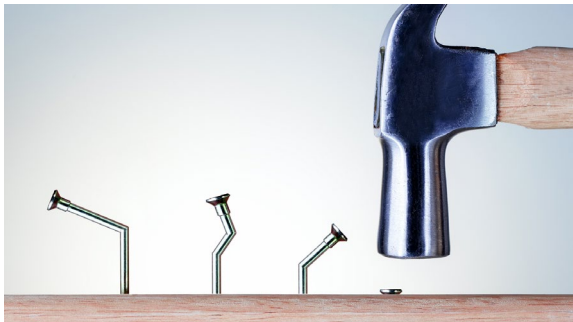


The Era of Disease Modifying Therapies: Challenges and Opportunities for Improved Patient Care and Research Advances Moving Forward

Greg Jicha, MD, PhD

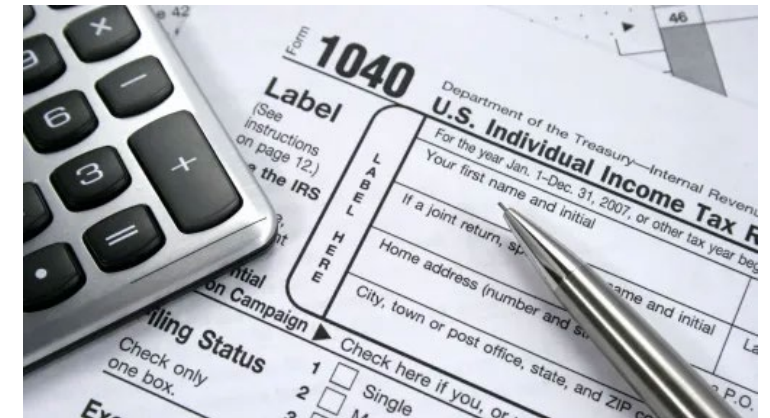
McCowan Endowed Professor of Neurology

University of Kentucky ADRC



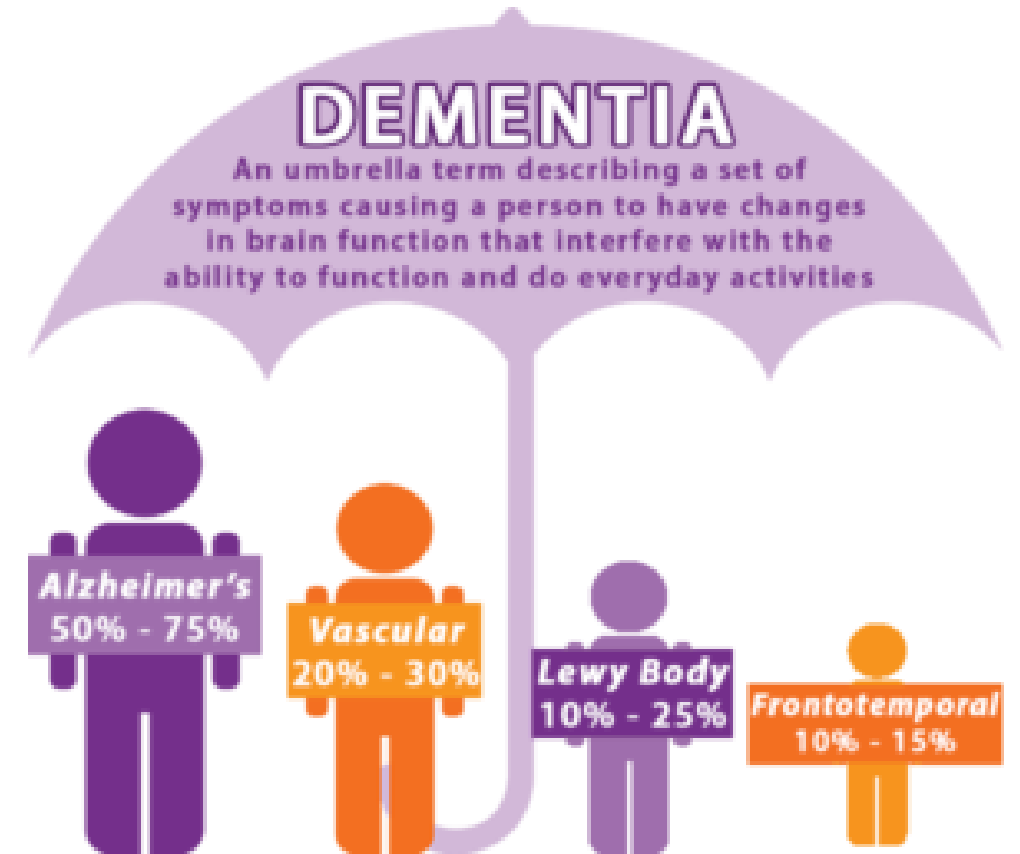
Disclosures

- **Grants**
 - NIH P30 AG072946, U24 AG057437, R01 AG053798, R01 AG063689, U19 AG010483, R01 AG054029, R01 AG061848
- **Contract Research**
 - Cassava, Cycleron, Eisai, Lilly, Suven, Vivoryon
- **Educational Programming**
 - Medscape, CEConcepts/ AAFP, Mid-America Institute on Aging and Wellness
- **Leadership Roles**
 - Alzheimer's Association ALZ-NET, ACTC, ADCS, AAN Education, ADRC Clinical Steering Committee & Task Force
- **Consulting/Speaker's Bureau**
 - None
- **Stock, Royalties, or Intellectual Property**
 - None

