The importance of failure: what trials' misfortune can teach us.

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

FAILURE IS THE GREATEST TEACHER

Alzheimer's Drug Trials Keep Failing—and That's Amazing

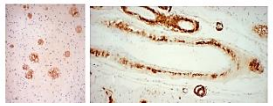
Negative results on groundbreaking experiments are helping scientists figure out how to beat the disease.

Sometimes by losing a battle you find a new way to win the war.

Donald Trump

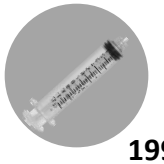
EVOLUTION OF ALZHEIMER'S DISEASE RESEARCH

1906 - 1999



1985
First visualization of Abeta plaques and vessel walls.

Neurofibrillary tangles and component proteins first isolated from AD brain.



1993
AD signature found in CSF: tau increased, Aβ42 decreased.

Immunization with amyloid-beta attenuates AD-like pathology in the **PDAPPmouse -** Nauture

Syndrome of MCI: amnestic, nonamnestic Forms.

1906

Alois Alzheimer describes case of Auguste Deter.

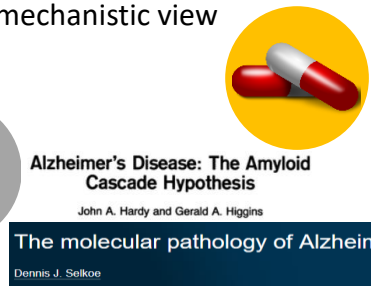
1974

1975 - 1985

1976 Cholinergic hypothesis of Alzheimer's disease.

1985 - 1995

1990
Amyloid hypothesis marks conceptual shift from descriptive to mechanistic view



1995

Tacrine is the first drug approved.

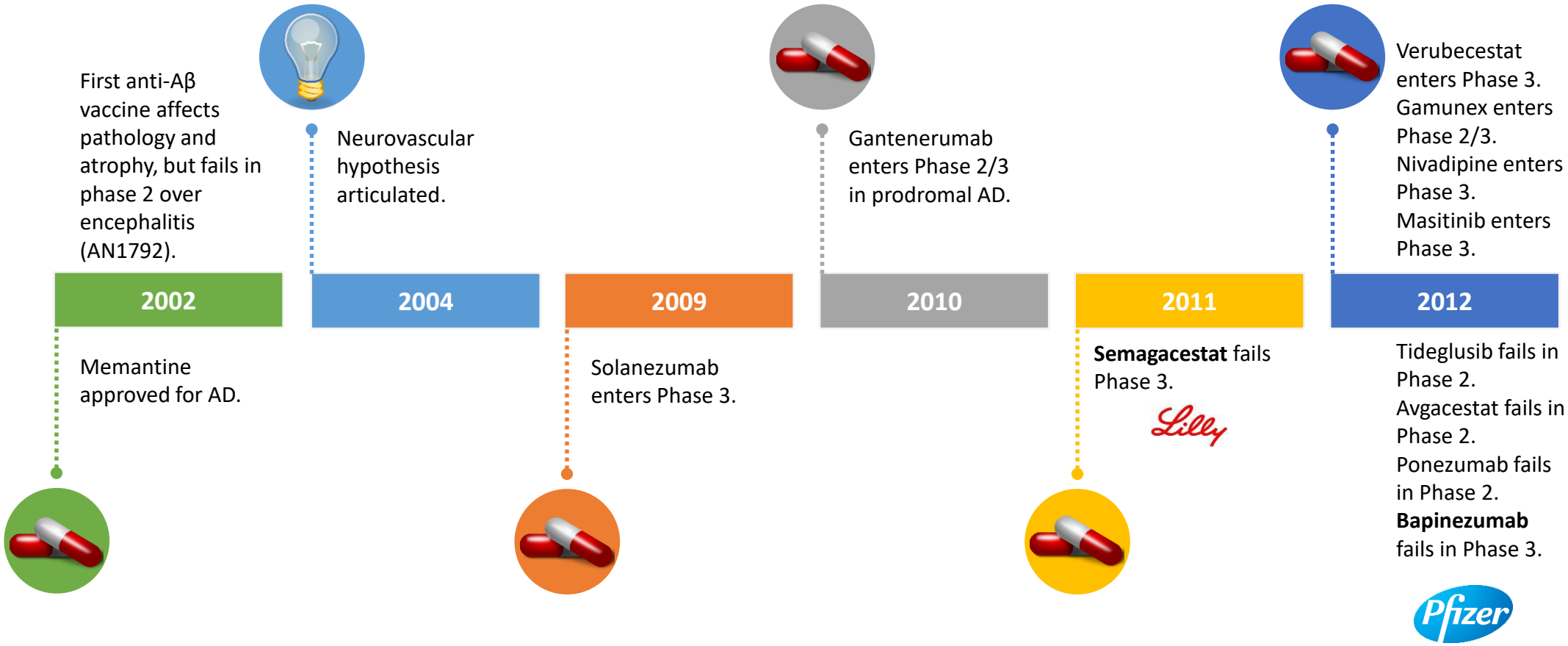
1996 Donepezil
1997 Rivastigmine

1999

Plaque, tangle pathology begin more than decade before symptoms. Represent 'preclinical' AD.

