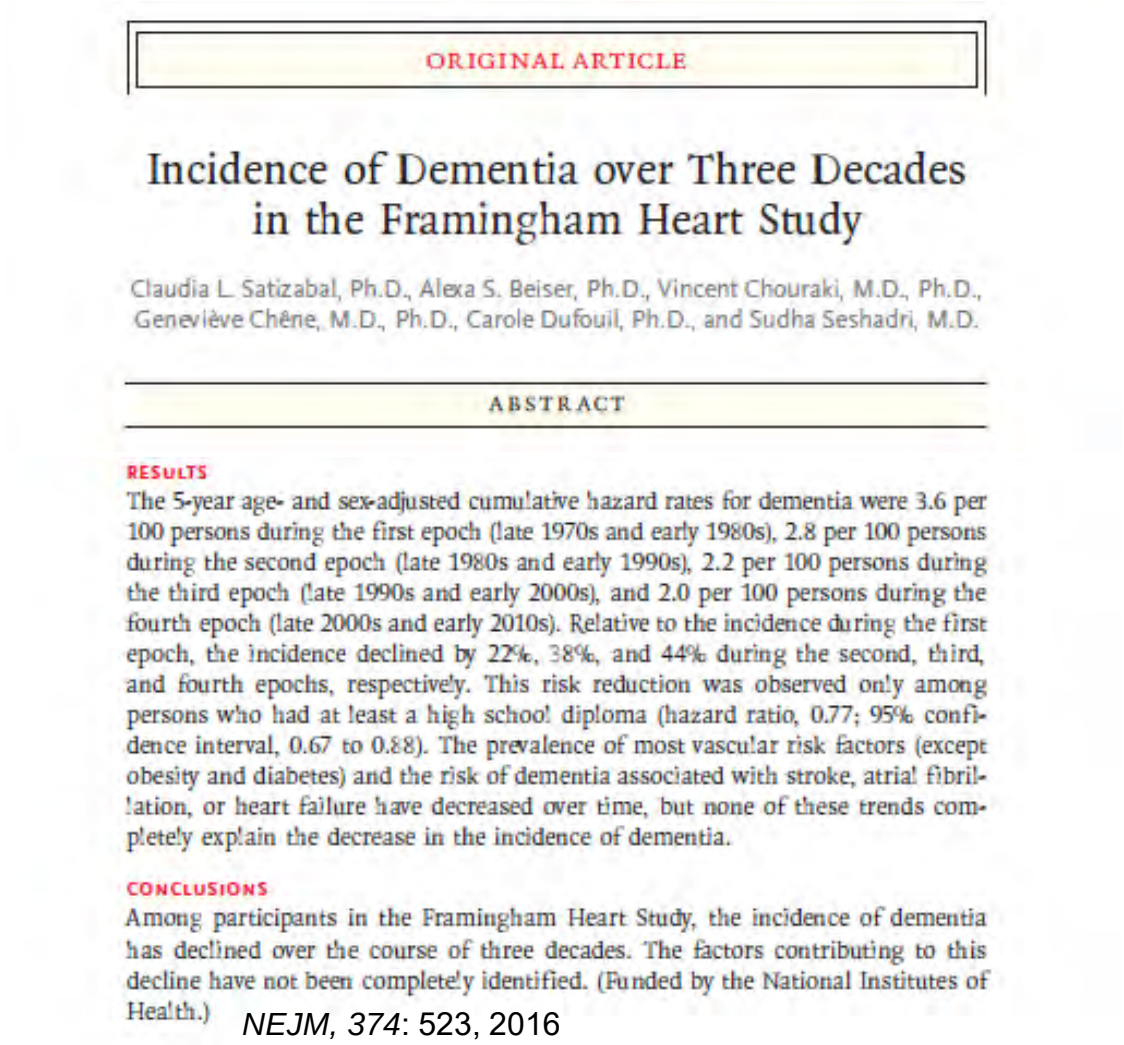
TABLE 2. *Frequency of postmortem diagnoses*

Postmortem diagnosis	N	% of cases
AD (all cases)	293	77
Pure AD	159	42
AD + LBD	54	14
AD + VaD	43	11
AD + HS	22	6
AD + LBD + VaD	5	1
AD + LBD + HS	5	1
AD + HS + VaD	5	1
LBD (all cases)	99	26
Pure LBD	30	8
LBD + AD	54	14
LBD + AD + VaD	5	1
LBD + AD + HS	5	1
LBD + HS	2	1
VaD (all cases)	70	18
Pure VaD	12	3
VaD + AD	43	11
VaD + AD + LBD	5	1
VaD + AD + HS	5	1
VaD + HS	3	1
FTD (all cases)	21	5
Pure FTD	14	4
FTD + HS	6	2
HS (all cases)	50	13
Pure HS	5	1
HS + AD	22	6
FTD + HS	6	1
HS + AD + LBD	5	1
HS + AD + VaD	5	1
HS + VaD	3	1
HS + LBD	2	1

Numbers do not add up to total for "all cases" because combinations of 4 or more pathologies are not shown.

AD, Alzheimer disease; LBD, Lewy body disease; VaD, vascular dementia; FTD, frontotemporal dementia; HS, hippocampal sclerosis.

Dementia rates are falling



ORIGINAL ARTICLE

Incidence of Dementia over Three Decades in the Framingham Heart Study

Claudia L. Satizabal, Ph.D., Alexa S. Beiser, Ph.D., Vincent Chouraki, M.D., Ph.D., Geneviève Chêne, M.D., Ph.D., Carole Dufouil, Ph.D., and Sudha Seshadri, M.D.

ABSTRACT

RESULTS

The 5-year age- and sex-adjusted cumulative hazard rates for dementia were 3.6 per 100 persons during the first epoch (late 1970s and early 1980s), 2.8 per 100 persons during the second epoch (late 1980s and early 1990s), 2.2 per 100 persons during the third epoch (late 1990s and early 2000s), and 2.0 per 100 persons during the fourth epoch (late 2000s and early 2010s). Relative to the incidence during the first epoch, the incidence declined by 22%, 38%, and 44% during the second, third, and fourth epochs, respectively. This risk reduction was observed only among persons who had at least a high school diploma (hazard ratio, 0.77; 95% confidence interval, 0.67 to 0.88). The prevalence of most vascular risk factors (except obesity and diabetes) and the risk of dementia associated with stroke, atrial fibrillation, or heart failure have decreased over time, but none of these trends completely explain the decrease in the incidence of dementia.

CONCLUSIONS

Among participants in the Framingham Heart Study, the incidence of dementia has declined over the course of three decades. The factors contributing to this decline have not been completely identified. (Funded by the National Institutes of Health.)

NEJM, 374: 523, 2016

Years	1970s	2000s
Incidence per 100 persons	3.6	2.0
Mean age at diagnosis (years)	80	85

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Alzheimer disease basics

Autopsy diagnosis is based on three things

ALZHEIMER DISEASE AND ASSOCIATED DISORDERS, 1(1):7–8, 1987
c 1987 BY THE WESTERN GERIATRIC RESEARCH INSTITUTE

ABOUT A PECULIAR DISEASE OF THE CEREBRAL CORTEX[1]

(Über eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin* 64:146–148, 1907)

By Alois Alzheimer
Translated by L. Jarvik and H. Greenson

A. reports on his observation of a patient at the insane asylum in Frankfurt/Main whose central nervous system he examined at the request of Director Sioli. The picture he presents is of a case so deviant even on clinical grounds alone that it does not fit into any of the known disease categories, and the anatomical findings diverge from all currently known disease processes.

Case Presentation[2]

The first noticeable symptom of illness shown by this 51-year-old woman was suspiciousness of her husband. Soon, a rapidly increasing memory impairment became evident; she could no longer orient herself in her own dwelling, dragged objects here and there and hid them, and at times, believing that people were out to murder her, started to scream loudly.

On observation at the institution, her entire demeanor bears the stamp of utter bewilderment. She is completely disoriented to time and place. Occasionally, she remarks that she does not understand anything and is at her wits' end. Sometimes she greets the doctor as if he were a visitor and excuses herself that she has not finished with her work; on other occasions, she screams that he wants to cut her open[3]; on others yet, she dismisses him, full of indignation and with expressions indicating that she fears him as a threat to her honor as a woman. At times she is totally delirious, drags her bedding around, calls for her husband or daughter, and seems to have auditory hallucinations. Often she screams for many hours in a horrible voice.

With her inability to understand her situation, she bursts into loud screams each time she is approached to be examined. Only through constantly repeated efforts was it possible to eventually establish some limited information.

Clinical Evaluation

Her ability to encode information[4] is most severely disturbed. If one shows her objects, she usually names them correctly. Immediately thereafter, however, she has forgotten everything. In reading, she confuses lines, reads by spelling, or with senseless intonation. When writing, she repeats single syllables many times, omits others and gets stuck altogether very quickly. When speaking, she frequently uses phrases indicating perplexity or embarrassment, or single paraphasic expressions (milk pourer instead of cup); sometimes one observes that she is completely at a loss for words. She clearly does not grasp some questions, and it seems that she no longer knows the use of certain objects.

Her gait is normal, and she can use her hands well. Patellar reflexes are present. Pupils react. Radial arteries are somewhat rigid; on percussion, there is no enlargement of cardiac dullness. Laboratory findings: No albumen.

Course of Illness

In the further course of illness, there appear what could be interpreted as focal symptoms, but they are very slight and variable—sometimes stronger, sometimes weaker. By contrast, general imbecility keeps progressing. The 4½ year illness ended in death. Terminally, the patient was totally dulled, lying in bed with legs drawn up, incontinent, and, despite all care, developed decubiti.

Autopsy

The autopsy reveals a consistently atrophic brain without macroscopic foci. The larger cerebral vessels show arteriosclerotic changes. Preparations stained with Bielschowsky's silver method reveal peculiar changes of the neurofibrils. Inside an otherwise apparently still normal cell, first one or more fibrils stand out prominently because of their unusual thickness and unusual ability to take up stain. Later on, there are many such fibrils lying next to each other, all changed in the same way. These are eventually seen clustering together in thick bundles which gradually emerge at the surface of the cell. Finally, the nucleus and the cell have fallen apart and only a tangled bundle of fibrils points to the place in which there once was a ganglion cell. Since these fibrils can be stained with methods other than those used to stain normal neurofibrils, a chemical change of the fibril substance must have taken place and might be the cause for the fibrils surviving the disintegration of the cell. The conversion of the fibril seems to go hand in hand with the storage of a pathologic metabolic product in the ganglion cell, a possibility which needs to be more deeply researched. About one-quarter to one-third of all ganglion cells in the cortex show such changes, and numerous ganglion cells, especially in the upper cell layers, have altogether disappeared.

Scattered over the entire cortex, and especially numerous in the upper layers, there are miliary foci distinguishable by the deposit in the cerebral cortex of a peculiar substance which can be recognized without stain and is, in fact, very refractory to staining.

The glia have formed abundant fibers, and many glial cells show large fatty sacs.

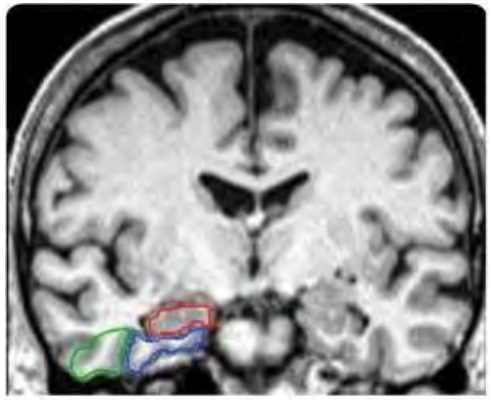
There is total absence of infiltration of the vessels; by contrast, one sees endothelial proliferation and also, occasionally, neovascularization.

* * *

All in all, we have before us the evidence for a specific disease process. In recent years the ascertainable number of such specific disease processes has been increasing. As this case report demonstrates, it behooves us not to be satisfied with attempts to force, by means of painstaking efforts, clinically unclear observations to fit one of the disease categories familiar to us. There are without doubt many more psychiatric illnesses than our textbooks mention. In some instances, the uniqueness of the case will be established by subsequent histologic examination. Then, we will gradually arrive at the stage where we will be able to separate out individual diseases from the larger disease categories of our textbooks and sharpen their clinical definition.