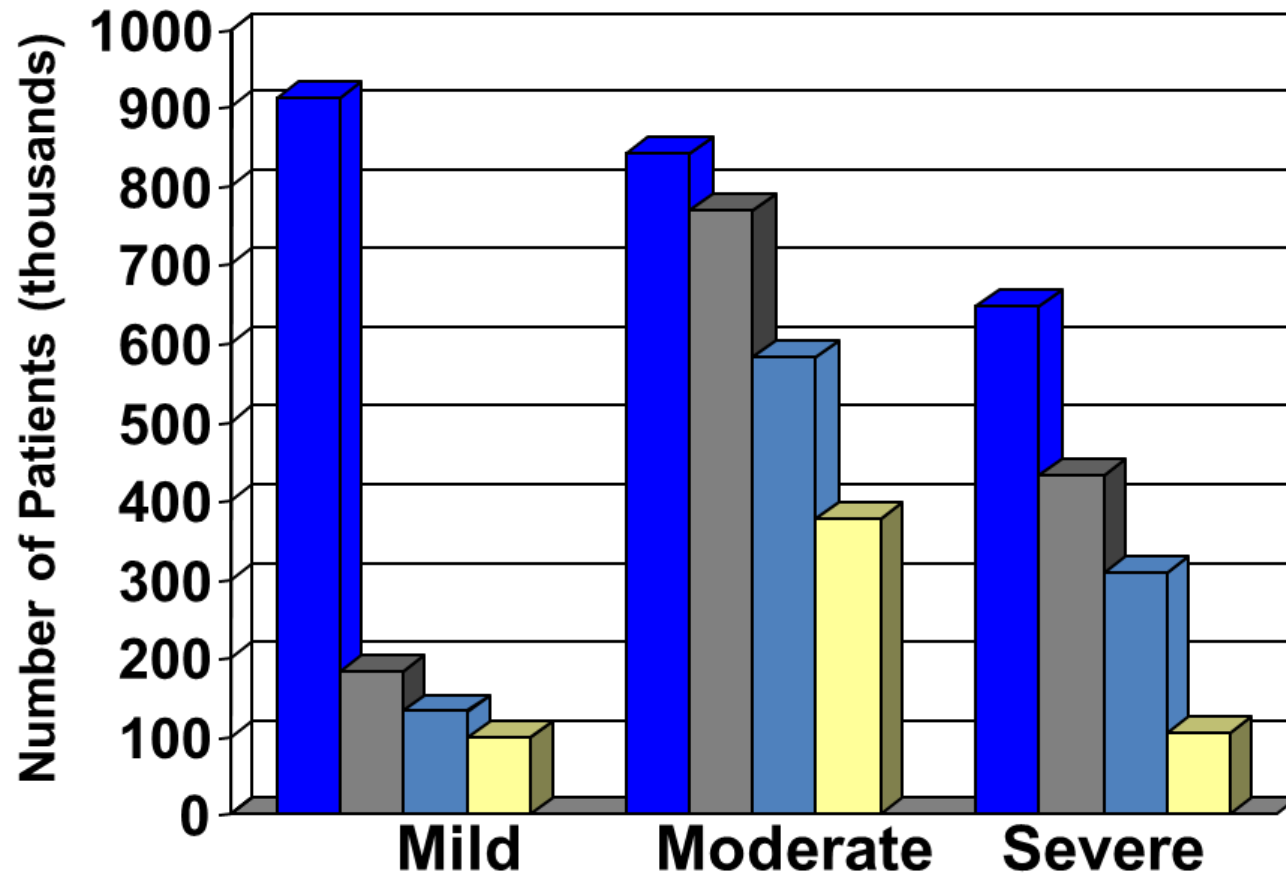


Learning objectives

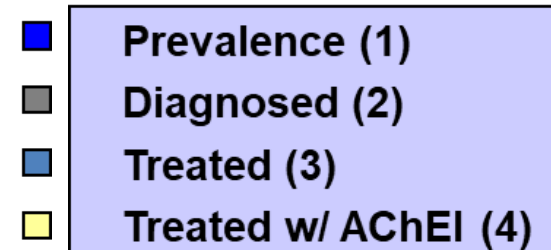
1. Describe the use of symptomatic medications for dementia
2. Discuss the appropriate use of disease-modifying anti-amyloid therapies
3. Summarize ongoing and needed clinical research to improve the care of persons with dementia