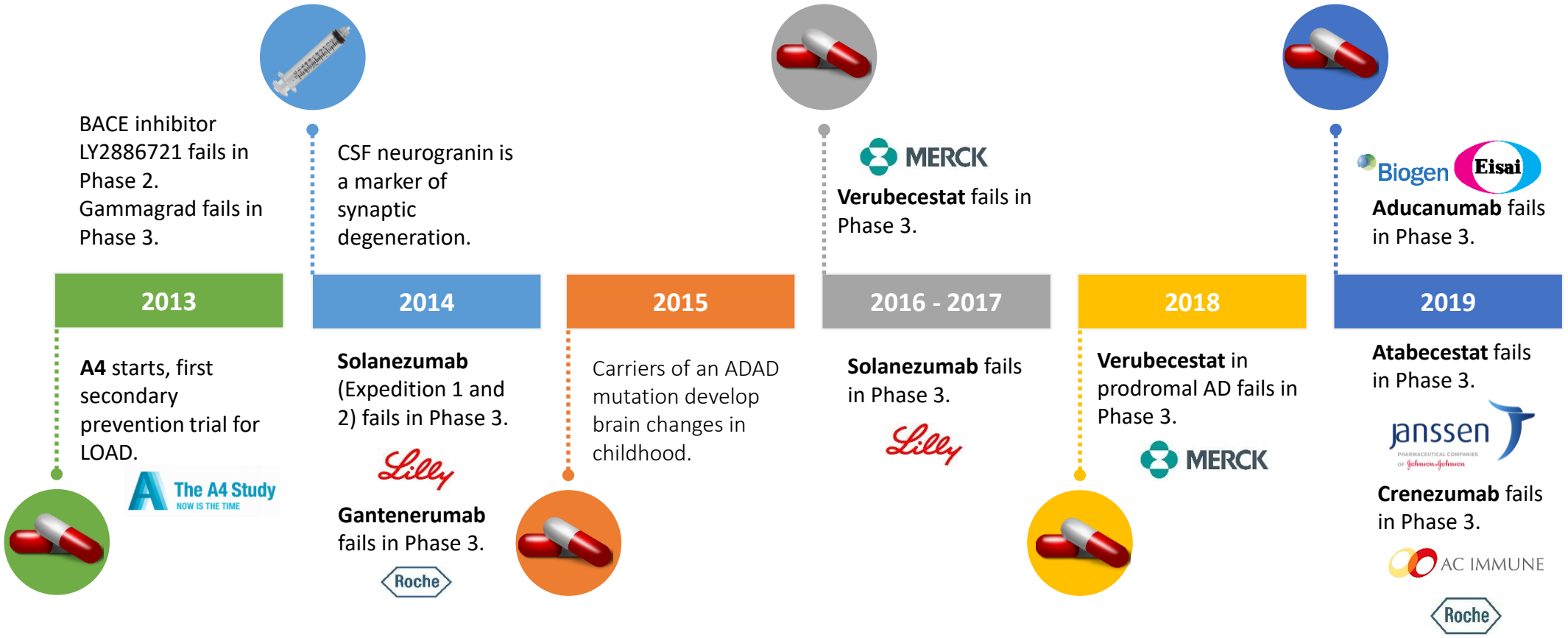
EVOLUTION OF ALZHEIMER'S DISEASE RESEARCH

2002 - 2012



EVOLUTION OF ALZHEIMER'S DISEASE RESEARCH

2013 - 2019



ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 195-214

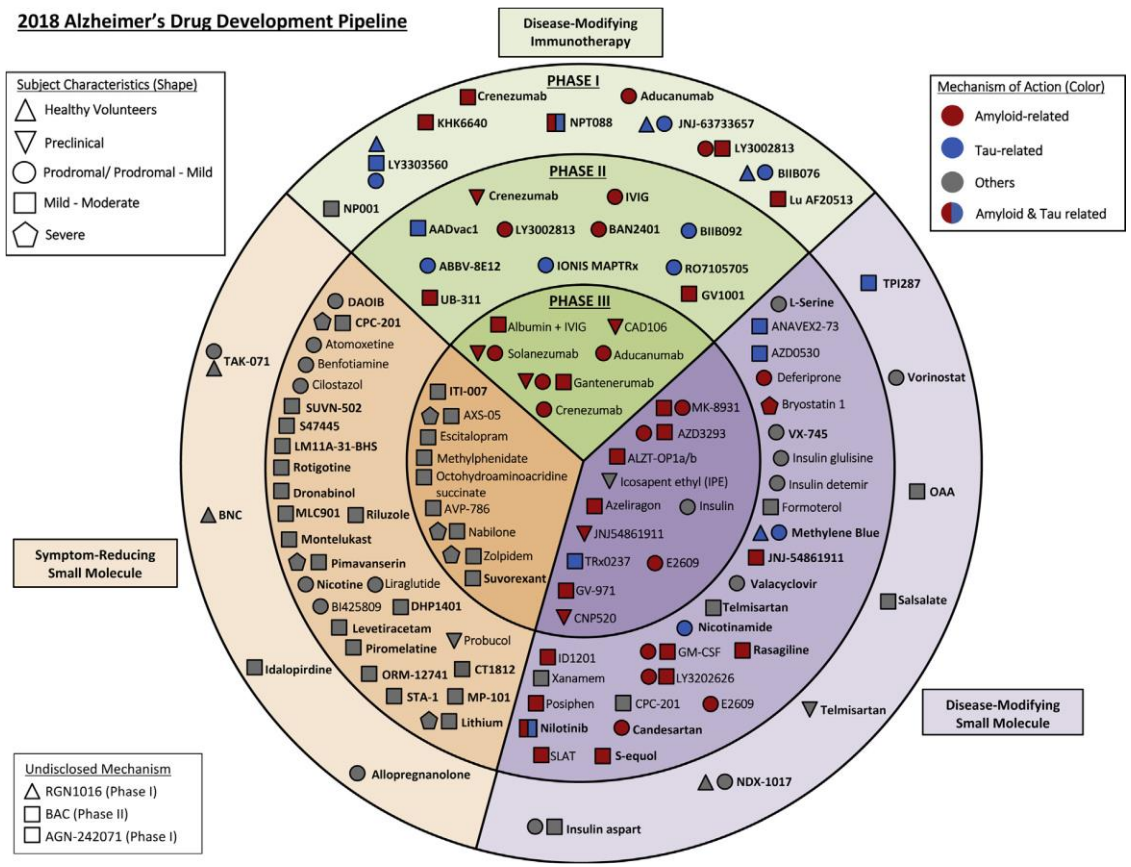
Alzheimer's & Dementia

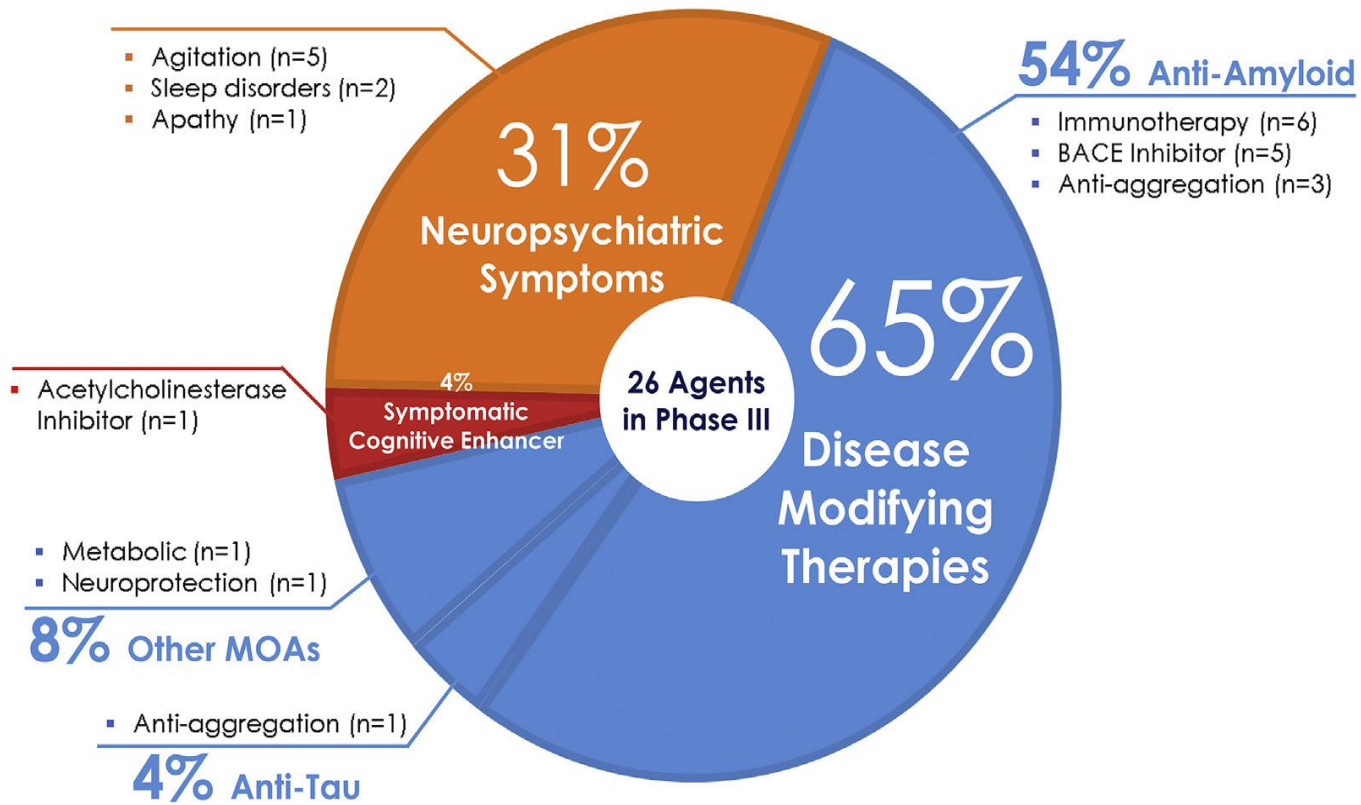
Featured Article

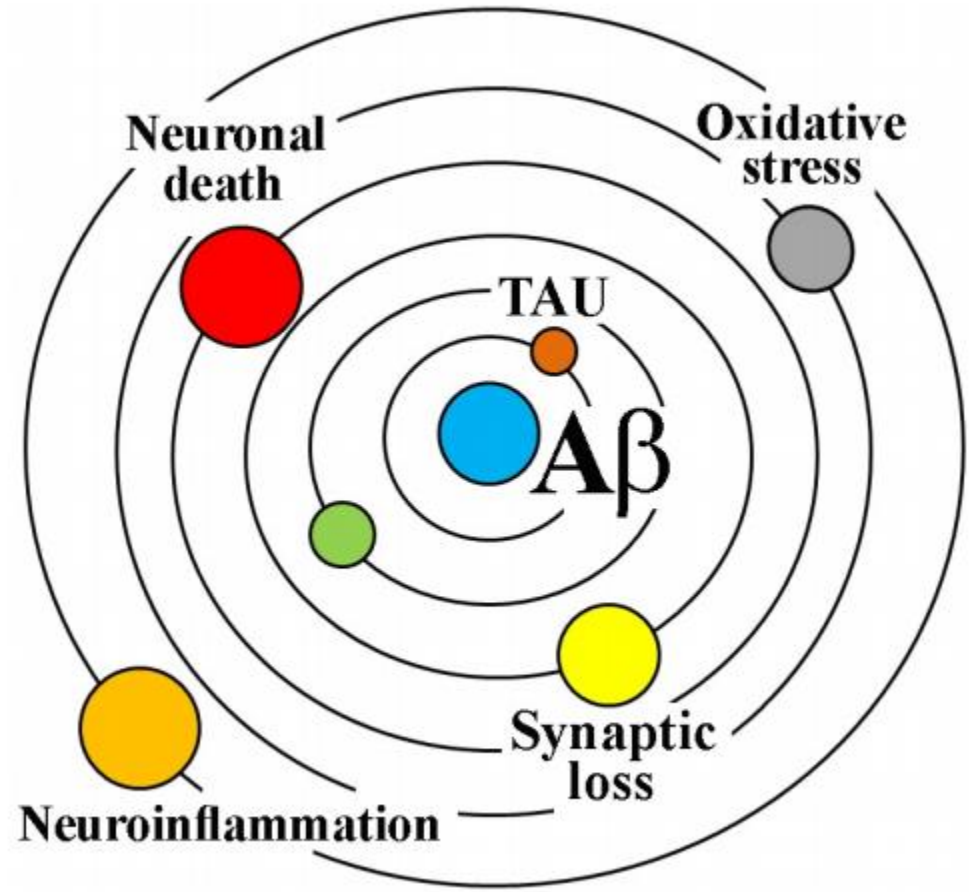
Alzheimer's disease drug development pipeline: 2018

Jeffrey Cummings[a,*], Garam Lee[a], Aaron Ritter[a], Kate Zhong[b]

[a]*Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA*
[b]*Global Alzheimer Platform, Washington, DC, USA*