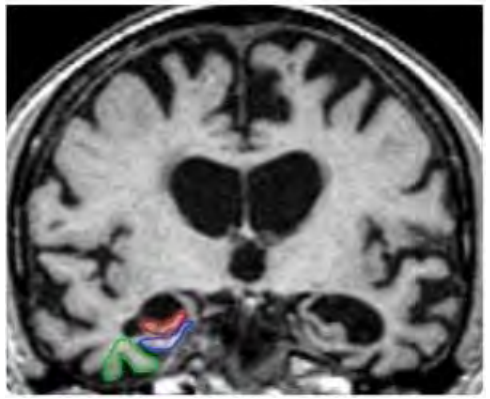
1. Dead / missing cells (neurodegeneration)

normal

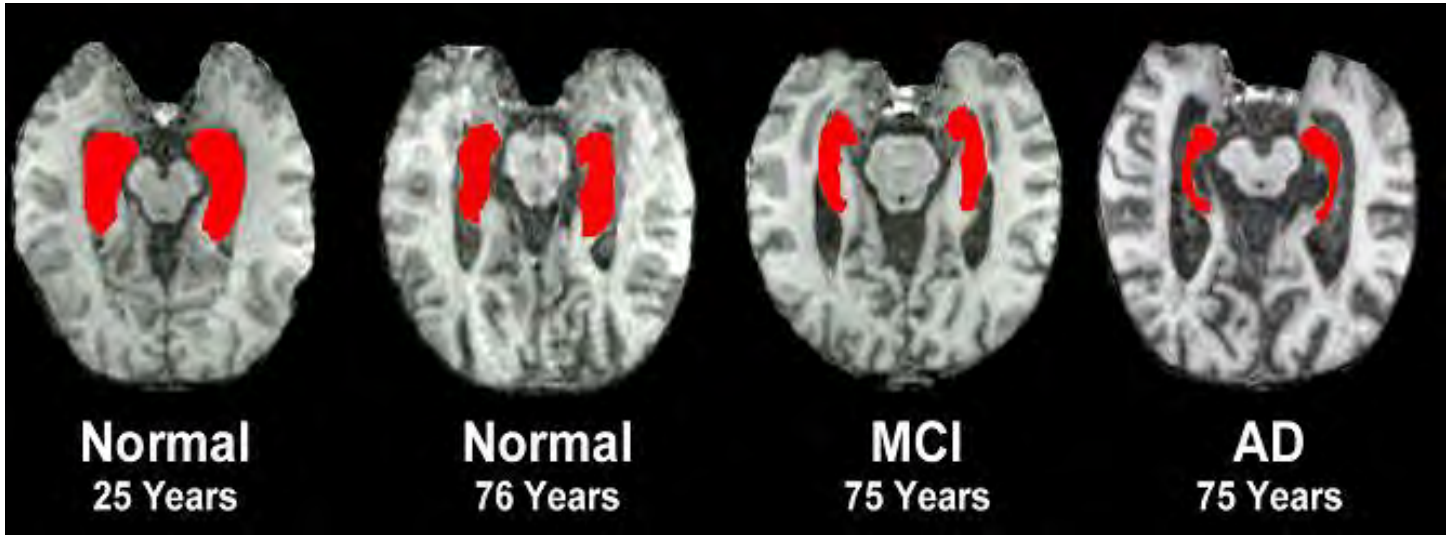


coronal T1 MRI

Alzheimer



coronal T1 MRI



axial T1 MRI

Adapted from de Leon (2005)

2. Amyloid plaque

PERSPECTIVE

Alzheimer's Disease: The Amyloid Cascade Hypothesis

John A. Hardy and Gerald A. Higgins

Alzheimer's disease causes dementia in many elderly people and in some individuals with Down syndrome who survive to age 50. Alzheimer's is characterized by various pathological markers in the brain—large numbers of amyloid plaques surrounded by neurons containing neurofibrillary tangles (*1*), vascular damage from extensive plaque deposition (*2*), and neuronal cell loss (*1*). Because it is not known if the amyloid plaques or the neurofibrillary tangles are the earliest lesion in the disease process, the role of these markers in the etiology of the disease is controversial.

cerebrospinal fluid (*9*). The APP secretase that cuts within the AβP region has an extraordinarily broad sequence specificity and recognizes the secondary structure of APP, cleaving at a defined distance from the membrane (*10*). Several recent studies suggest that APP can also be processed by the endosomal-lysosomal pathway, after recycling of membrane-bound APP and possibly via an intracellular metabolic route (*11–13*). Carboxyl-terminal fragments containing the entire AβP sequence can be derived from this alternate normal processing of APP (*12, 14*) and may eventually lead to amyloid

Alzheimer's disease. These mutations all occur at codon 717 of the protein (*15, 16*) and change the native valine, located three residues from the COOH-terminal end of AβP, to isoleucine, phenylalanine, or glycine (Fig. 1). It is unclear how these mutations cause amyloid deposition, but they may inhibit the breakdown of a COOH-terminal fragment of APP that contains AβP (*15*), alter the anchoring of APP in the cell membrane, or stabilize AβP-containing amyloidogenic fragments within lysosomes (*12, 15*).

Our cascade hypothesis states that AβP itself, or APP cleavage products containing AβP, are neurotoxic and lead to neurofibrillary tangle formation and cell death. Thus, two successive events are needed to produce Alzheimer's pathology. First, AβP must be generated as an intact entity, either by accumulation of AβP or as an AβP-containing fragment of APP. Second, this molecule must facilitate or cause neuronal death and neurofibrillary tangle formation.

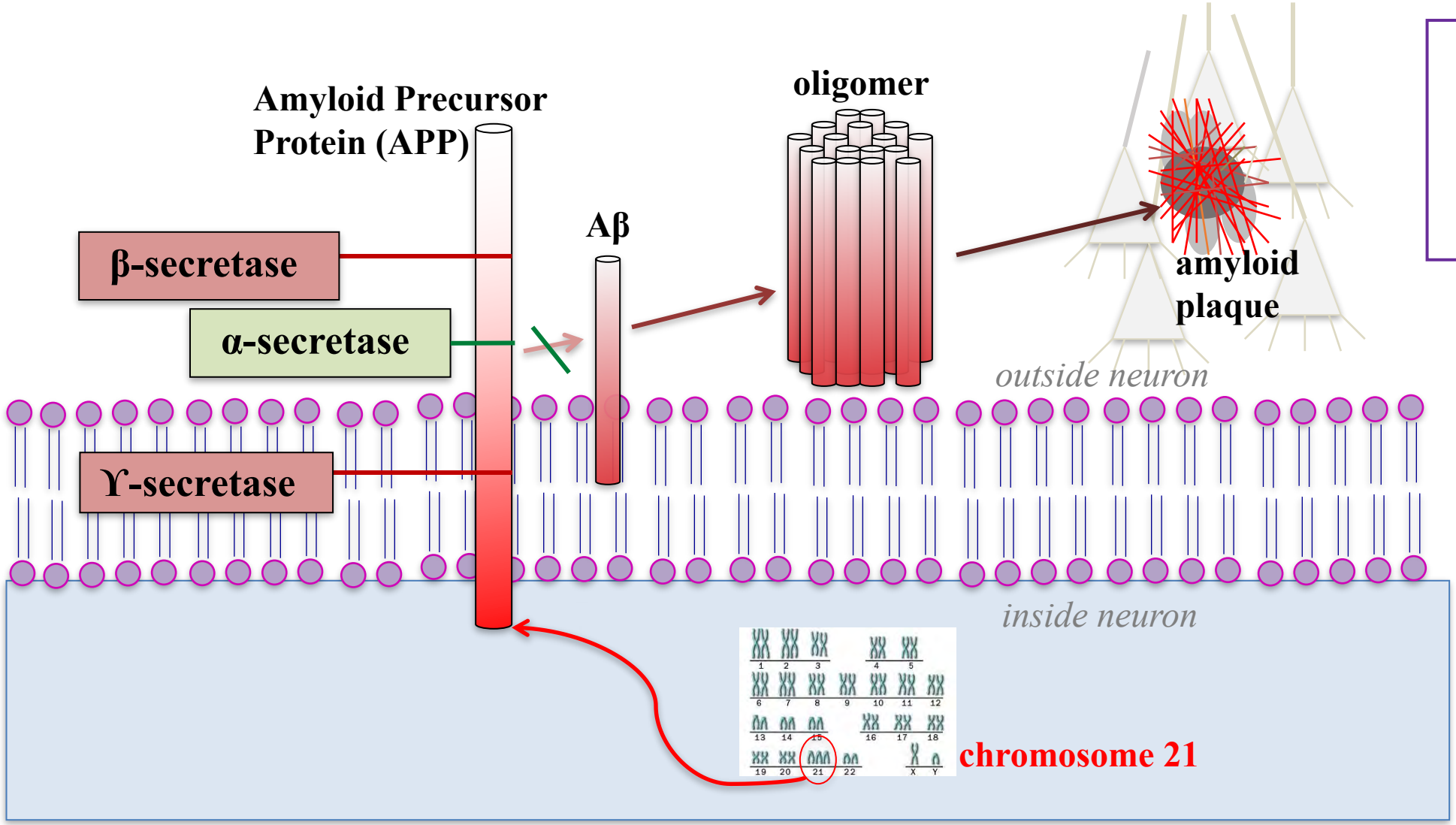
Hospital Medical School, London W2 1PG, U.K., and Department of Psychiatry, University of South Florida, Tampa, FL 33612.
G. A. Higgins, Molecular Neurobiology, Laboratory of Biological Chemistry, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224.

of the apparent lack of sequence specificity of the enzyme (*10*).

Three mutations have been described within the APP gene that cause familial

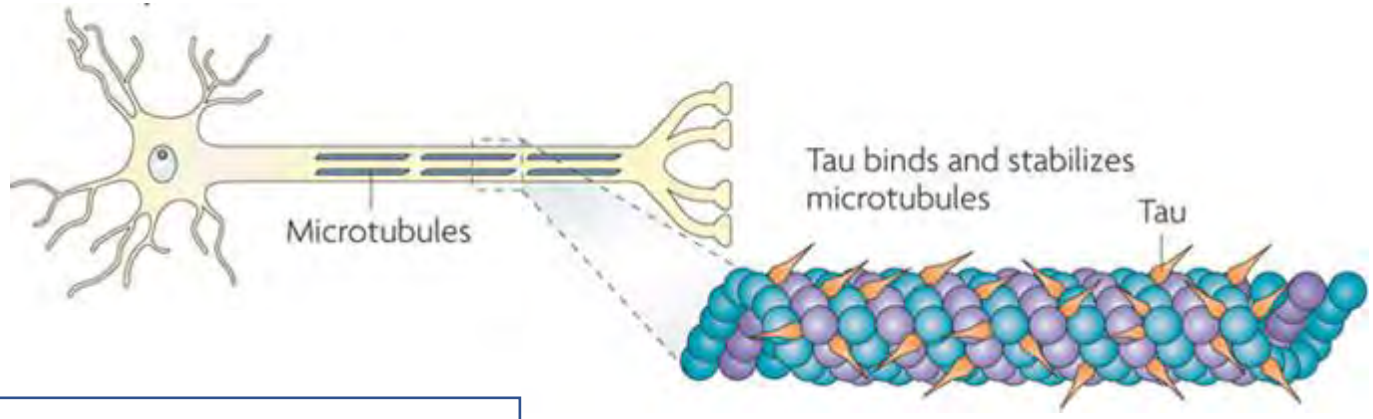
neurofibrillary tangles form. The tangles are largely composed of paired helical filaments formed from a hyperphosphorylated form of the microtubule associated protein, tau (*6*),