ALZHEIMER'S DISEASE PREVALENCE, DIAGNOSIS, & TREATMENT BY STAGE



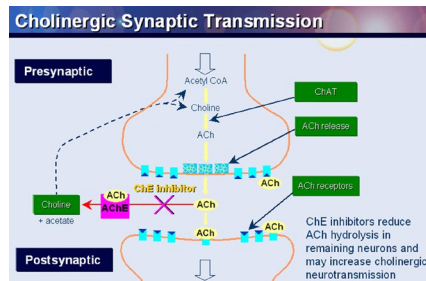
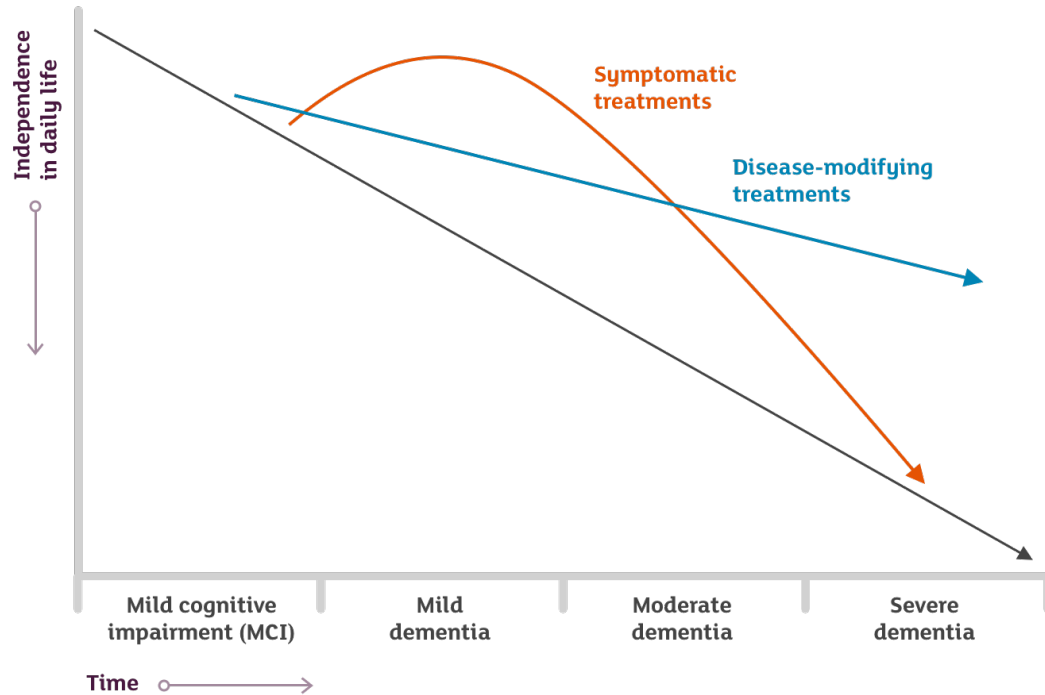
- Far less than half of all AD patients are even treated!
- This is most true for early and late stage patients!