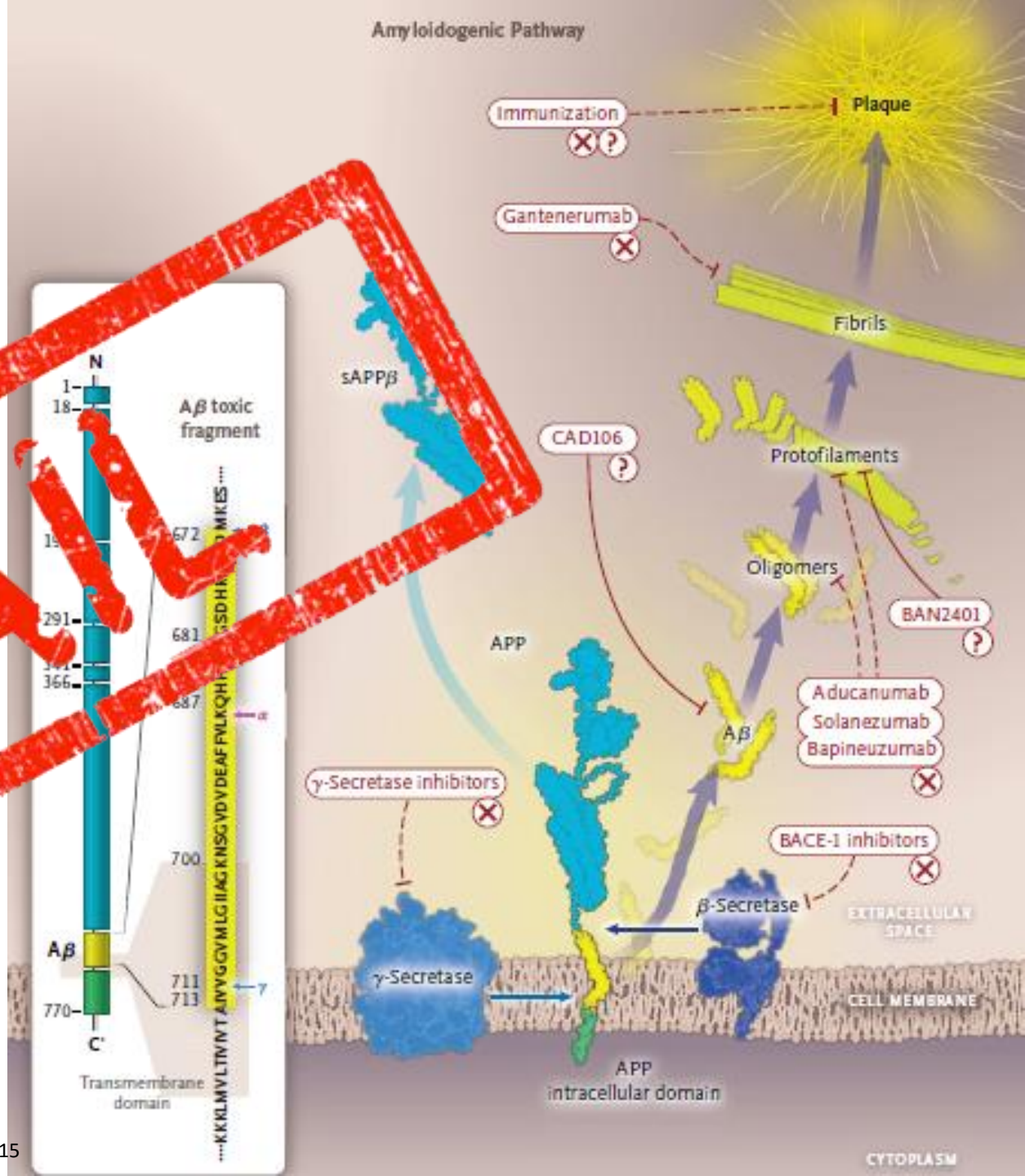



Neuronal death
Oxidative stress
TAU
Aβ
Synaptic loss
Neuroinflammation

Failed *Aßcentric* drugs

1. Active vaccines (AN 1792)
2. γ-secretase inhibitors (Semagace[illegible]at…)
3. Anti Aß monoclonal antibo[illegible]es (Solanezumab, Bapine[illegible]nab, Gantenerumab, C[illegible]ezuma[illegible] Aducanumab…
4. ß-site amyloid pr[illegible]cursor protei[illegible] cleaving enzyme ([illegible]ACE) inhibitors (verubecestat, atab[illegible]cestat…)
5. Nutraceuticals (tramiprosato/homotaurina)

FAIL



David S. Knopman, Lowering of Amyloid-Beta by ß-Secretase Inhibitors – some informative failures, N Engl J Med, 380; 15

Are the therapeutic targets correct?

Published online: March 29, 2016

Review

The amyloid hypothesis of Alzheimer's dise… 25 years

Dennis J Selkoe[1,†] & John Hardy[2,*,†]

EMBO Molecular Medici…

Morris… *…unications* 2014, **2**:135
http:/… …nt/2/1/135

ACTA NEUROPATHOLOGICA COMMUNICATIONS

Open Access

…nd Controversies Surrounding …ypothesis of Alzheimer's Disease

…[2], la… and Bryce Vissel[1,2*]

926 *Current Neuropharmacolog… 15*, 926-935

REVIEW ARTICLE

The Amyloid Cascade Hypothesis … er's … Change Our Mind

Roberta Ricciarelli[1,*] and Ernesto Fedele[2,3,*]

…ENCE'S COMPASS • REVIEW

…EW: MEDICINE

The Am… …ypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics

John Hardy[1] and Dennis J. Selkoe[2]*

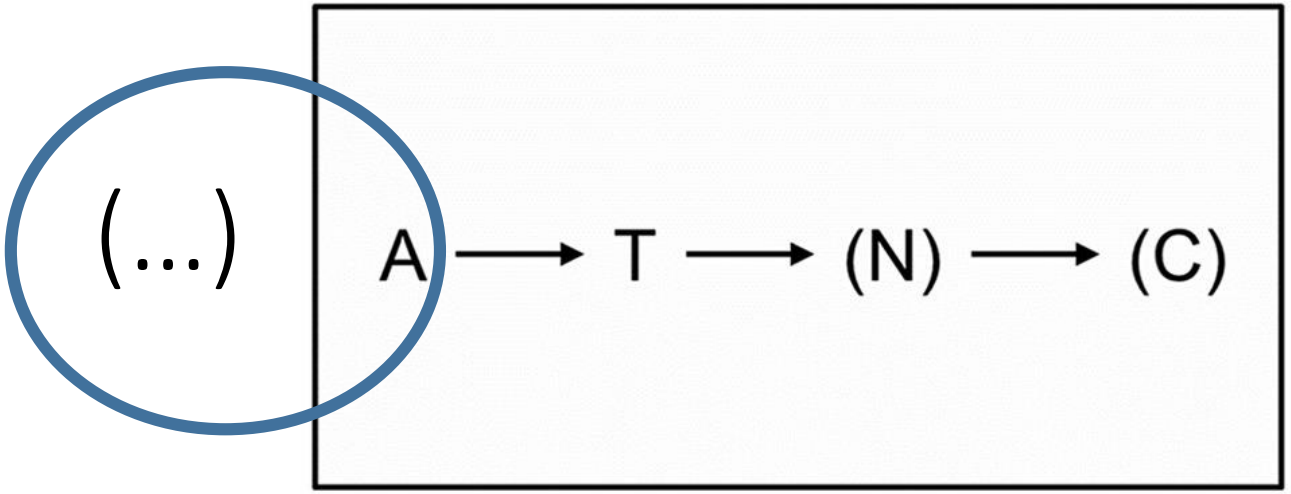
The amyloid cascade hypothesis

The failure of semagacestat will inevitably be interpreted as additional evidence against the amyloid hypothesis. Such a conclusion would be premature; none of the failed drugs or trials represents an adequate pharmacological test of the amyloid hypothesis (Table 1). The amyloid hypothesis would be challenged by a trial in which an agent is shown to adequately engage the target and decrease amyloid to prespecified meaningful levels without impacting clinical function. These criteria have not been met in any of the reported trials. No information is available on whether biomarker observations were made in the semagacestat trial that may impact this discussion.

«Supporting the central role of Aß in AD is not equivalent to establishing Aß as the first cause of AD».

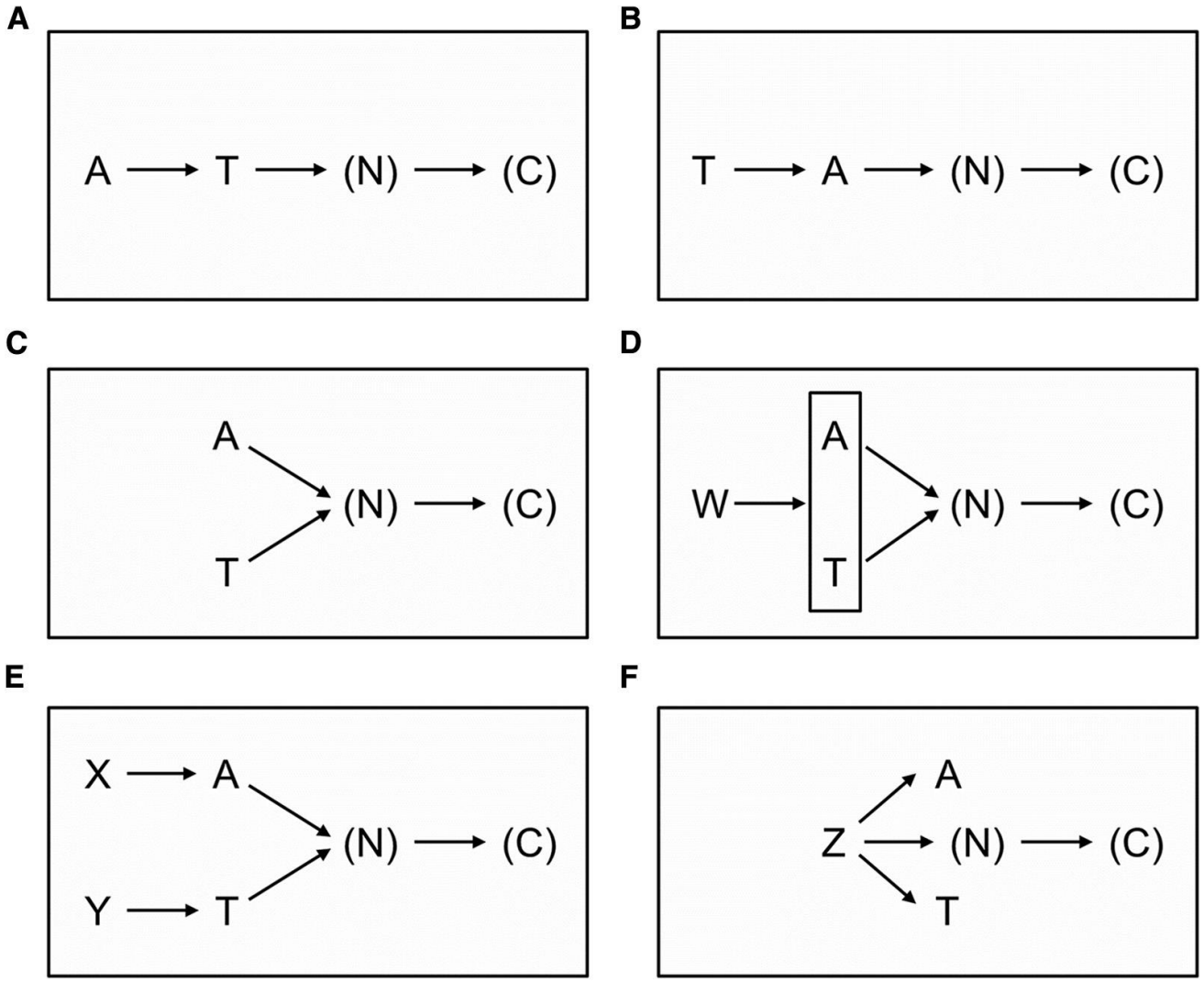
Cummings J. What can be inferred from the interruption of the Semagestat trial for treatment of Alzheimer's Disease?, BIOL PSYCHIATRY 2010; 68:876-878