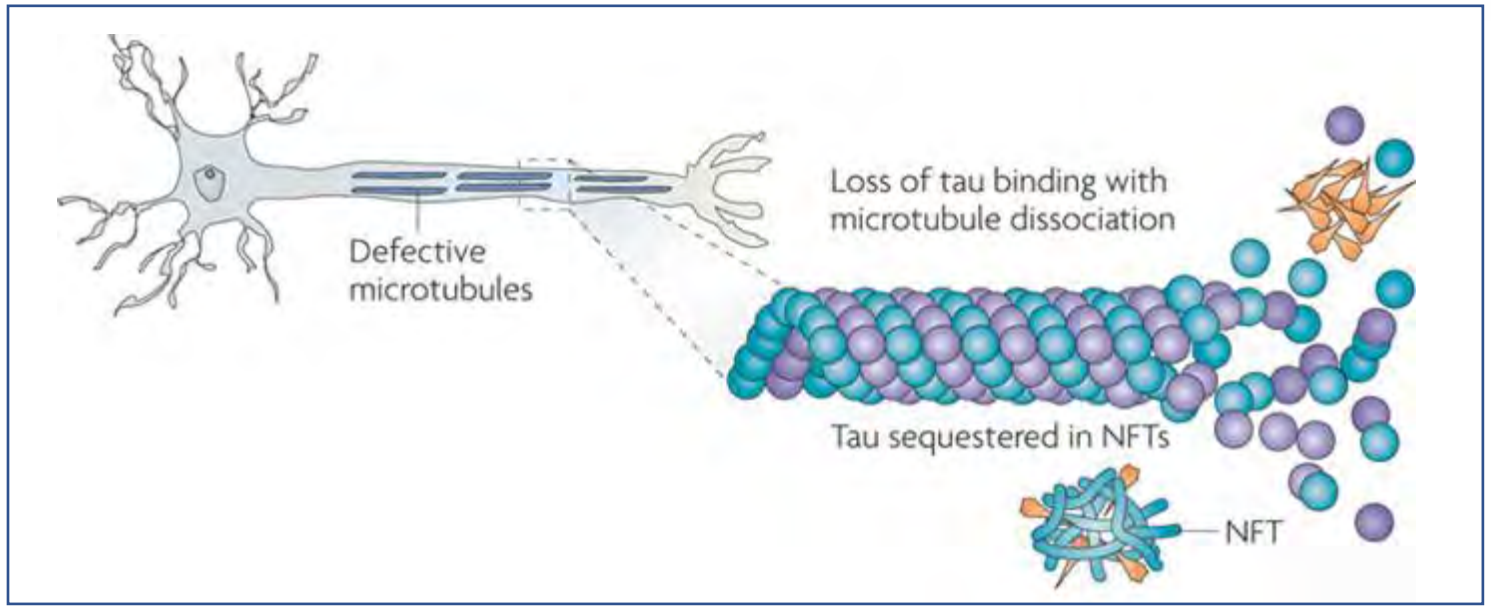
2. Amyloid plaque



Amyloid plaque formation

3. Neurofibrillary tangles

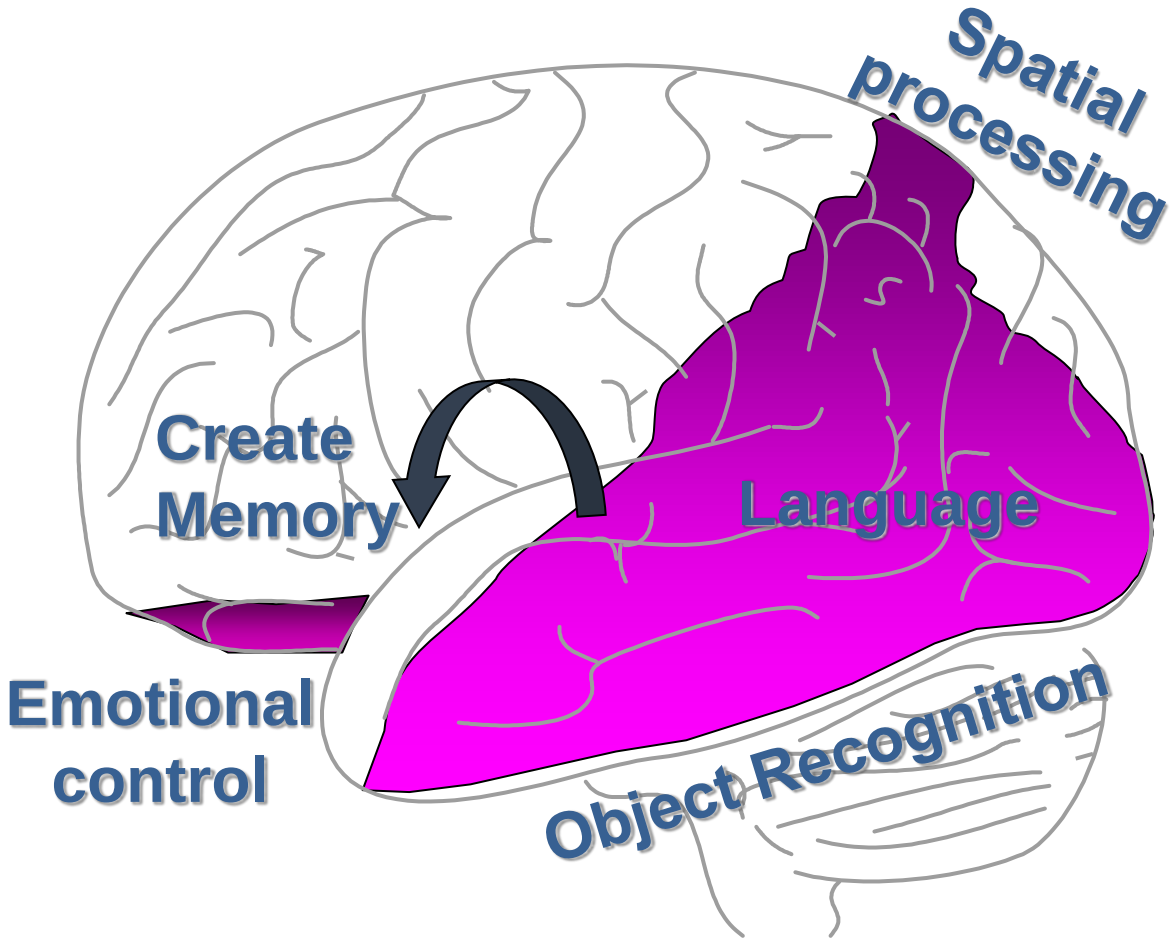




Brunden et al., (2009). *Nature Reviews Drug Discovery, 8,* 783–793.

3. Neurofibrillary tangles

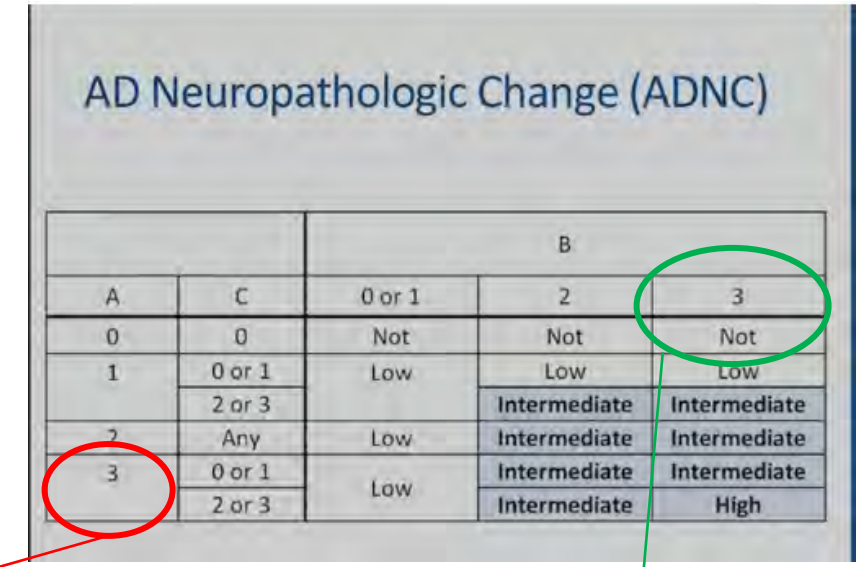
Symptoms come from areas of most ***neurofibrillary tangles***



Adapted from Geldmacher (2003)

"ABCs" of Alzheimer neuropathology

- Thal amyloid phase (A0 – A3)
  - Spatial distribution of all AB plaques
- Braak stage (B0 – B3)
  - Spread of neurofibrillary tangles
  - B1 = Braak ½, B2 = Braak II/IV, B3 = Braak V/VI
- CERAD score (C1 – C3)
  - Highest density of neuritic plaques
  - C1 = sparse, C2 = moderate, C3 = frequent

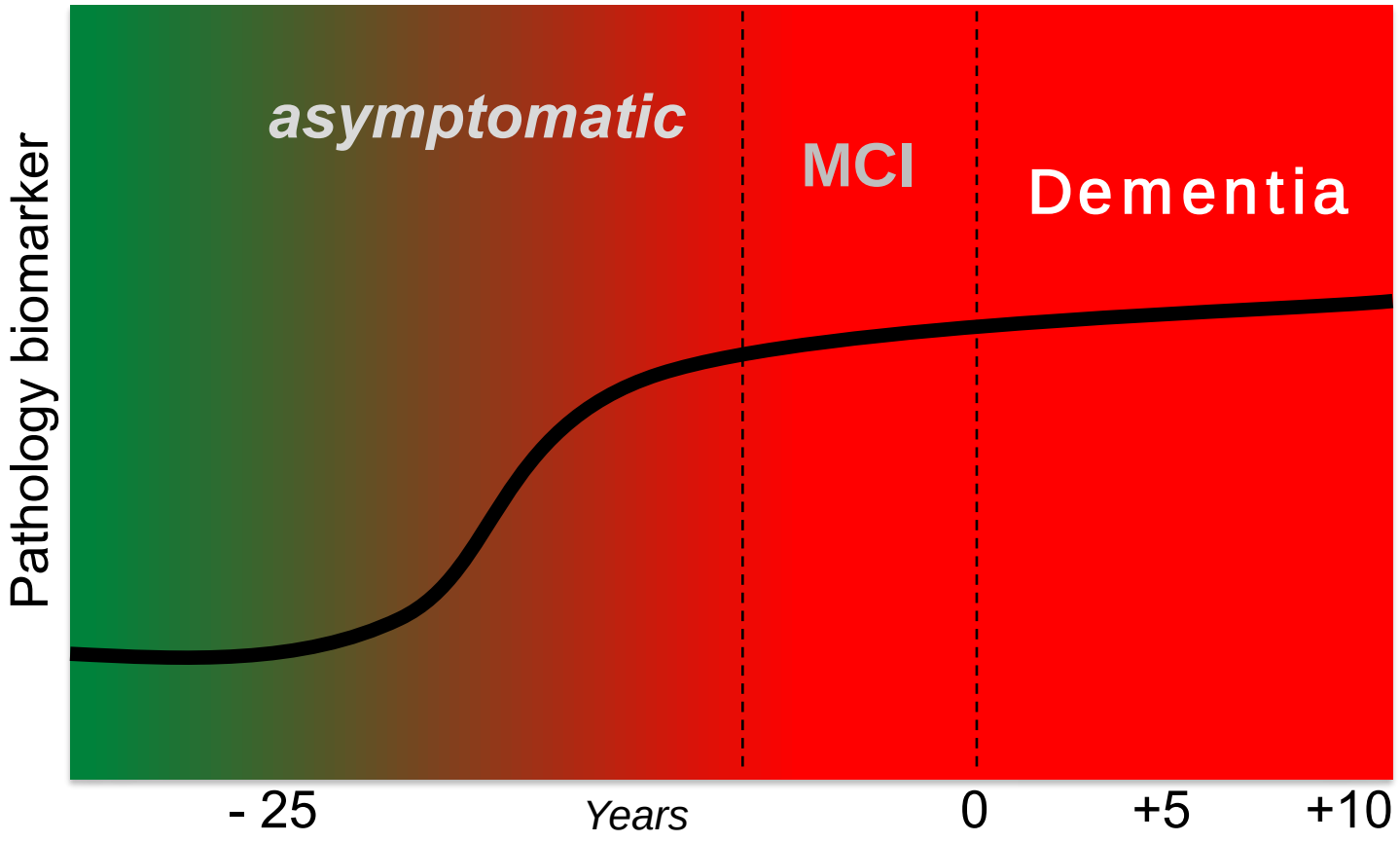


		B		
A	C	0 or 1	2	3
0	0	Not	Not	Not
1	0 or 1	Low	Low	Low
	2 or 3		Intermediate	Intermediate
2	Any	Low	Intermediate	Intermediate
3	0 or 1	Low	Intermediate	Intermediate
	2 or 3		Intermediate	High

*high **amyloid** burden is necessary but not sufficient for high neuropathology certainty for Alzheimer disease*

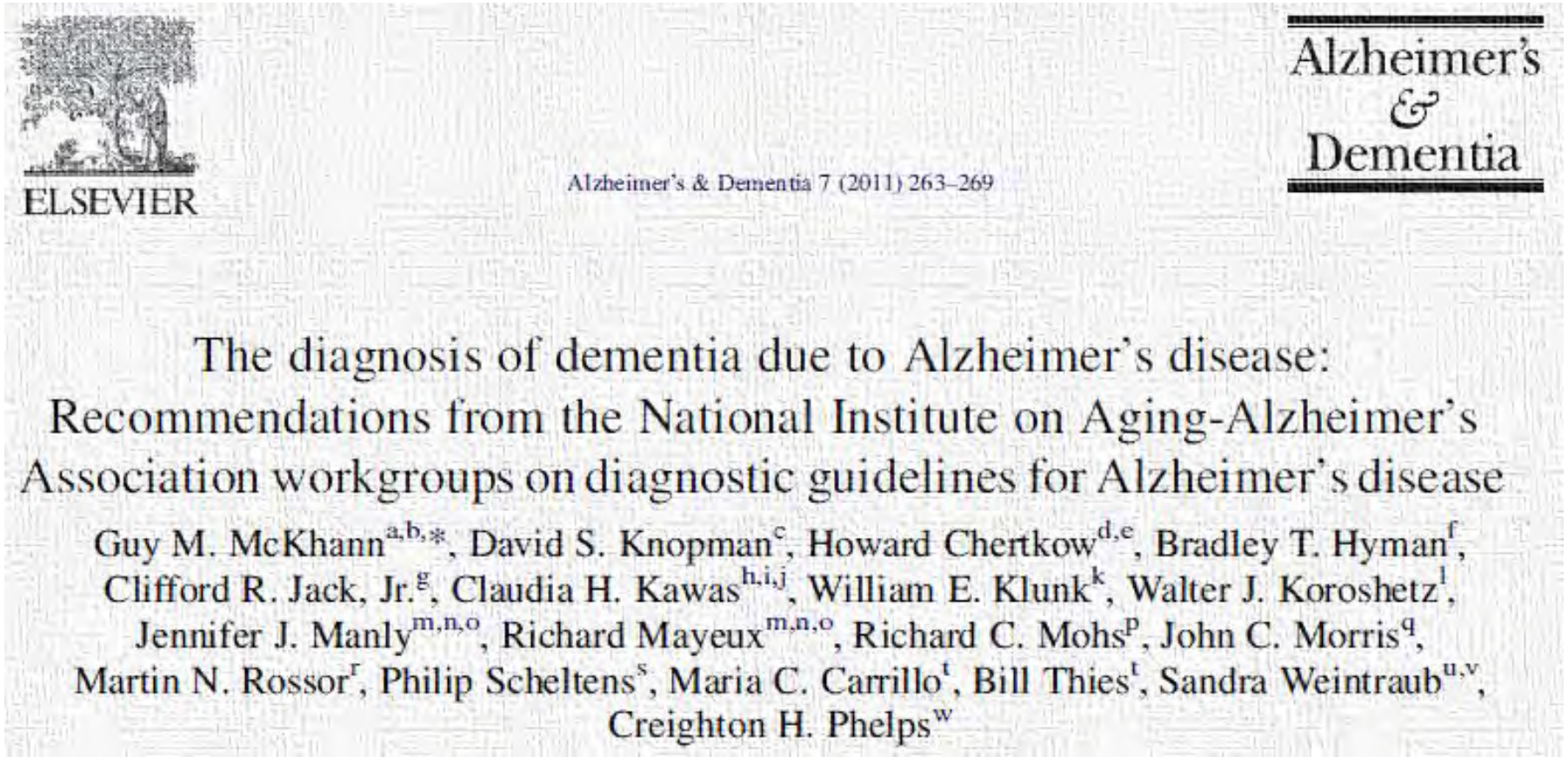
*high **neurofibrillary tangle** burden is necessary but not sufficient for high neuropathology certainty for Alzheimer disease*