- We need to keep pushing for diagnosis and treatment if we are to help those we serve
- Hopefully, we are doing better than we were 20 years ago...

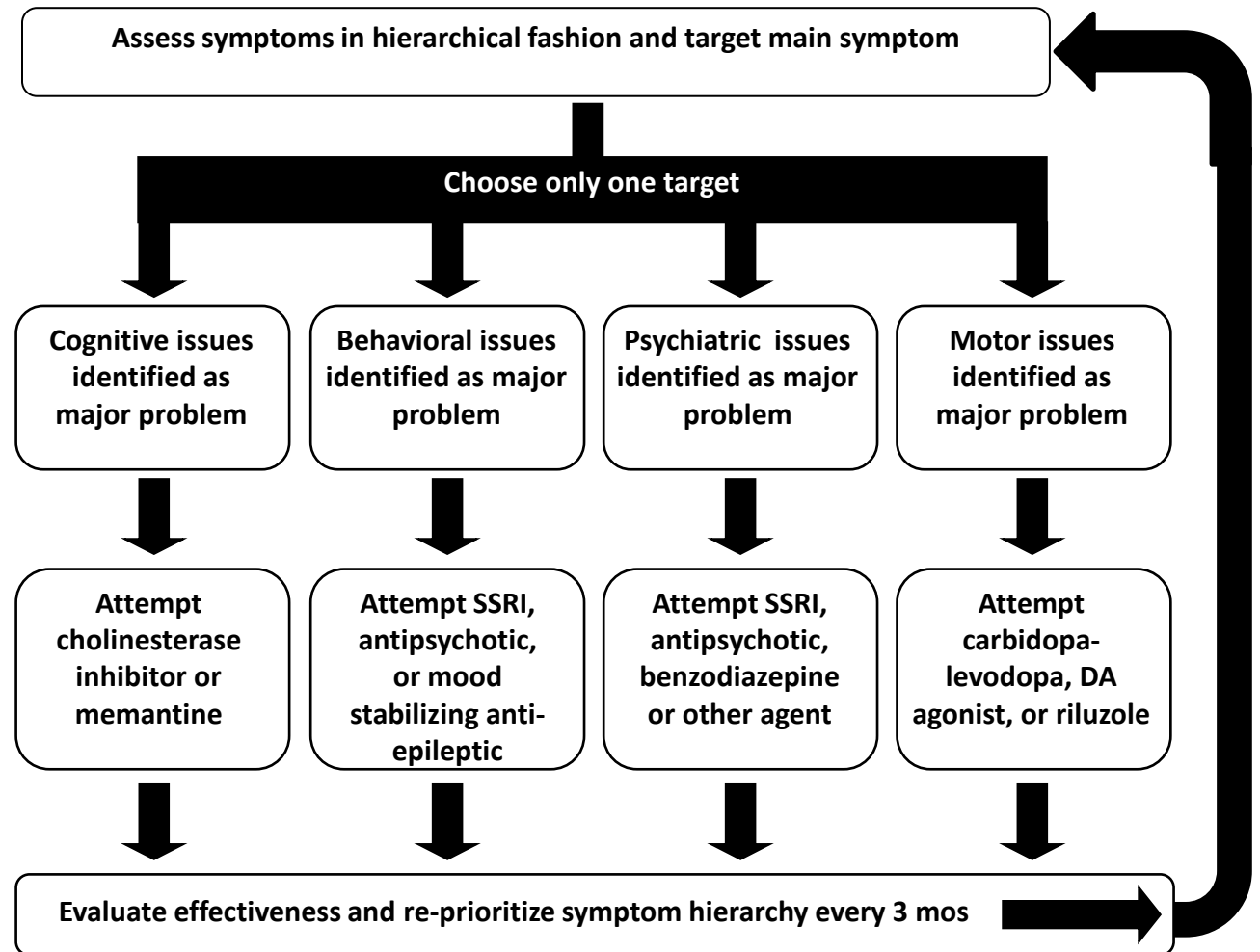
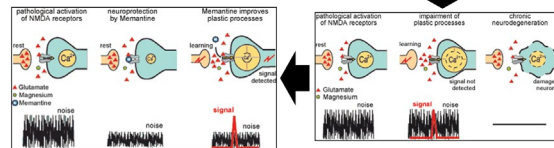
Sources: (1) Brookmeyer et al. *AJPH*. 1998; (2) *PDDA*. 1998; (3) & (4) *Market Measures*. 1998.