Modified amyloid cascade hypothesis



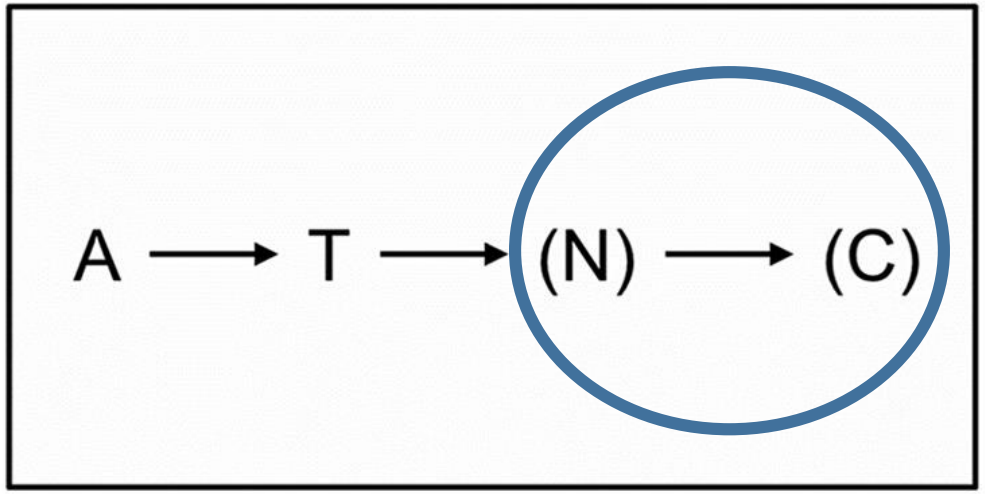
Jack CR et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dementia 2018 Apr;14(4):535-562

Modified amyloid cascade hypothesis



Modified amyloid cascade hypothesis

(...)



Which diagnostic criteria have to be used?

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

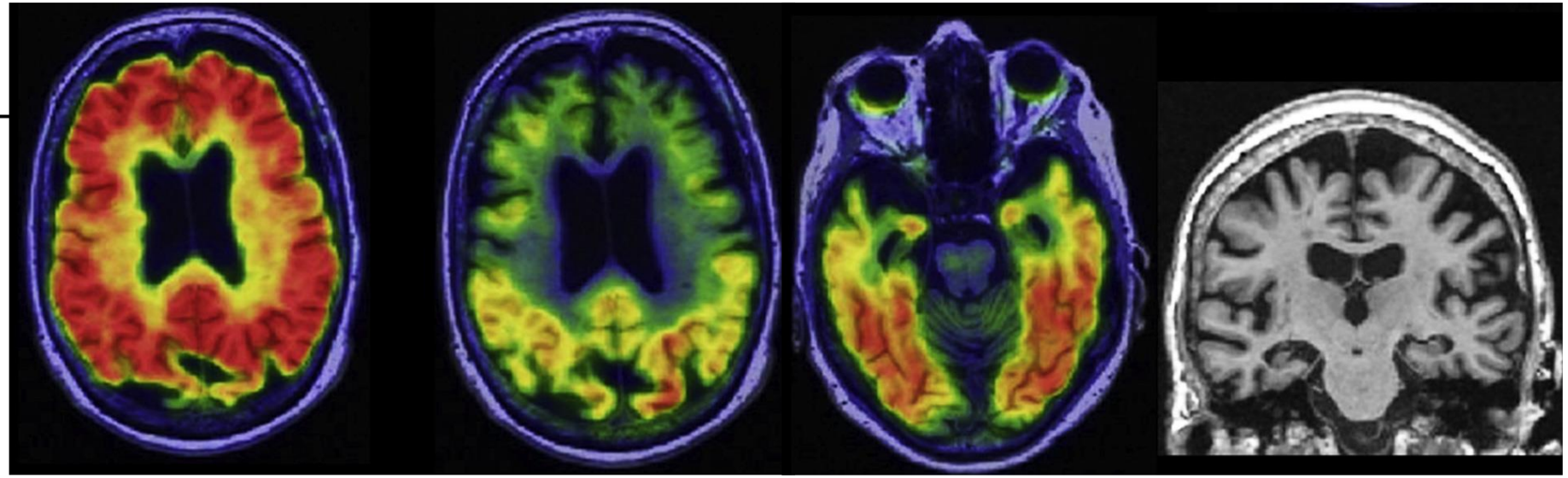
Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]**:** Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

AD as a purely a biological construct.

Table 1
AT(N) biomarker grouping

A: Aggregated Aβ or associated pathologic state
CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
Amyloid PET
T: Aggregated tau (neurofibrillary tangles) or associated pathologic state
CSF phosphorylated tau
Tau PET
(N): Neurodegeneration or neuronal injury
Anatomic MRI
FDG PET
CSF total tau



A+T+N+ (S+)

Is it too LATE?

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

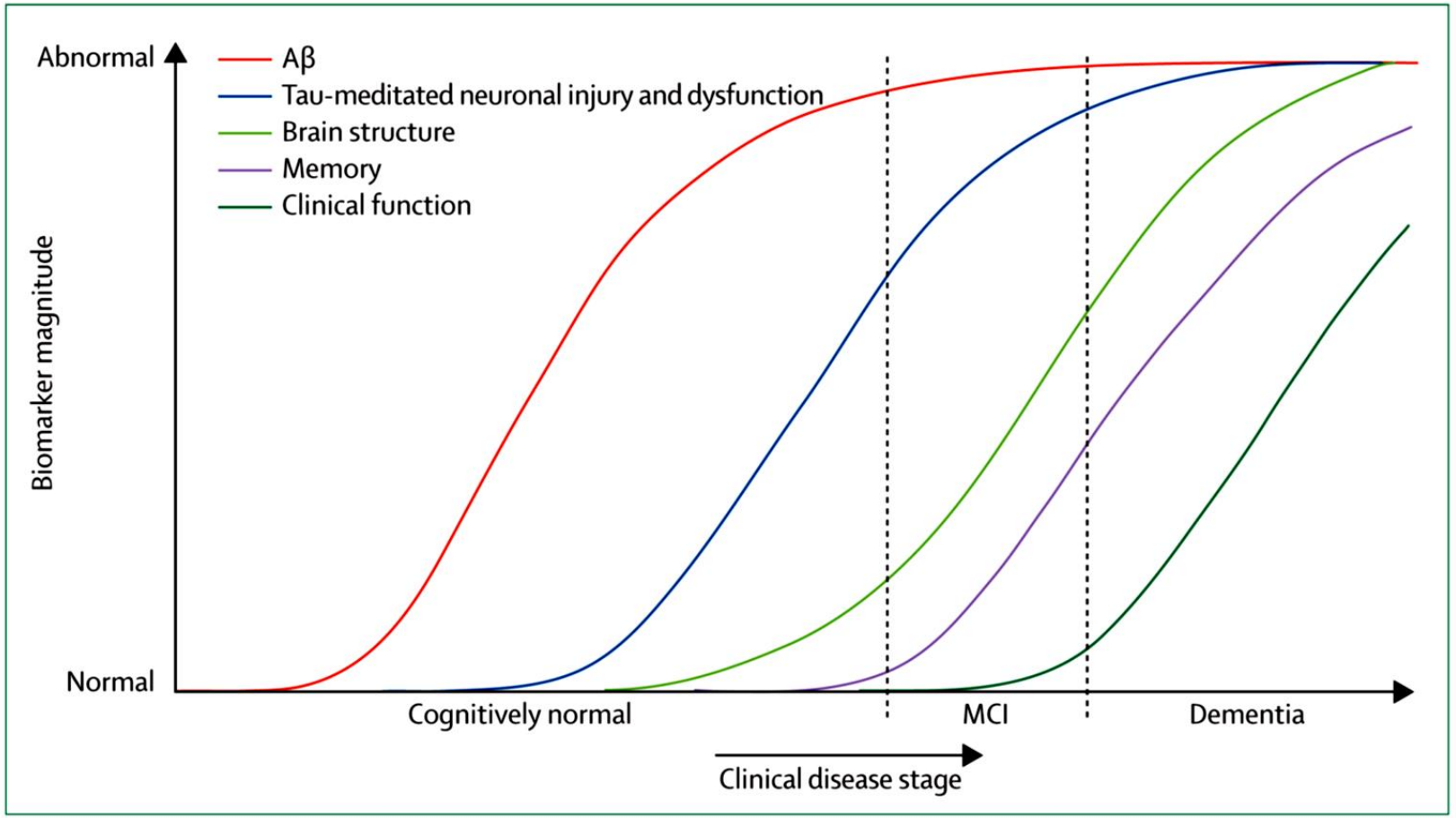
Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson,[1] Dennis W. Dickson,[2] John Q. Trojanowski,[3] Clifford R. Jack Jr.,[4]

«…LATE-NC, when coexisting with ADNC, will have the potential to **obscure the effects of a potential disease modifying agent** on cognitive assessment results in living subjects…»

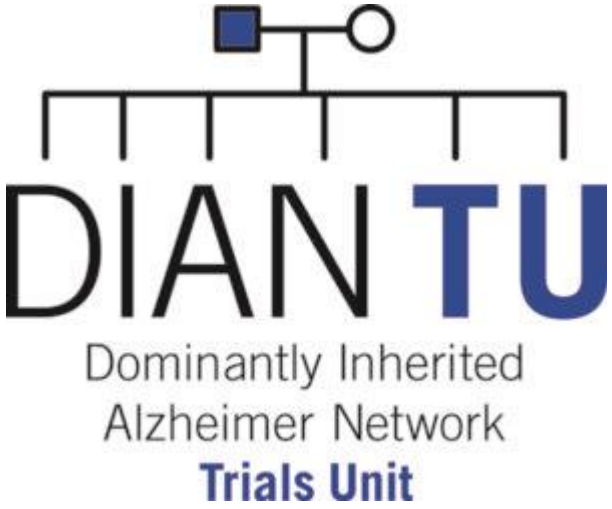
How early is early enough?