How Alzheimer disease behaves



Adapted from Frisoni, G. B. (2012) Biomarker trajectories across stages of Alzheimer disease. *Nat. Rev. Neurol.*

How Alzheimer disease behaves



ELSEVIER

Alzheimer's & Dementia 7 (2011) 263–269

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carrillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

How Alzheimer disease behaves

Dementia 2° cognitive/behavioral sx that

1. **Affects usual activities**
2. **↓ from baseline**
3. **Not 2° delirium / psychiatric dx**
4. **Cognition ↓ per history (patient /informant)**
5. **Cognition ↓ per objective testing**
6. **Cognition ↓ involves ≥ 2 domains**

Dementia *has* inclusive features

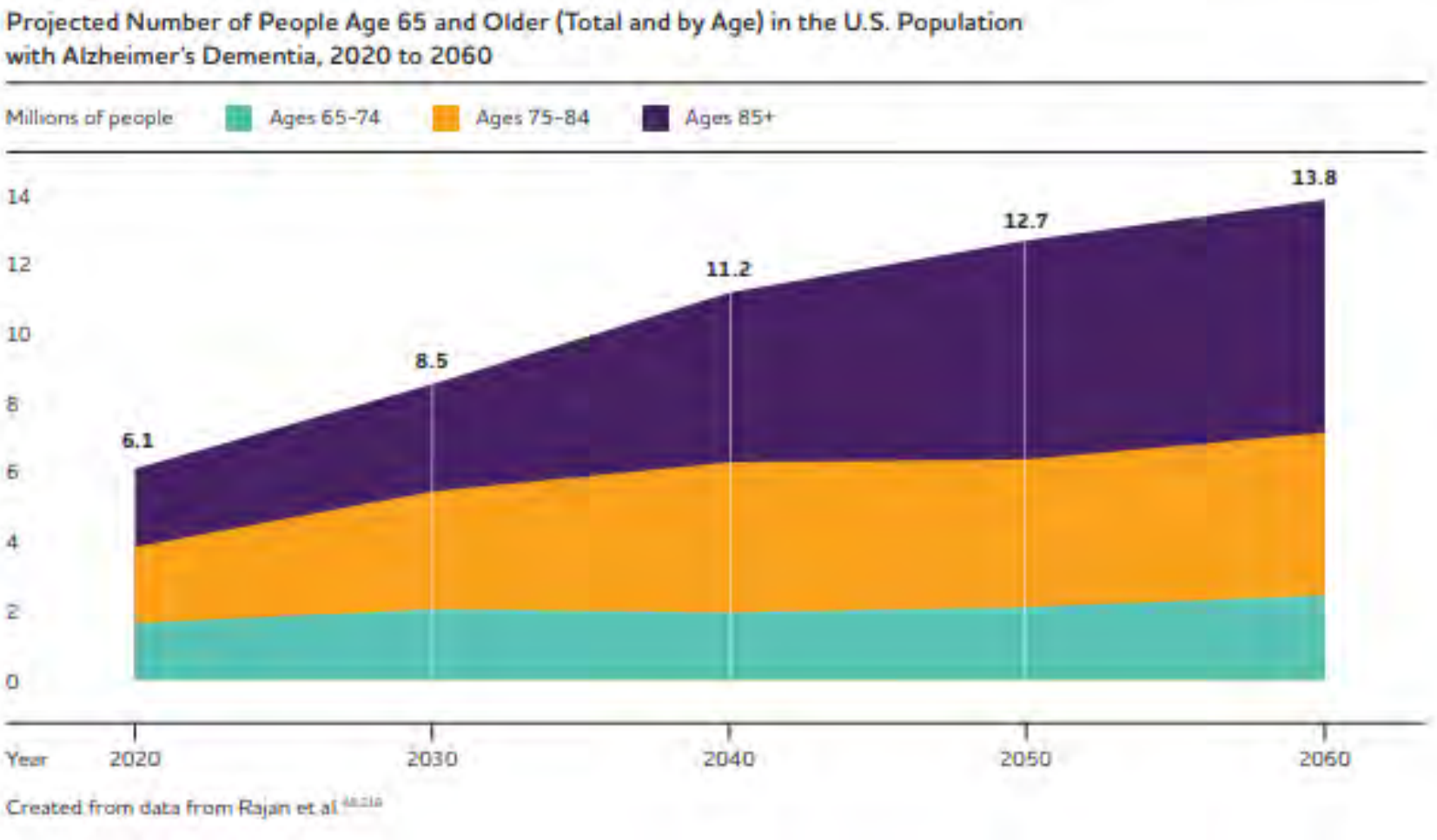
1. **Insidious onset**
2. **Clear ↓ per report / observation**
3. **Initial and most prominent sx ≥ 1 of**
   a. **↓ anterograde memory for experiences**
   b. **↓↓ language**
   c. **↓↓ visuospatial function**
   d. **↓↓ executive function**

Dementia *lacks* exclusionary features

1. **Substantial concomitant cerebrovascular dz**
   a. **Extensive severe CV damage, or**
   b. **Clinical stroke timed to onset/worsening**
2. **Prominent si non-Alzheimer dementia syndrome**
3. **Another active disease / drug could ↓↓ cognition**

McKhann et al., 2011, *Alzheimer's & Dementia, 7*(3):263-9

How Alzheimer disease behaves



2021 ALZHEIMER'S DISEASE FACTS AND FIGURES

6.1 million dementia

12.4 million MCI

~2/3 are women

↑African/Hispanic descent

↓Asian descent.

Alzheimer's Associations 2021 Alzheimer disease facts and figures. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

How Alzheimer disease behaves

2021 ALZHEIMER'S DISEASE FACTS AND FIGURES

In 2021, Alzheimer's and other dementias will cost the nation

$355 BILLION

By 2050, these costs could rise to

$1.1 TRILLION

OVER

11

MILLION

Americans provide unpaid care for people with Alzheimer disease or other dementias.

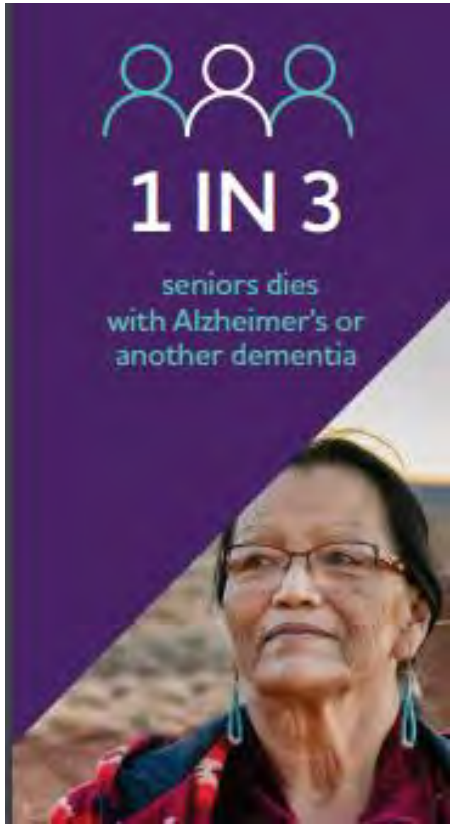
These caregivers provided an estimated 15.3 billion hours a year valued at nearly

$257

BILLION

Alzheimer's Associations 2021 Alzheimer disease facts and figures. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

How Alzheimer disease behaves



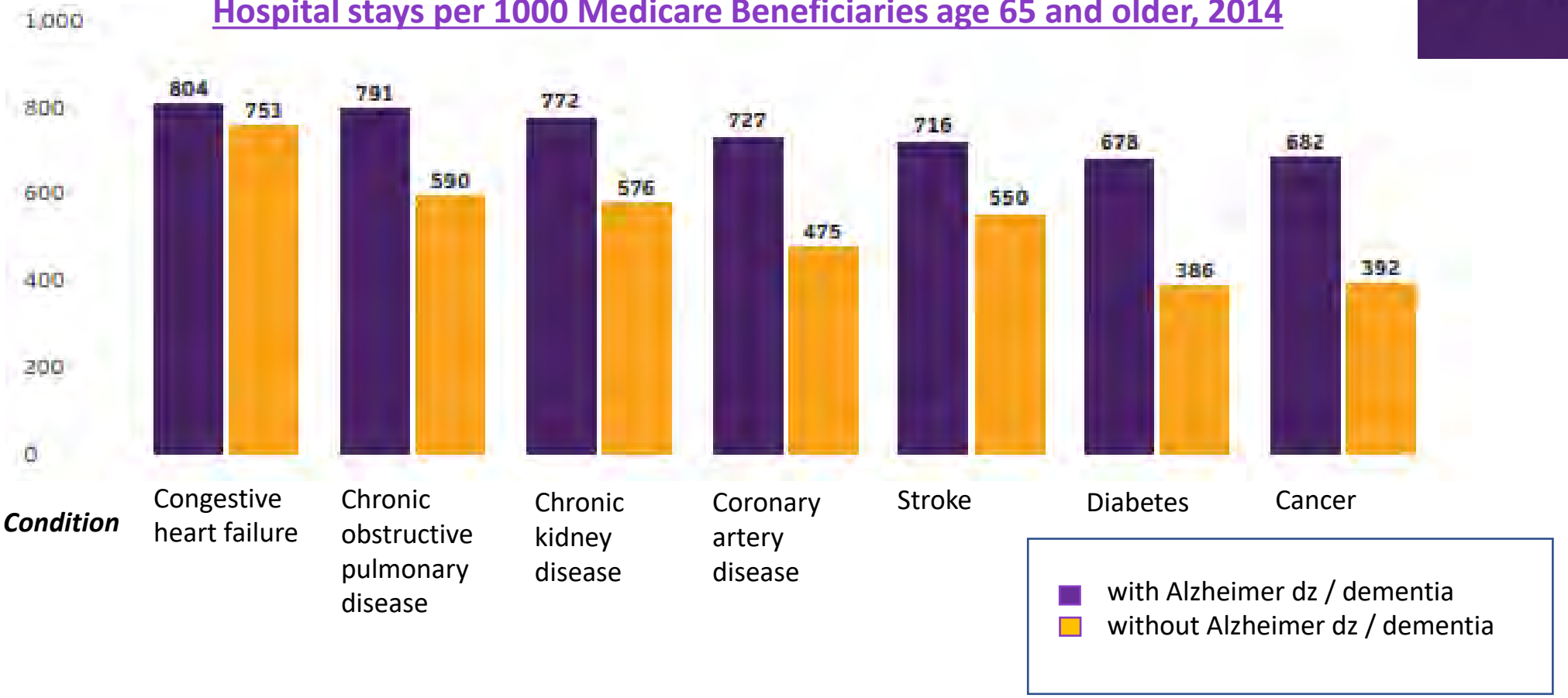
2021 ALZHEIMER'S DISEASE FACTS AND FIGURES

Deaths 2000-2019

- Breast cancer ↑ 1.1%
- Prostate cancer ↑ 1.8%
- Heart disease ↓7.3%
- Stroke ↓10.5%
- HIV ↓65.2%
- **Alzheimer disease ↑145.2%.**

How Alzheimer disease behaves

2021 ALZHEIMER'S DISEASE FACTS AND FIGURES



Alzheimer's Associations 2021 Alzheimer disease facts and figures. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

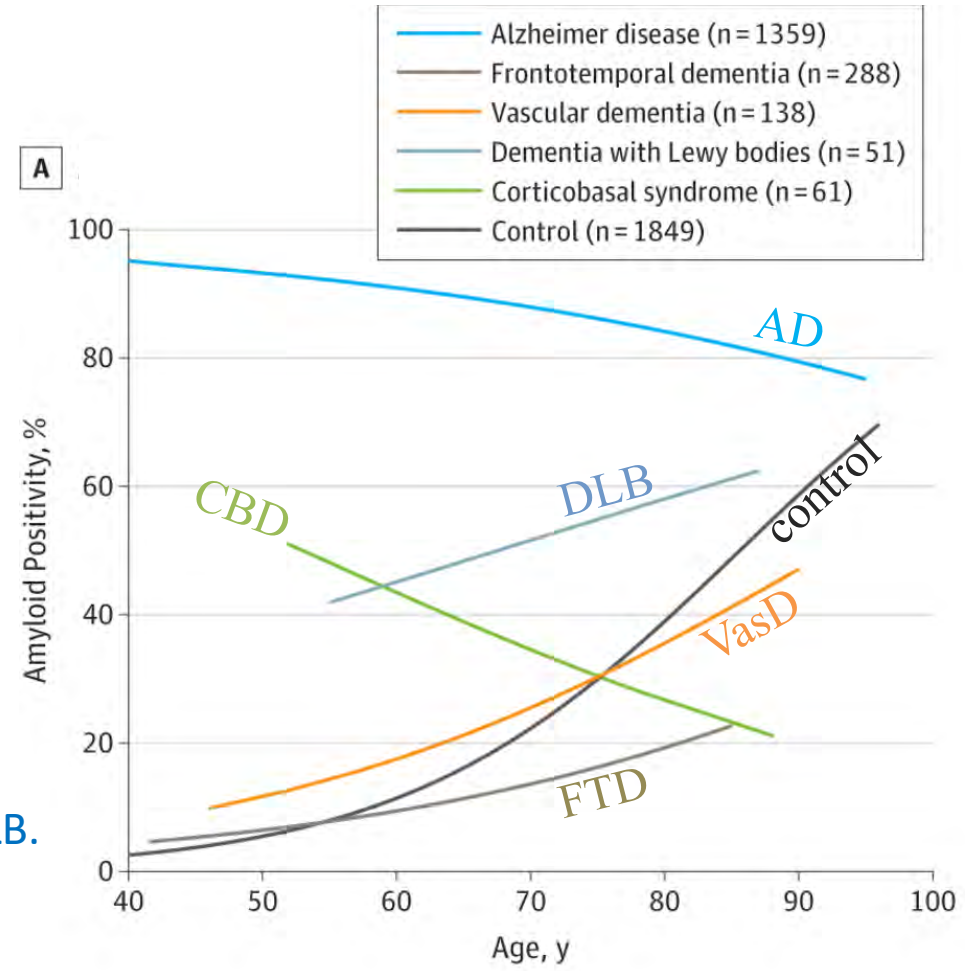
School of Medicine
University of Missouri Health

The new world

Evolving understanding of pathologies

Amyloid plaques are not unique to Alzheimer disease

Amyloid brain PET



Note:

- most helpful if negative
- not helpful in oldest patients
- not helpful to distinguish Alzheimer vs. DLB.