CSF Aβ42

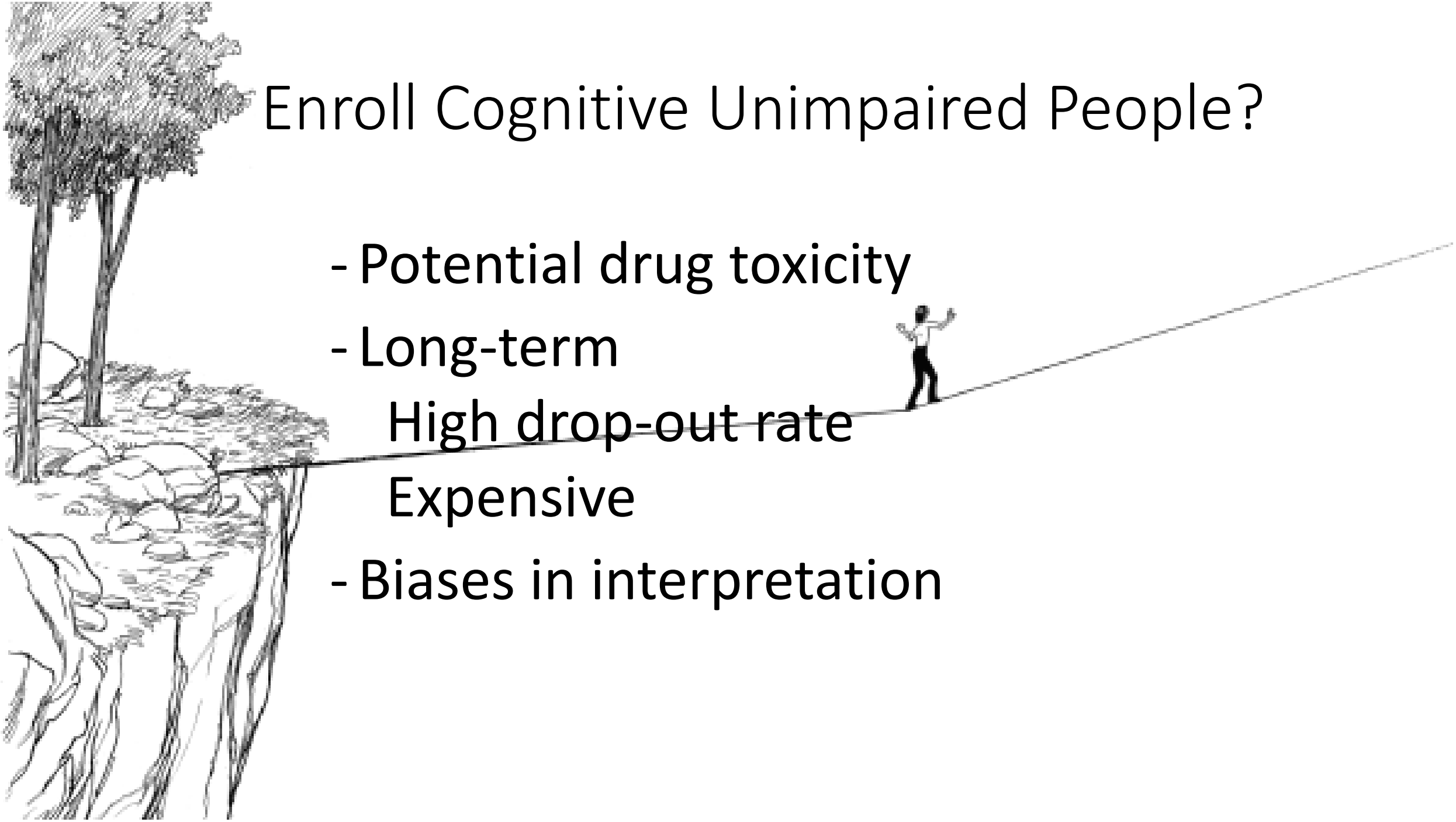


Jack CR Jr et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010 Jan;9(1):119-28.

Enroll Cognitive Unimpaired People?



Enroll Cognitive Unimpaired People?



- Potential drug toxicity
- Long-term
  - High drop-out rate
  - Expensive
- Biases in interpretation

How much?

Too much?

The NEW ENGLAND JOURNAL of MEDICINE

Lowering of Amyloid-Beta by β-Secretase Inhibitors — Some Informative Failures

David S. Knopman, M.D.

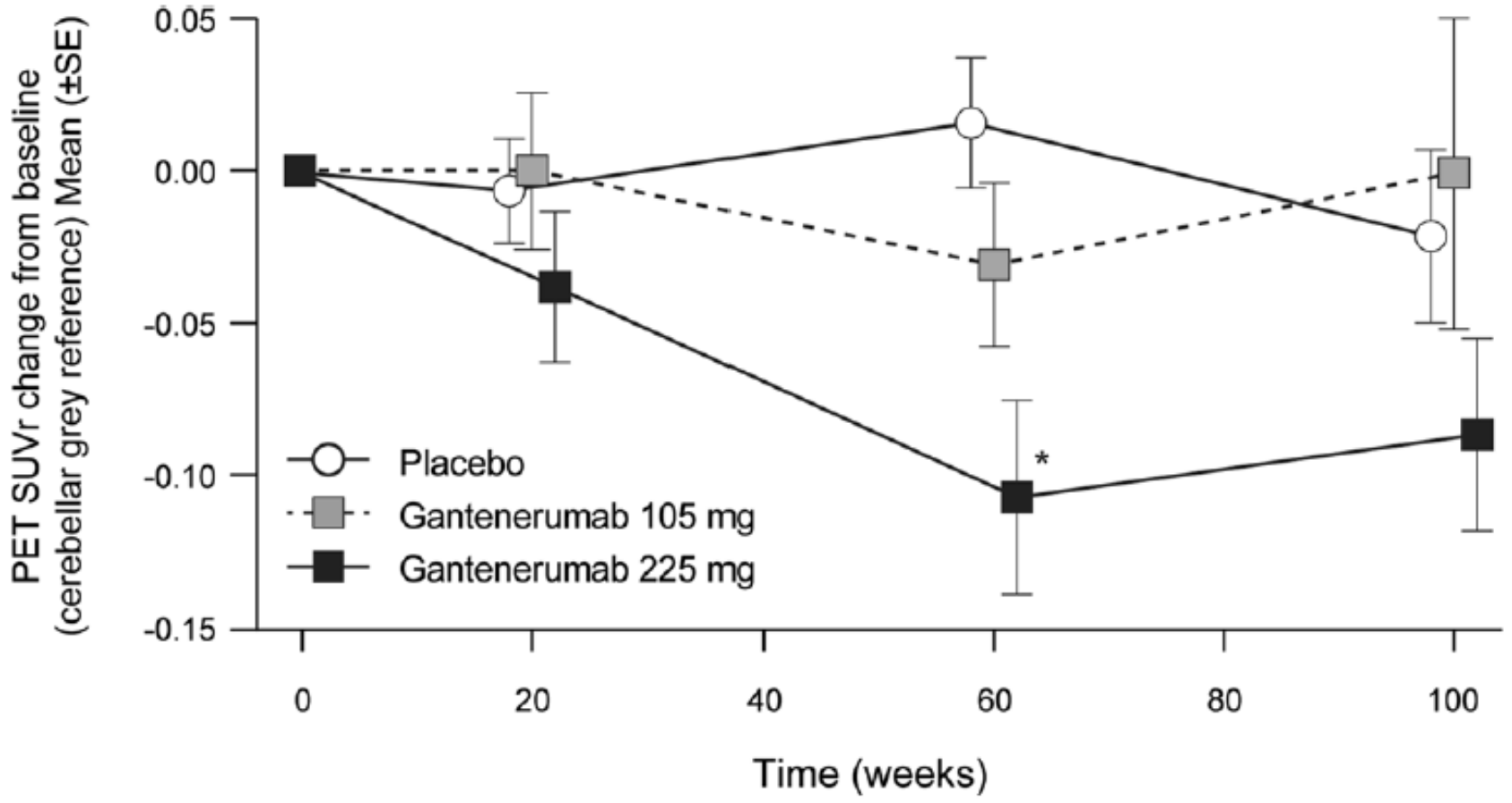
Verubecestat

«…perhaps only a **modest degree of BACE-1 inihibition** is necessary to mitigate the toxic effects of Aβ production….»

«…Adjustement in the dose to a narrow window of BACE-1 inihibition would be difficult to accomplish in a clinical trial until there are **peripheral biomarkers that reflect** the activity of the agent in the brain….»

Not enough?