Ossenkopelle et al (2015) Prevalence of Amyloid PET Positivity in Dementia Syndromes: A Meta-analysis *JAMA;313*(19):1939-1950. doi:10.1001/jama.2015.4669

Evolving understanding of pathologies

Neurofibrillary tangles are not unique to Alzheimer disease

Formerly “dementia pugilistica”

Brain Pathol. 2015 May ; 25(3): 350–364. doi:10.1111/bpa.12248.

The Neuropathology of Chronic Traumatic Encephalopathy

Ann C. McKee[1,2,3,4,5], **Thor D. Stein**[1,2,3,4], **Patrick T. Kiernan**[4,5], and **Victor E. Alvarez**[4,5]

Abstract

Repetitive brain trauma is associated with a progressive neurological deterioration, now termed as chronic traumatic encephalopathy (CTE). Most instances of CTE occur in association with the play of sports, but CTE has also been reported in association with blast injuries and other neurotrauma. Symptoms of CTE include behavioral and mood changes, memory loss, cognitive impairment and dementia. Like many other neurodegenerative diseases, CTE is diagnosed with certainty only by neuropathological examination of brain tissue. CTE is a tauopathy characterized by the deposition of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles, astrocytic tangles and neurites in striking clusters around small blood vessels of the cortex, typically at the sulcal depths. Severely affected cases show p-tau pathology throughout the brain. Abnormalities in phosphorylated 43 kDa TAR DNA-binding protein are found in most cases of CTE; beta-amyloid is identified in 43%, associated with age. Given the importance of sports participation and physical exercise to physical and psychological health as well as disease resilience, it is critical to identify the genetic risk factors for CTE as well as to understand how other variables, such as stress, age at exposure, gender, substance abuse and other exposures, contribute to the development of CTE.

Evolving understanding of pathologies

Neurofibrillary tangles are not unique to Alzheimer disease

Acta Neuropathol (2014) 128:755–766
DOI 10.1007/s00401-014-1349-0

CONSENSUS PAPER

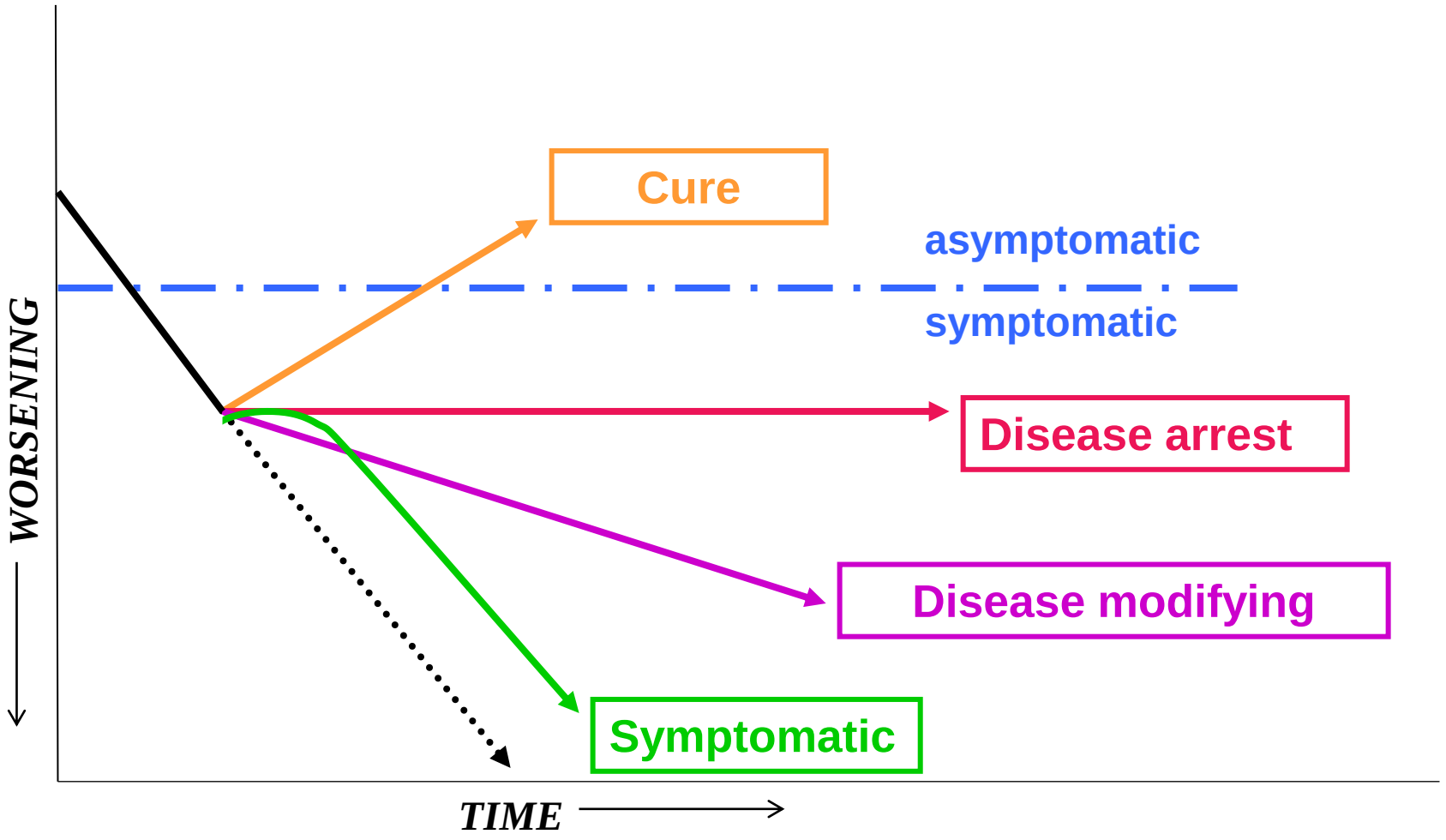
Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff · Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha · Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah · Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H. Neltner · Ismael Santa-Maria · William W. Seeley · Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masaki Takao · Dietmar R. Thal · Jonathan B. Toledo · Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer · Masahito Yamada · Peter T. Nelson

- Amnestic disorder, especially in very aged, profound dementia rare
- Little or no amyloid plaque
- “tangle-only dementia,” “NFT predominant dementia.”

FDA approved treatments for neurocognitive disorders

generic	brand name	approved for	approval date
donepezil	Aricept	Alzheimer, all stages dementia	1996
galantamine	Razadyne	Alzheimer, mild-moderate dementia	2001
memantine	Namenda	Alzheimer, moderate-severe dementia	2003
rivastigmine	Exelon	Alzheimer, all stages dementia Parkinson disease dementia	2000 2006
caprylidene	Axona	Alzheimer, mild-moderate dementia	2009
donepezil + memantine	Namzeric	Alzheimer, moderate-severe dementia	2014


Cure
asymptomatic
symptomatic
Disease arrest
Disease modifying
Symptomatic
WORSENING
TIME

FDA approved treatments for neurocognitive disorders

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Disease modifying therapy has begun

FDA approved treatments for neurocognitive disorders

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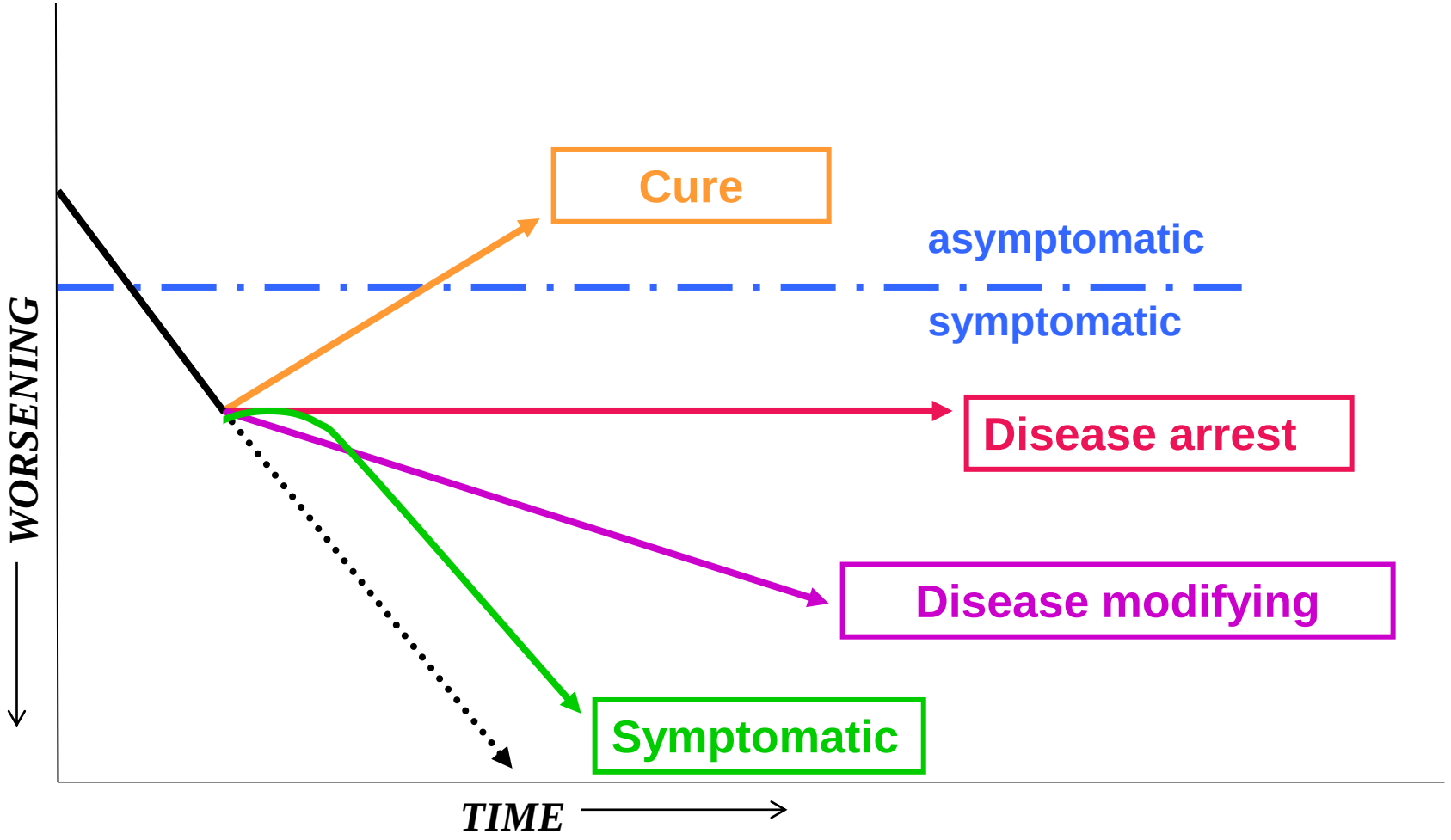
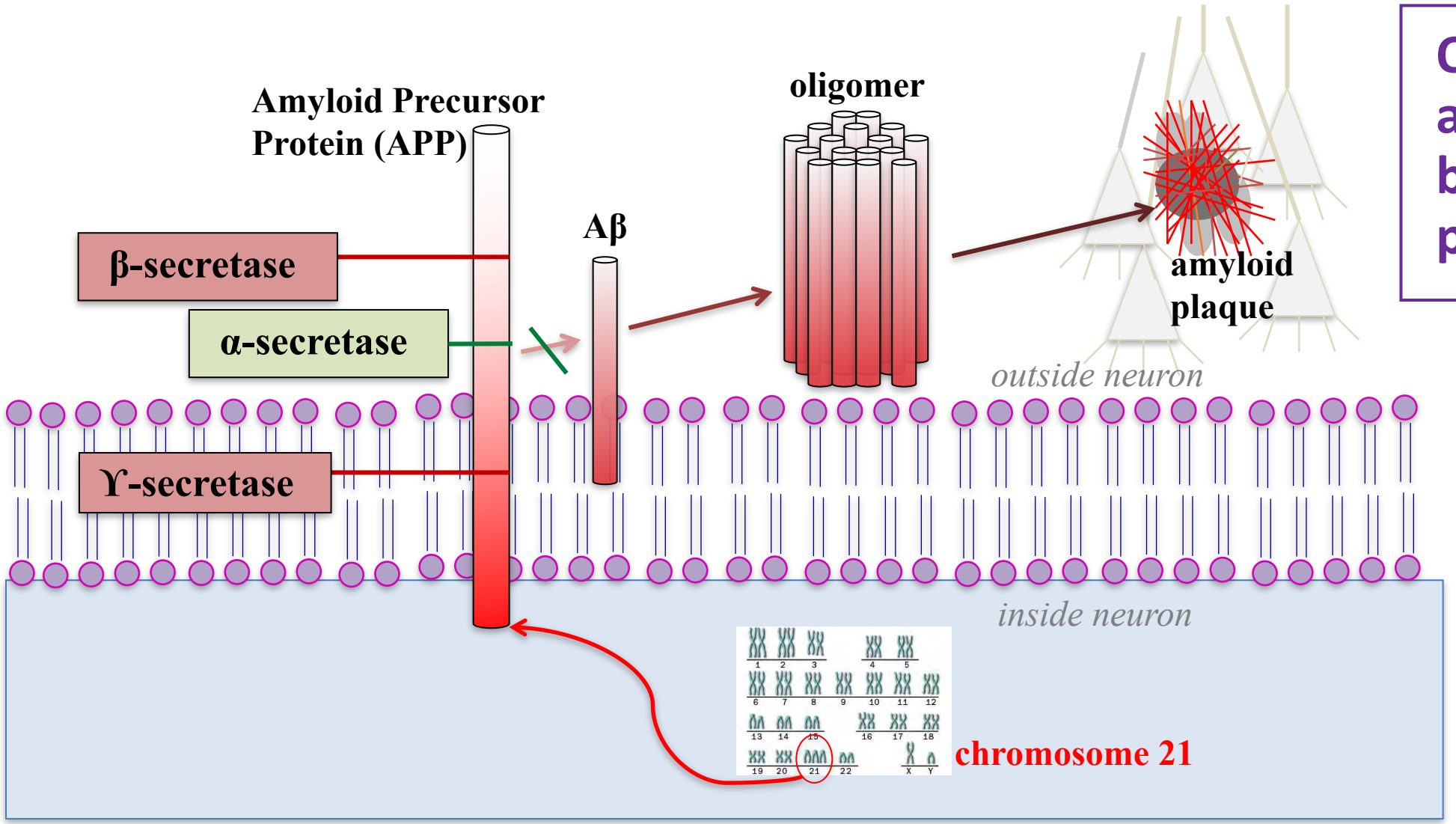
donepezil + memantine	Namzeric	Alzheimer, moderate-severe dementia	2014
aducanumab	Aduhelm	Alzheimer, MCI or mild dementia	2021

Disease modifying therapy has begun



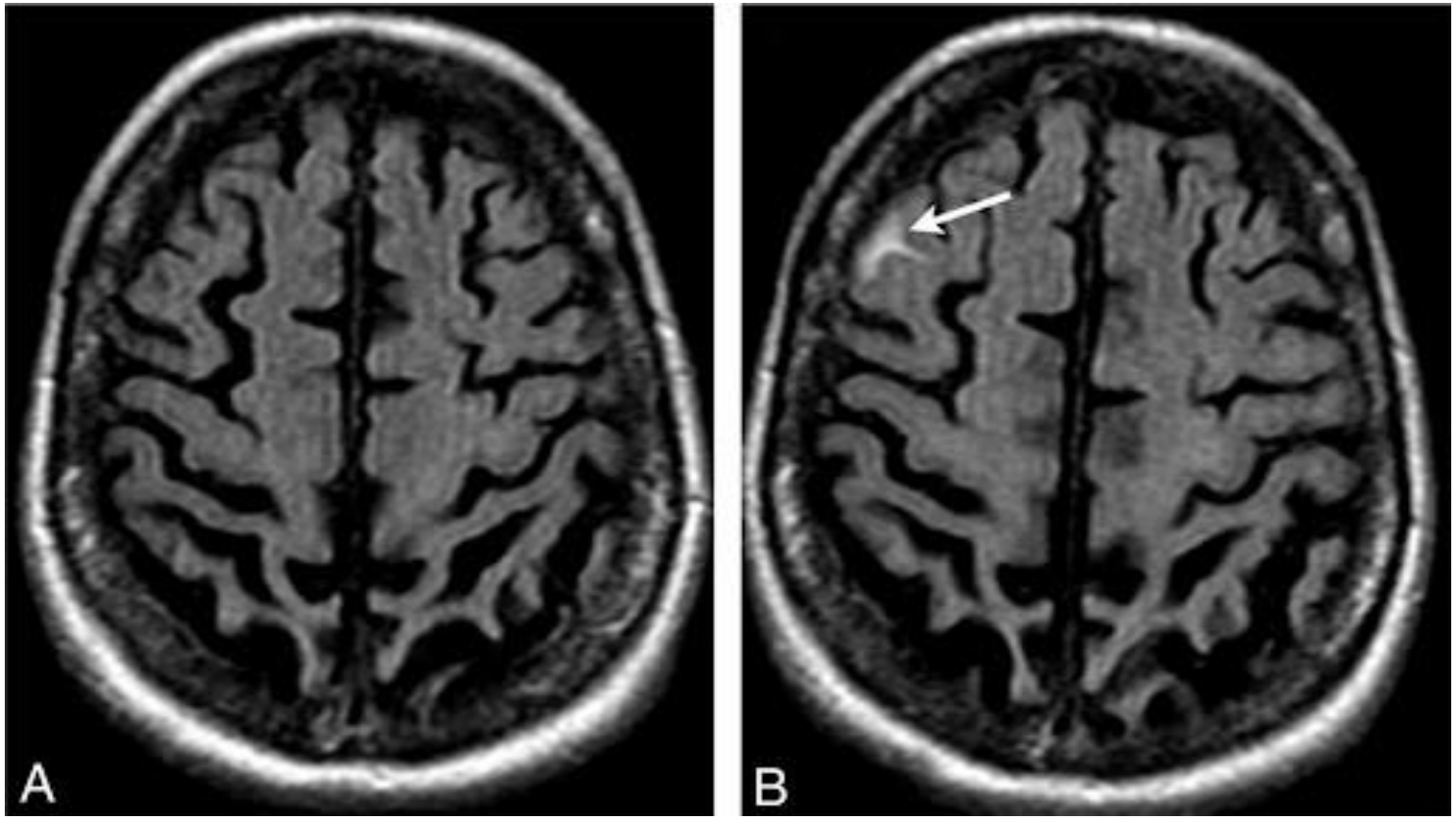
Disease modifying therapy has begun



One place to attack may be amyloid pathway

Disease modifying therapy has begun

Amyloid related imaging abnormalities (ARIA)

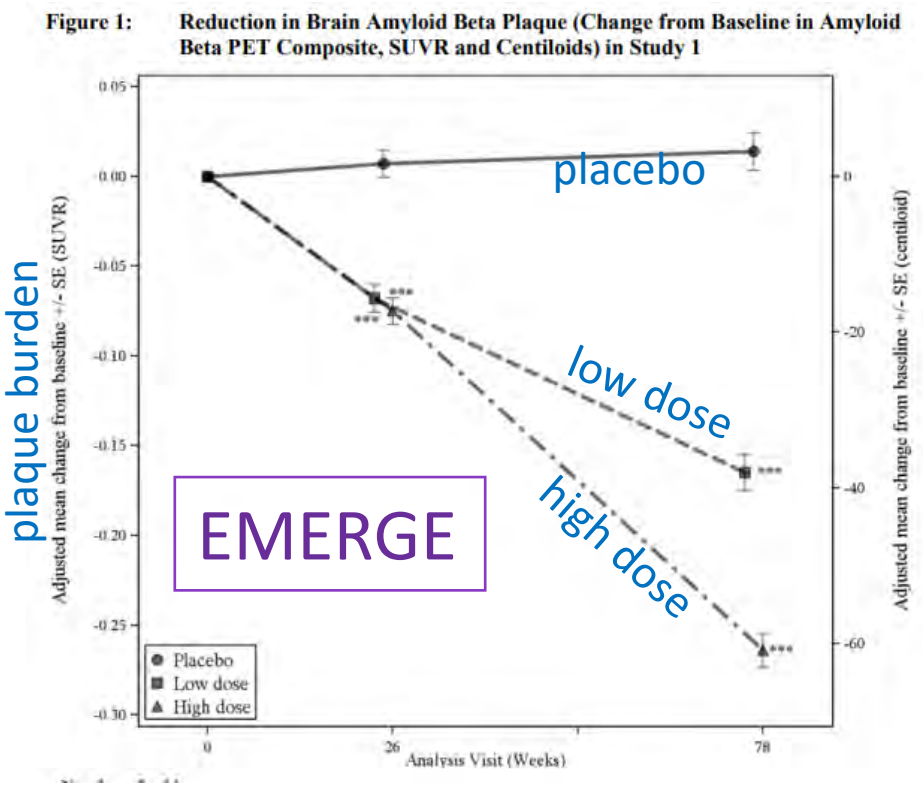


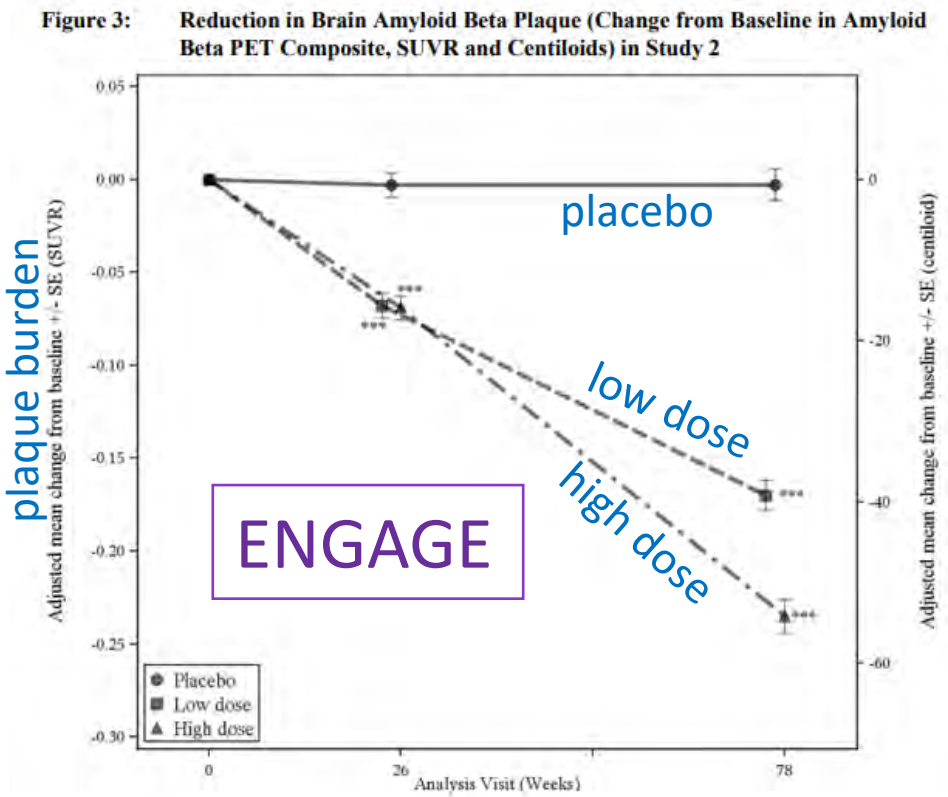
http://www.ajnr.org/content/34/10/1958

Disease modifying therapy has begun

Aduhelm® (aducanumab)

Both pivotal trials reduced amyloid plaque



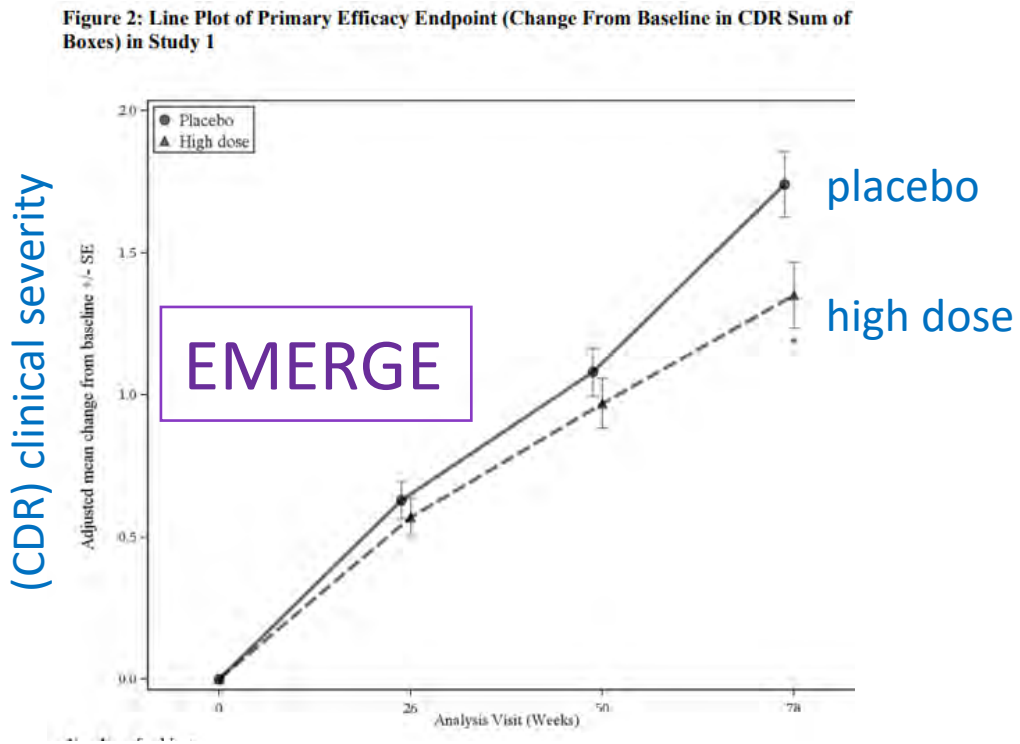


https://www.biogencdn.com/us/aduhelm-pi.pdf

Disease modifying therapy has begun

Aduhelm® (aducanumab)

Only one pivotal trial showed clinical benefit



https://www.biogencdn.com/us/aduhelm-pi.pdf

Disease modifying therapy has begun

Aduhelm® (aducanumab)

November 6, 2020

BIOPHARMA

FDA advisory panel vote against approving Biogen's drug for Alzheimer's

The nonbinding panel recommendation to reject the drug goes against what FDA scientists presented but they throw up another obstacle for the drug, which is trying to succeed on a front where others have failed.