Gantenerumab



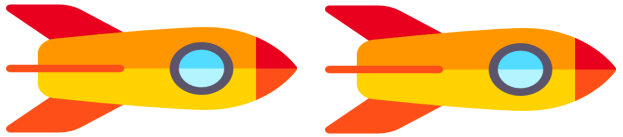
Susanne Ostrowitzki et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimer's Research & Therapy 20179:95

Bapinezumab – 301 and 302

«… **doses** of bapinezumab used in these studies **were limited** because of higher rates of amyloid-related imaging abnormalities with effusion or edema (ARIA-E) at higher doses…»

«… a decrease rate of accumulation of amyloid on PIB-PET was seen in APO-ε4 carriers who received bapinezumab, but the difference was smaller than that seen in **phase 2 studies, which included the 2.0-mg**-per-kilogram dose…»

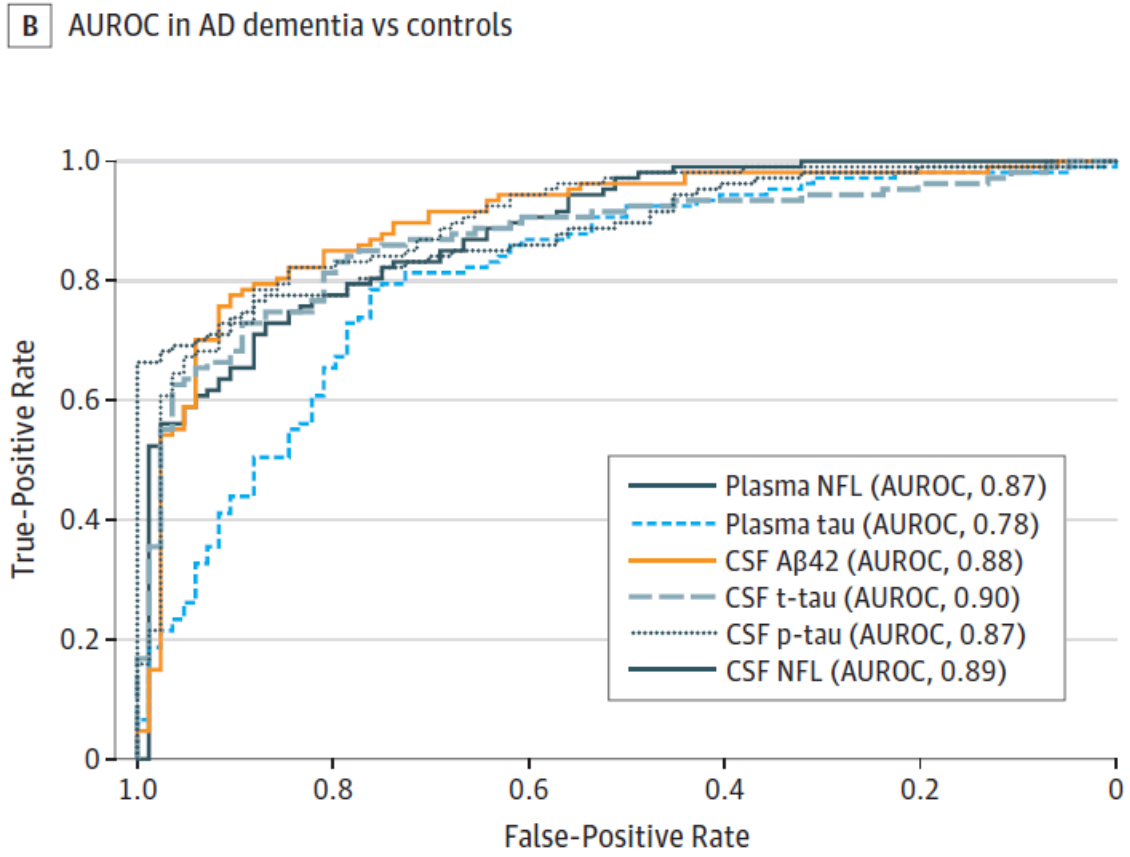
Future Directions



Future directions

1. New ultrasensitive immunoassay techniques:
   plasma neurofilament light protein, plasma tau, plasma amyloid-β measures, **TDP-43 biomarkers**…
2. Tau treatments
3. Gene therapy
4. Deep brain stimulation
5. Adaptive trials (es. BAN2401, CNP520)

1. New ultrasensitive immunoassay techniques



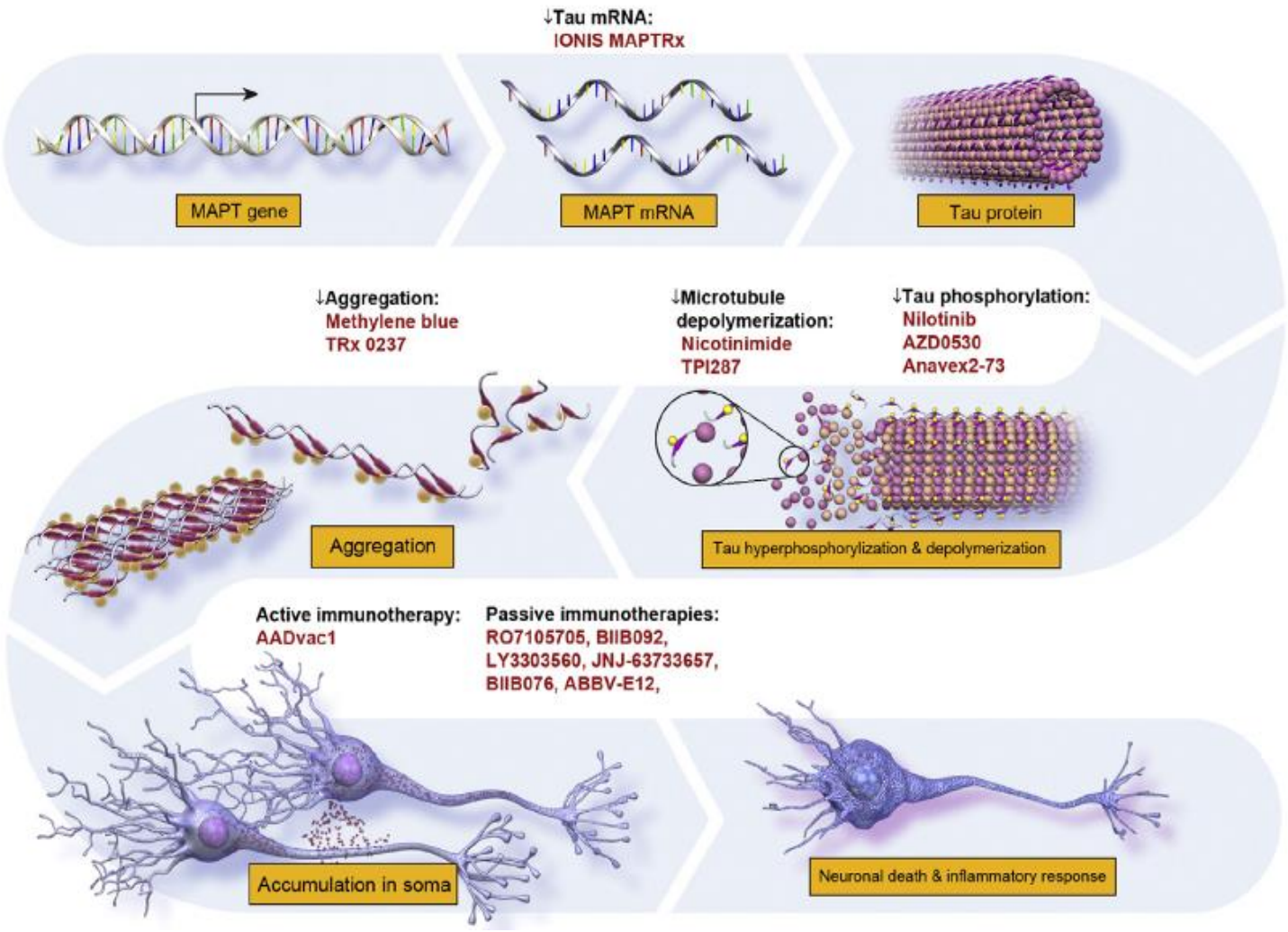
Not specific.

N Mattsson et al. Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease. JAMA Neurol. 2017 May; 74(5): 557–566.

2. Tau treatments

«… neurofibrillary tangles burden more **closely correlate with cognitive decline** than amyloid plaque load…»

1. Which tau epitope?
2. What site of activity?
3. What level of target engagement?



H. Braak E. Braak, Evolution of the neuropathology of Alzheimer's disease, Acta Neurol Scand Suppl 1996; 165:3-12

3. Gene therapy

Original Investigation

July 2018

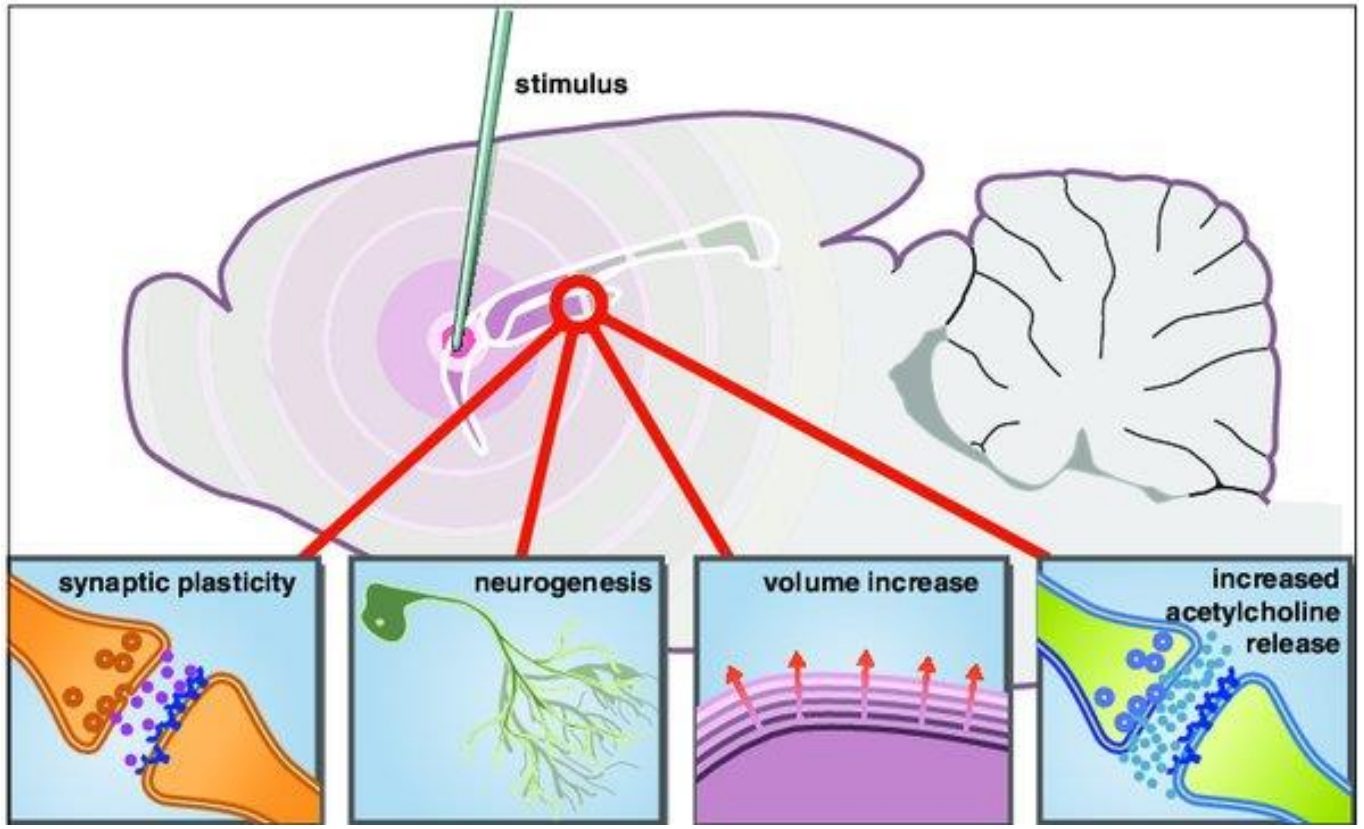
Adeno-Associated Viral Vector (Serotype 2)–Nerve Growth Factor for Patients With Alzheimer Disease

A Randomized Clinical Trial

Michael S. Rafii, MD, PhD[1,2]; Mark H. Tuszynski, MD, PhD[2]; Ronald G. Thomas, PhD[2]; et al

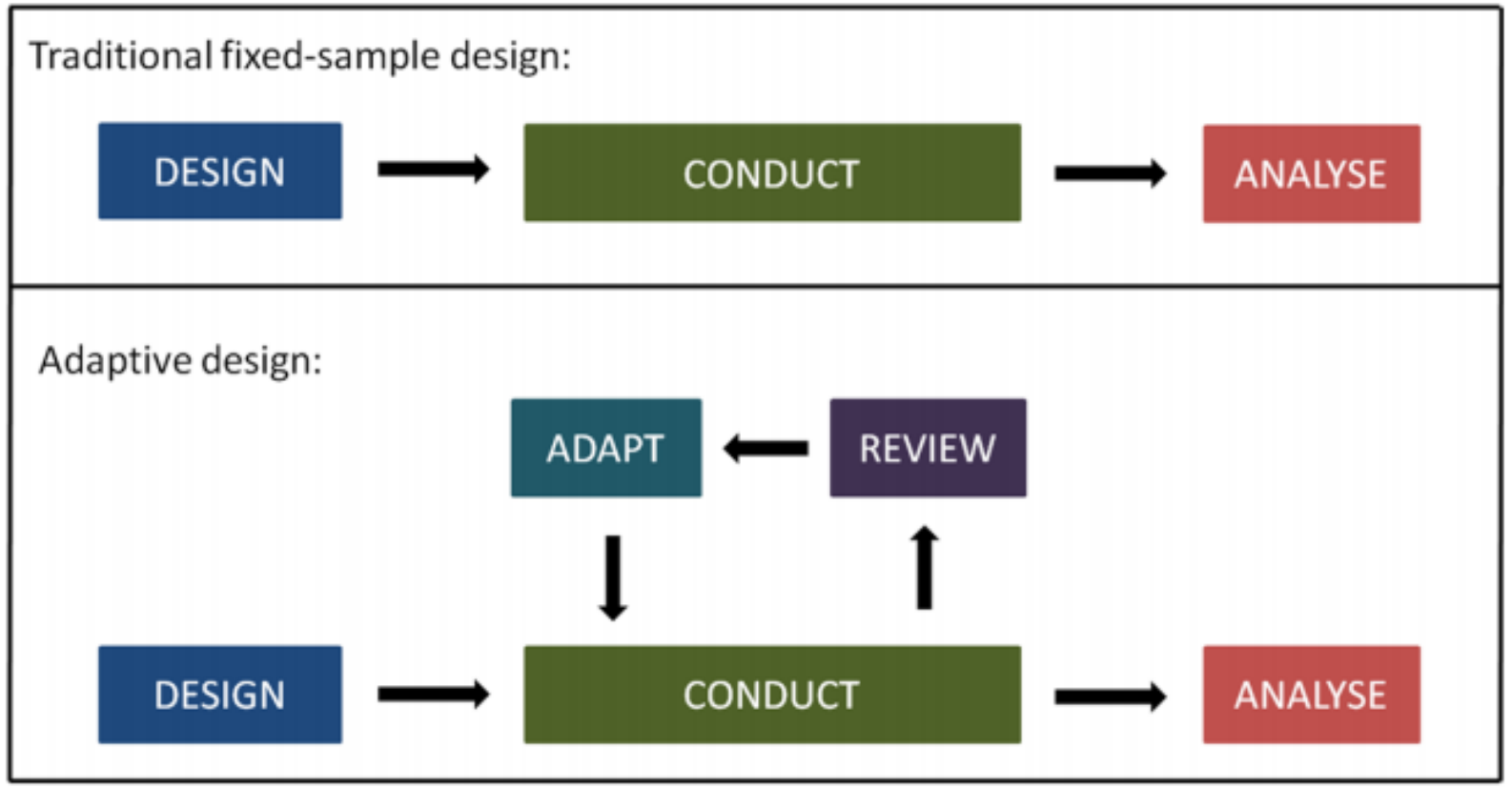
«this trial demonstrated the **feasibility of sham-surgery**, (…) but did **not affect clinical outcomes** or selected AD biomarkers…»

4. Deep brain stimulation



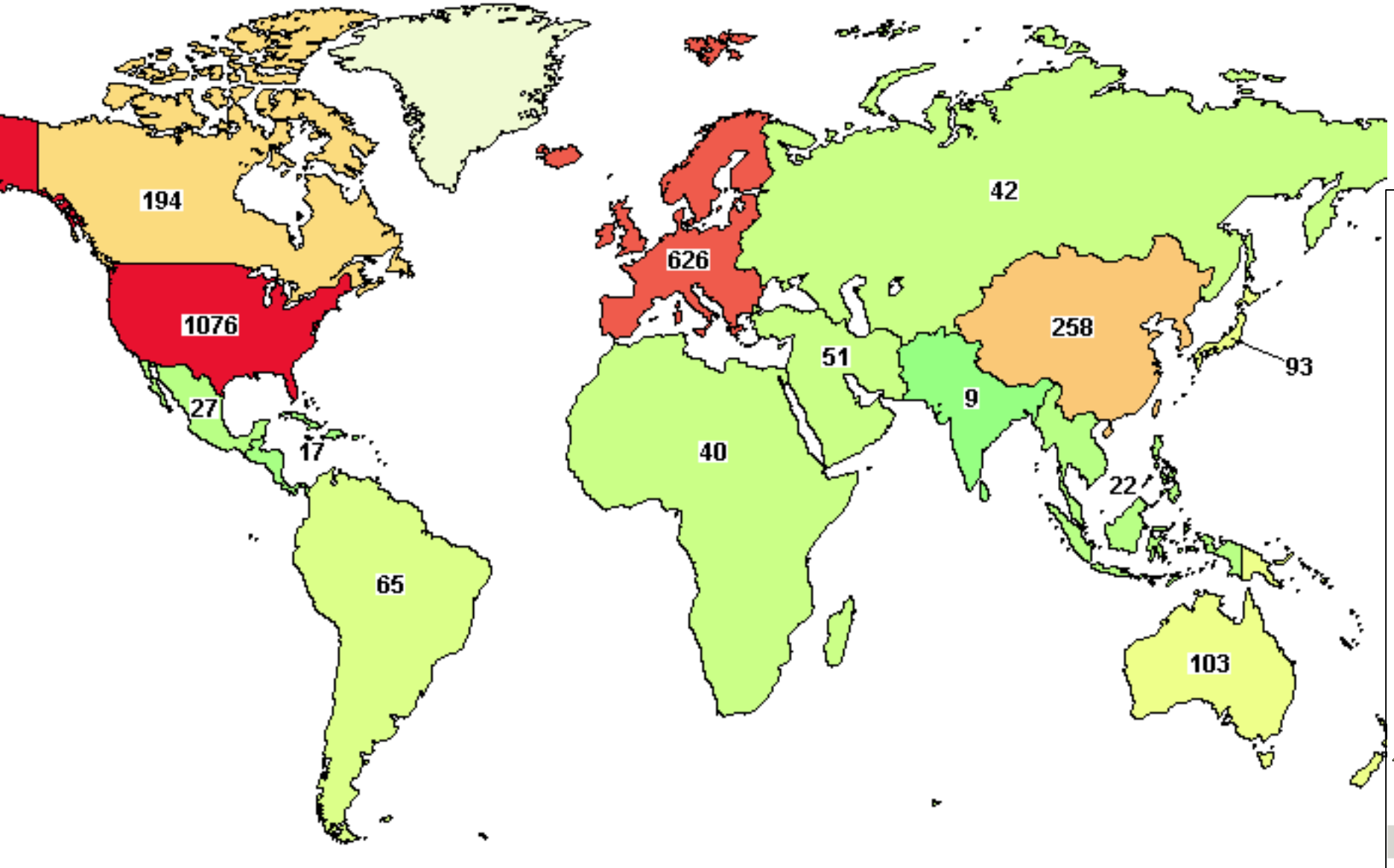
Majed Aldehr, Deep brain stimulation for Alzheimer's Disease: An update, Surg Neurol Int. 2018; 9: 58.