By JOEL BERG

Post a comment / Nov 6, 2020 at 5:57 PM

https://medcitynews.com/2020/11/fda-panel-rejects-studies-on-biogen-drug-for-alzheimers/

Disease modifying therapy has begun

Aduhelm® (aducanumab)

June 7, 2021

FDA's Decision to Approve New Treatment for Alzheimer's Disease

By Dr. Patrizia Cavazzoni, Director, FDA Center for Drug Evaluation and Research

Today FDA approved Aduhelm (aducanumab) to treat patients with Alzheimer's disease using the Accelerated Approval pathway, under which the FDA approves a drug for a serious or life-threatening illness that may provide meaningful therapeutic benefit over existing treatments when the drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients and there remains some uncertainty about the drug's clinical benefit.

This approval is significant in many ways. Aduhelm is the first novel therapy approved for Alzheimer's disease since 2003. Perhaps more significantly, Aduhelm is the first treatment directed at the underlying pathophysiology of Alzheimer's disease, the presence of amyloid beta plaques in the brain. The clinical trials for Aduhelm were the first to show that a reduction in these plaques—a hallmark finding in the brain of patients with Alzheimer's—is expected to lead to a reduction in the clinical decline of this devastating form of dementia.

https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease

Disease modifying therapy has begun

Aduhelm® (aducanumab)

A Letter from Biogen's CEO on ADUHELM

JUNE 7, 2021 • COMPANY STATEMENTS

Today, on behalf of my Biogen colleagues, I am incredibly humbled to share that the U.S. Food and Drug Administration (FDA) has granted accelerated approval for ADUHELM™ (aducanumab-avwa), the first-ever therapy to address a defining pathology of Alzheimer's disease—amyloid beta plaque.

https://investors.biogen.com/news-releases/news-release-details/letter-biogens-ceo-aduhelm

Disease modifying therapy has begun

Aduhelm® (aducanumab)

Alzheimer's Association Welcomes FDA Approval of Aducanumab

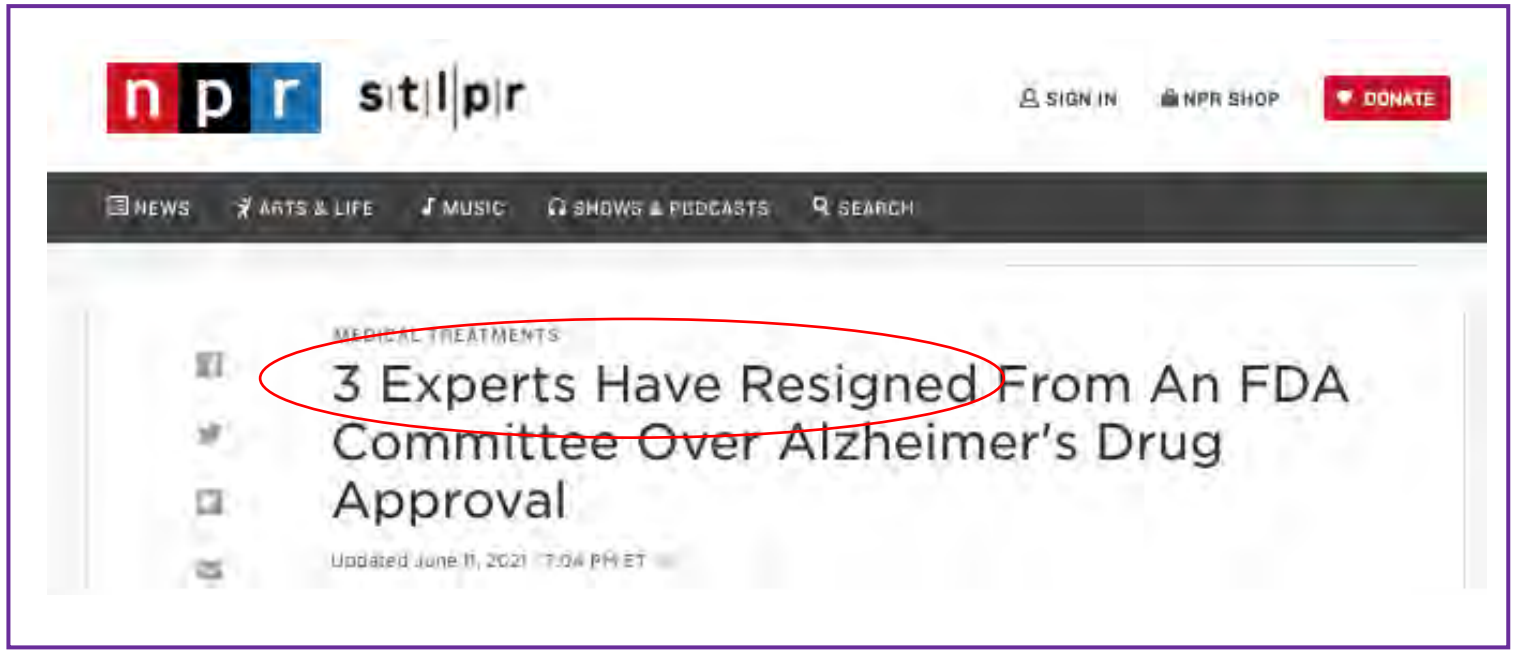
CHICAGO, June 7, 2021 — On behalf of those impacted by Alzheimer's disease, the Alzheimer's Association enthusiastically welcomes today's historic FDA approval of aducanumab (Biogen/Eisai) for treatment of Alzheimer's disease.

"This approval is a victory for people living with Alzheimer's and their families," said Harry Johns, Alzheimer's Association president and chief executive officer. "This is the first FDA-approved drug that delays decline due to Alzheimer's disease. This means individuals may have more time to actively participate in daily life, have sustained independence and hold on to memories longer. We can experience longer — the relationships we hold most dear — our families and friends."

https://www.alz.org/news/2021/alzheimers-association-fda-approval-aducanumab

Disease modifying therapy has begun

Aduhelm® (aducanumab)



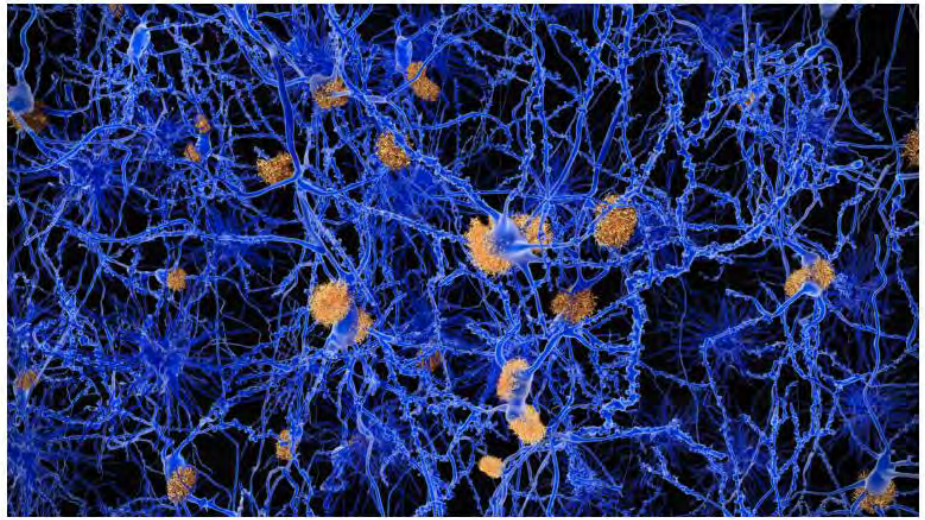
https://www.npr.org/2021/06/11/1005567149/3-experts-have-resigned-from-an-fda-committee-over-alzheimers-drug-approval

Disease modifying therapy has begun

Aduhelm® (aducanumab)

Bad medicine: aducanumab is a lackluster drug with a high price tag

By Karl Herrup and Jonathan Goulazian June 8, 2021 Reprints



https://www.statnews.com/2021/06/08/aducanumab-lackluster-drug-high-price/

The New York Times

How an Unproven Alzheimer's Drug Got Approved

Though some of its own senior officials said there was little evidence of benefit for patients, the F.D.A. nonetheless greenlighted Biogen's Aduhelm, or aducanumab.

https://www.nytimes.com/2021/07/19/health/alzheimers-drug-aduhelm-fda.html

Disease modifying therapy has begun

Aduhelm® (aducanumab)

THE WALL STREET JOURNAL.

Cleveland Clinic, Mount Sinai and Providence Won't Give Biogen's New Alzheimer's Drug

By Joseph Walker

Updated July 15, 2021 8:04 pm ET

The three hospital operators are holding off on administering Aduhelm amid a debate over its effectiveness

Three large hospitals are declining to administer Biogen Inc.'s new Alzheimer's treatment, Aduhelm, the latest rupture to emerge from the Food and Drug Administration's controversial approval of the drug last month.

The Cleveland Clinic, Mount Sinai Health System in New York and Providence in Renton, Wash., said they wouldn't administer Aduhelm, which is also called aducanumab, to patients amid a debate about the drug's effectiveness and whether the FDA lowered its standards in approving the medicine.

https://www.wsj.com/articles/cleveland-clinic-mount-sinai-wont-give-biogens-new-alzheimers-drug-11626366968

Disease modifying therapy has begun

Aduhelm® (aducanumab)

- FDA-approved while Phase 4 study proceeds (≤9 years)
- Monoclonal antibody to Aß oligomer
- Only for minimally affected patients
- Only for *Alzheimer* disease, specifically
- Only if amyloid biomarker positive (CSF, amyloid PET)
- Monthly IV infusions
- Titrate up over time to limit ARIA
- Brain MRIs monitor for ARIA at 0, 7, 12 months)
- $56K/year.

Disease modifying therapy has begun

Disease modifying therapy has begun

Alzheimer disease therapy—moving from amyloid-β to tau

Ezio Giacobini and Gabriel Gold

Abstract | Disease-modifying treatments for Alzheimer disease (AD) have focused mainly on reducing levels of amyloid-β (Aβ) in the brain. Some compounds have achieved this goal, but none has produced clinically meaningful results. Several methodological issues relating to clinical trials of these agents might explain this failure; an additional consideration is that the amyloid cascade hypothesis—which places amyloid plaques at the heart of AD pathogenesis—does not fully integrate a large body of data relevant to the emergence of clinical AD. Importantly, amyloid deposition is not strongly correlated with cognition in multivariate analyses, unlike hyperphosphorylated tau, neurofibrillary tangles, and synaptic and neuronal loss, which are closely associated with memory deficits. Targeting tau pathology, therefore, might be more clinically effective than Aβ-directed therapies. Furthermore, numerous immunization studies in animal models indicate that reduction of intracellular levels of tau and phosphorylated tau is possible, and is associated with improved cognitive performance. Several tau-related vaccines are in advanced preclinical stages and will soon enter clinical trials. In this article, we present a critical analysis of the failure of Aβ-directed therapies, discuss limitations of the amyloid cascade hypothesis, and suggest the potential value of tau-targeted therapy for AD.