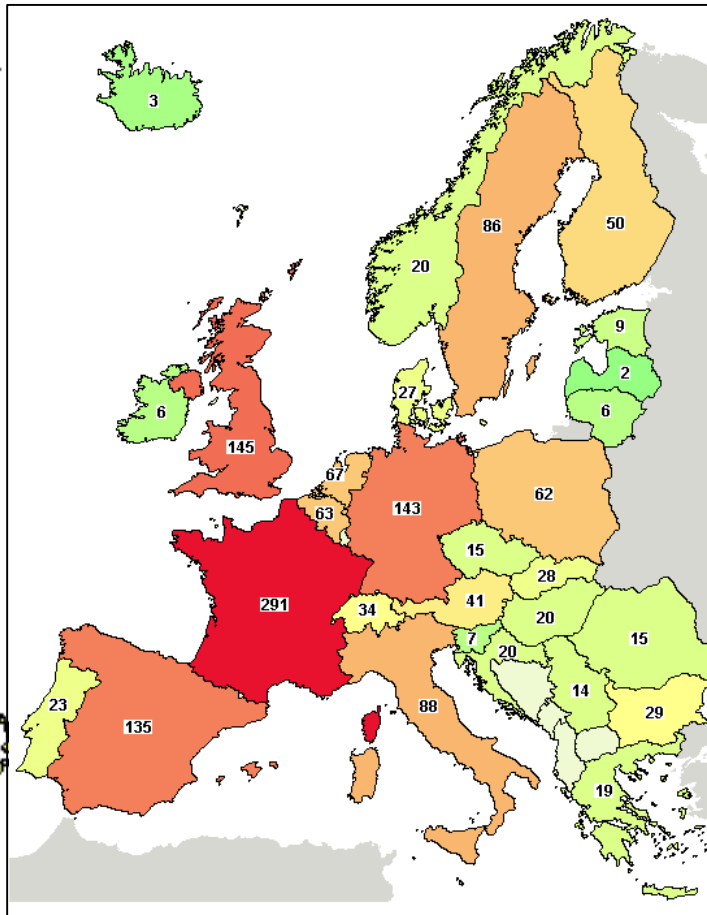
5. Adaptive trials



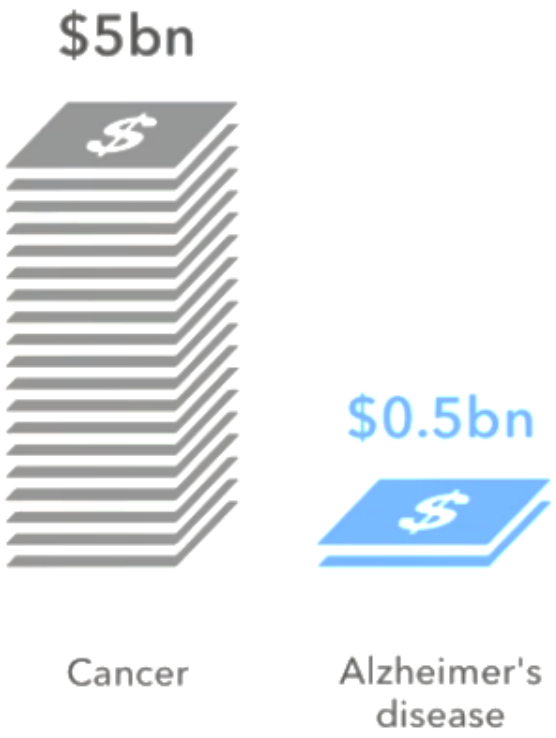
Pallmann et al. Adaptive designs in clinical trials: why use them, and how to run and report them, BMC Med. 2018; 16: 29.

Clinicaltrials.gov





Research funding
per year

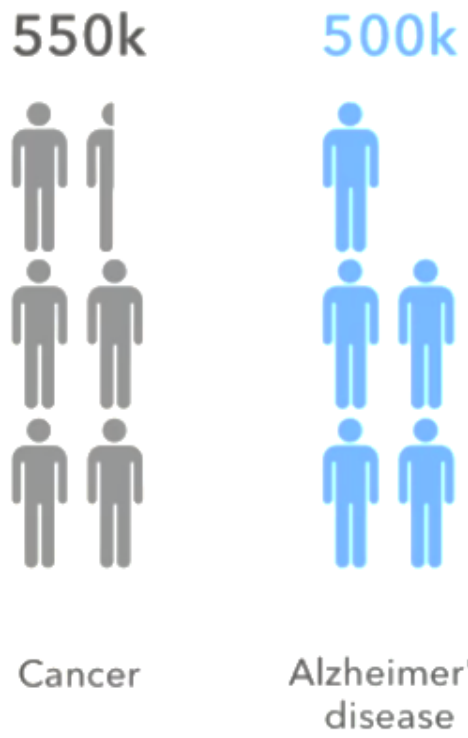


Source: US National Institute of Health

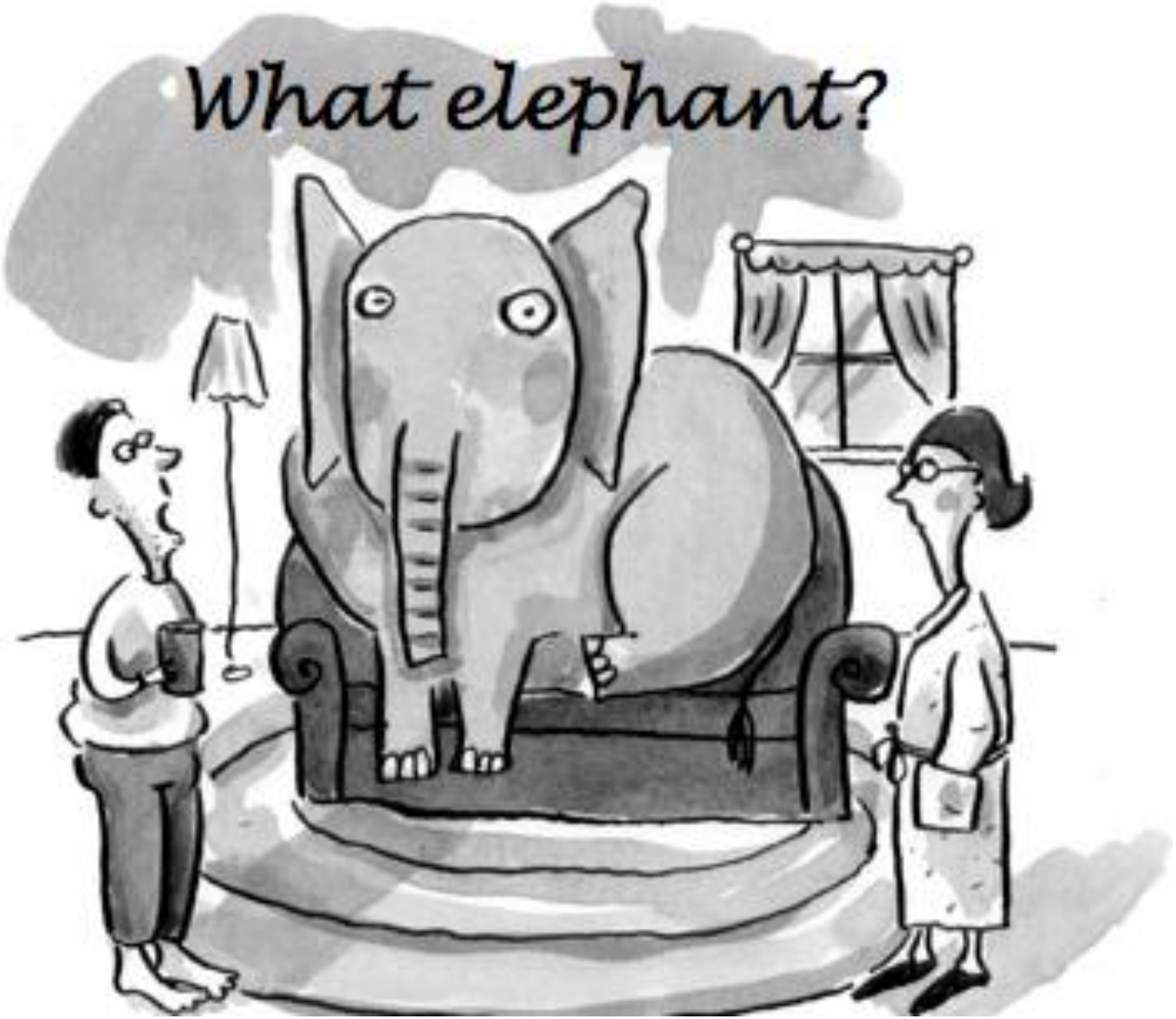
Cost of care
per year

Source: Alzheimer Association, American cancer Society

Deaths caused
per year



Source: US American Academy of Neurology (James et al., 2014), US Centers of Disease Control and Prevention



Everyone with a brain is at risk


GRAZIE

Aducanumab

«… **first time** that a lowering effect on Abeta brain load was coupled with a positive effect on cognition with dose-dependent trends…»

«… the trial was not powered for the **exploratory** clinical endpoints, thus the clinical cognitive results should be interpreted with caution…»

Sevigny J et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016 Sep 1;537(7618):50-6.

Unresolved issues

Clearing previously deposited amyloid from the brain is more important than preventing its production?