Giacobini, E. & Gold, G. *Nat. Rev. Neurol.* **9**, 677–686 (2013); published online 12 November 2013; doi:10.1038/nrneurol.2013.223

Giacobini, E., Gold, G. Alzheimer disease therapy—moving from amyloid-β to tau. *Nat Rev Neurol* **9,** 677–686 (2013). https://doi.org/10.1038/nrneurol.2013.223

Disease modifying therapy has begun

Alzheimer's vaccine shows promise in Phase II trial

Study results show AADvac1, a first-in-man Alzheimer's disease tau vaccine, is safe and potentially of benefit for patients with mild disease.

https://www.europeanpharmaceuticalreview.com/news/156676/alzheimers-vaccine-shows-promise-in-phase-ii-trial/

New Vaccine Formulation Shows Promise for Alzheimer's Target

Published: Feb 11, 2021 | By Mark Terry

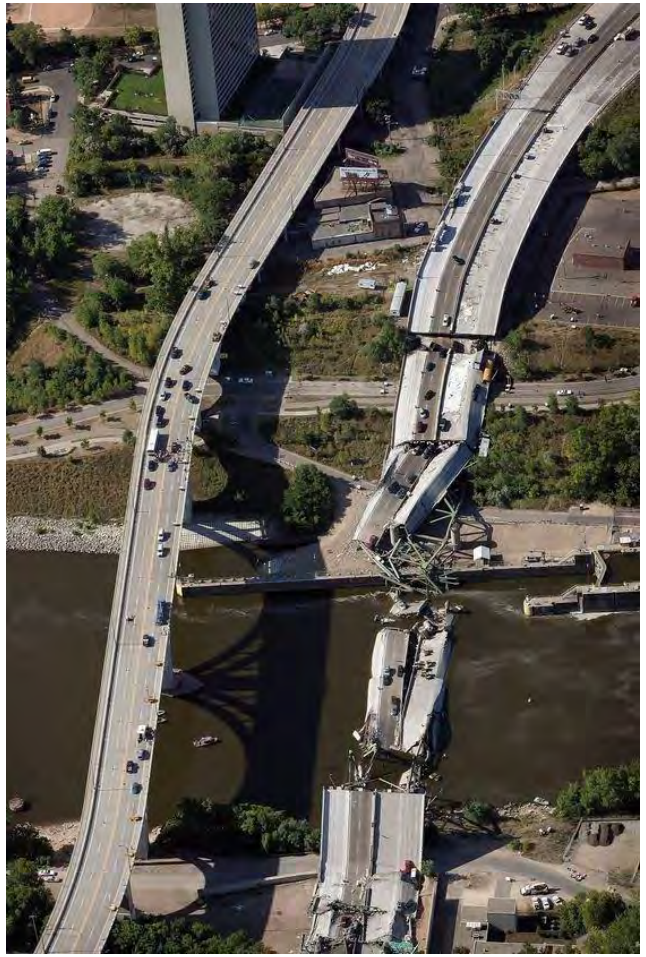
AC Immune CEO Andrea Pfeifer pictured above. Photo courtesy of AC Immune.

Switzerland-based **AC Immune SA announced** positive interim results from its ongoing Phase Ib/IIa clinical trial of ACI-35.030 for Alzheimer's disease. The vaccine showed a potent antigen-specific antibody response against phosphorylated tau (pTau) in 100% of older patients with early Alzheimer's.

https://www.biospace.com/article/ac-immune-s-alzheimer-s-vaccine-shows-promise-in-early-stage-trial/

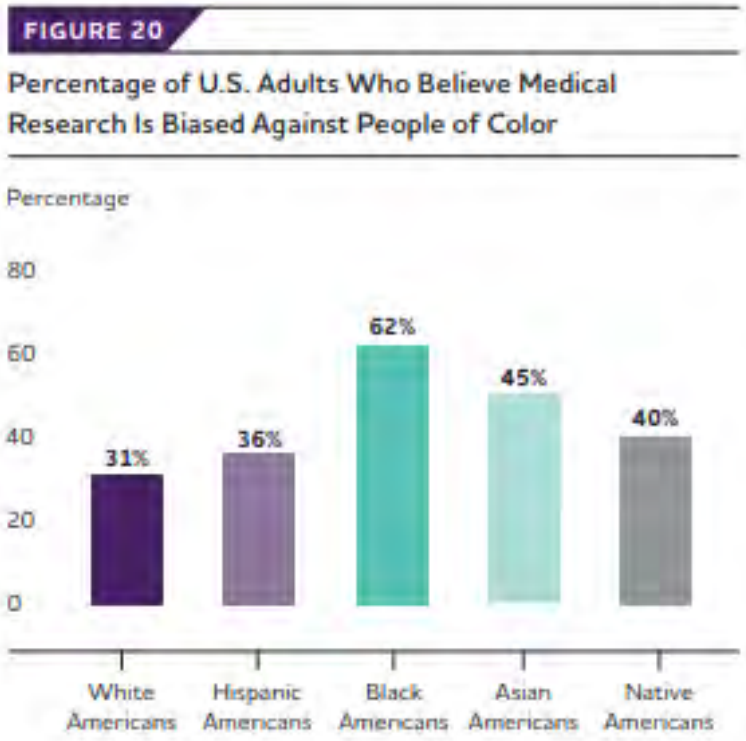
Evaluate earlier, include biomarkers

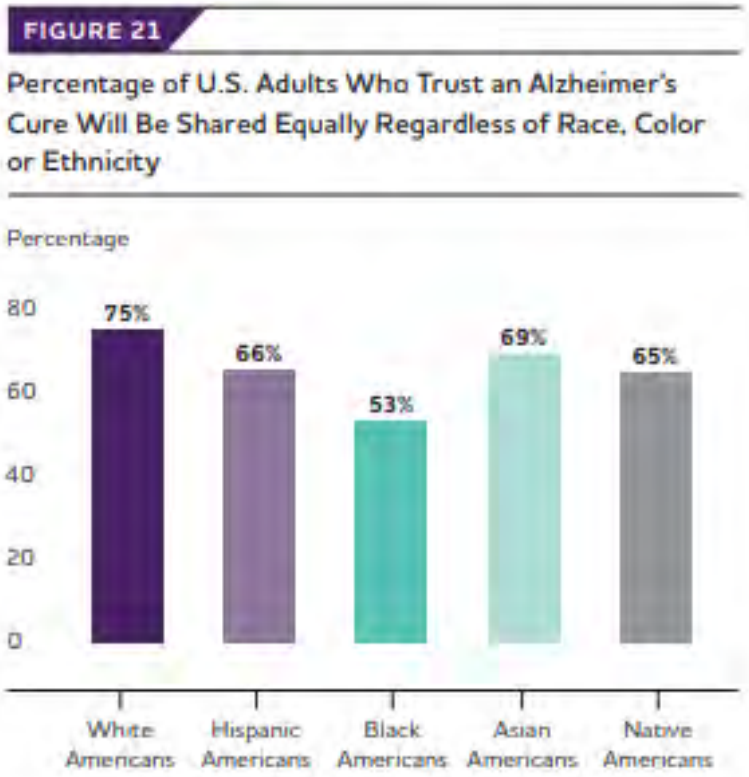
Evaluate earlier, include biomarkers



https://www.nytimes.com/2007/08/03/us/03safety.html

Ethical, medicolegal challenges





Alzheimer's Associations 2021 Alzheimer disease facts and figures. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf

Ethical, medicolegal challenges

Underdiagnosis of Dementia: an Observational Study of Patterns in Diagnosis and Awareness in US Older Adults

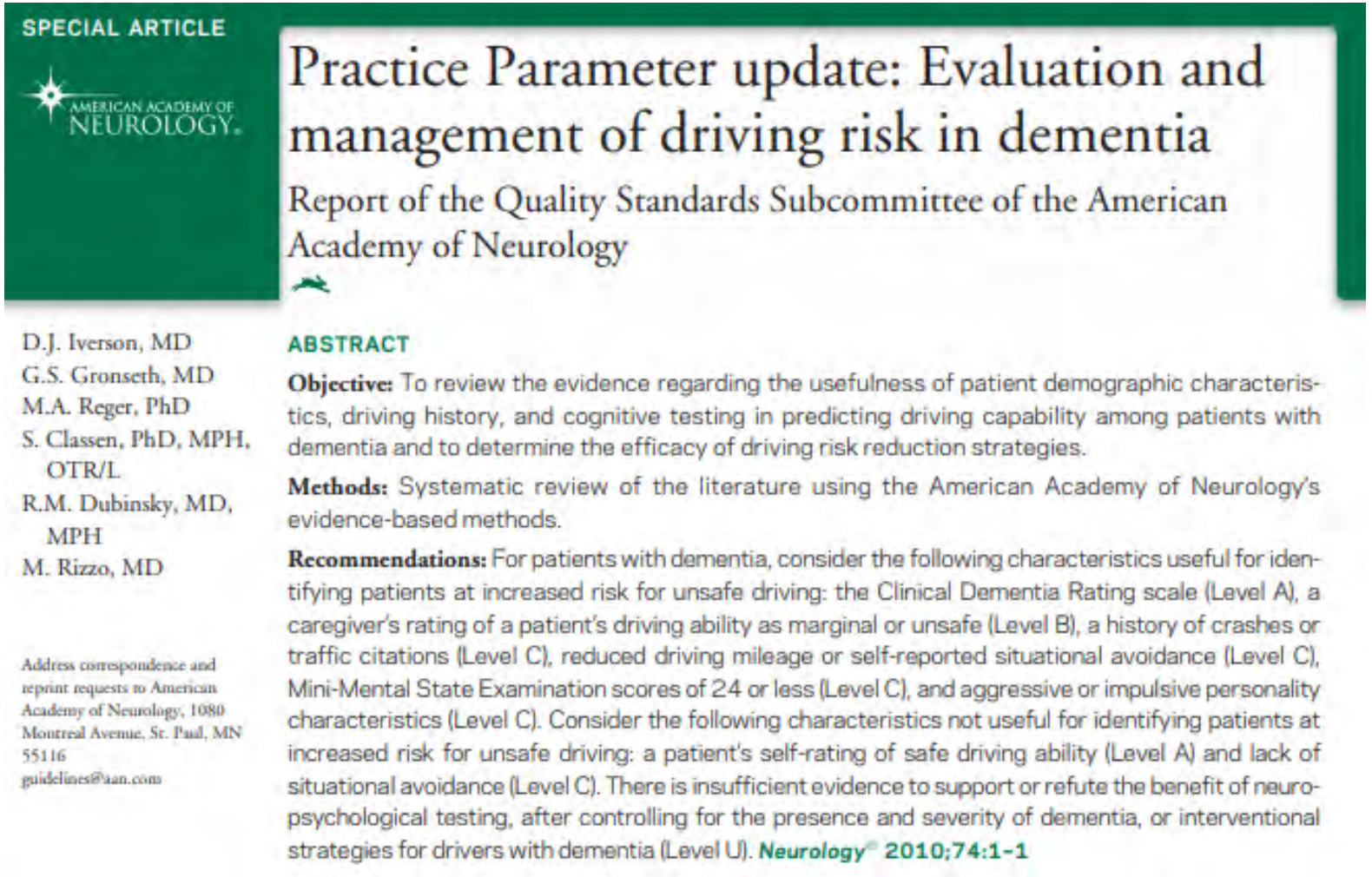
Halima Amjad, MD, MPH[1,2], David L. Roth, PhD[1,2], Orla C. Sheehan, MD, PhD[1,2], Constantine G. Lyketsos, MD, MHS[3], Jennifer L. Wolff, PhD[2,4], and Quincy M. Samus, PhD[2,3]

" … The majority of older adults with dementia are either undiagnosed or unaware of the diagnosis …"

"… [people with] dementia who attended medical visits alone were twice as likely to be undiagnosed by their physicians as those who took a companion …"

Amjad, H., Roth, D.L., Sheehan, O.C. *et al.* (2018). *J GEN INTERN MED* **33,** 1131–1138. https://doi.org/10.1007/s11606-018-4377-y

Ethical, medicolegal challenges



SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice Parameter update: Evaluation and management of driving risk in dementia

Report of the Quality Standards Subcommittee of the American Academy of Neurology

D.J. Iverson, MD
G.S. Gronseth, MD
M.A. Reger, PhD
S. Classen, PhD, MPH, OTR/L
R.M. Dubinsky, MD, MPH
M. Rizzo, MD

Address correspondence and reprint requests to American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN 55116
guidelines@aan.com

ABSTRACT

Objective: To review the evidence regarding the usefulness of patient demographic characteristics, driving history, and cognitive testing in predicting driving capability among patients with dementia and to determine the efficacy of driving risk reduction strategies.

Methods: Systematic review of the literature using the American Academy of Neurology's evidence-based methods.

Recommendations: For patients with dementia, consider the following characteristics useful for identifying patients at increased risk for unsafe driving: the Clinical Dementia Rating scale (Level A), a caregiver's rating of a patient's driving ability as marginal or unsafe (Level B), a history of crashes or traffic citations (Level C), reduced driving mileage or self-reported situational avoidance (Level C), Mini-Mental State Examination scores of 24 or less (Level C), and aggressive or impulsive personality characteristics (Level C). Consider the following characteristics not useful for identifying patients at increased risk for unsafe driving: a patient's self-rating of safe driving ability (Level A) and lack of situational avoidance (Level C). There is insufficient evidence to support or refute the benefit of neuropsychological testing, after controlling for the presence and severity of dementia, or interventional strategies for drivers with dementia (Level U). *Neurology*® 2010;74:1–1

School of Medicine
University of Missouri Health

School of Medicine
University of Missouri Health

Some basic ground rules

Clinical states

- Subjective cognitive decline
- Mild cognitive impairment
- Dementia

Diagnoses (etiologies)

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Alzheimer disease basics

Defining neuropathology

- Dead / missing brain cells
- Amyloid plaque
- Neurofibrillary tangles

How Alzheimer disease behaves

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University of Missouri Health

The new world

Evolving understanding of pathologies

Disease modifying therapy has begun

Evaluate *earlier*

***Include* biomarkers**

Ethical, medicolegal challenges

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University of Missouri Health

Controversy and Update on Dementia and Dementia-Causing Disease

Joel Shenker MD PhD

shenkerj@health.missouri.edu