Let's talk about symptomatic treatments



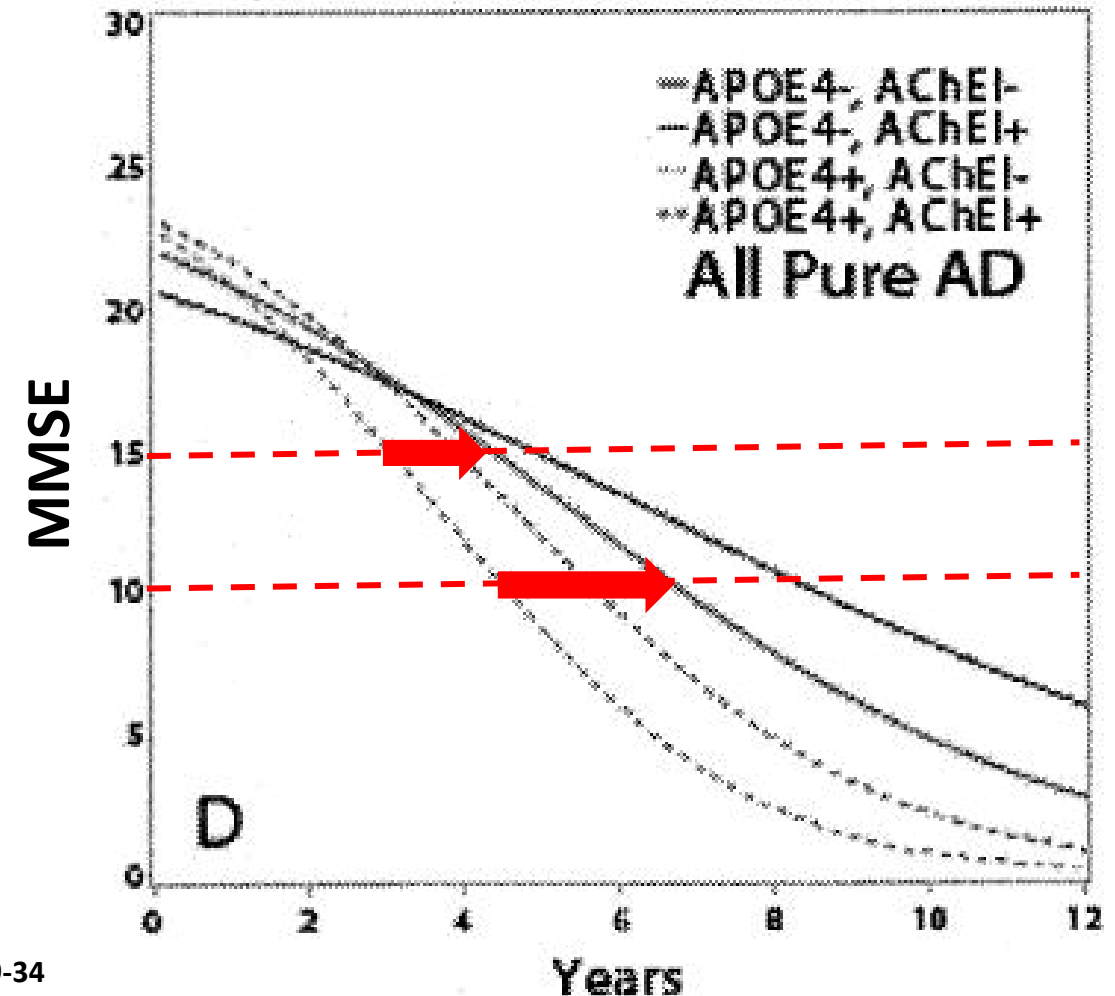
• Memantine

— Acts via glutamate receptors found widespread through the cortex

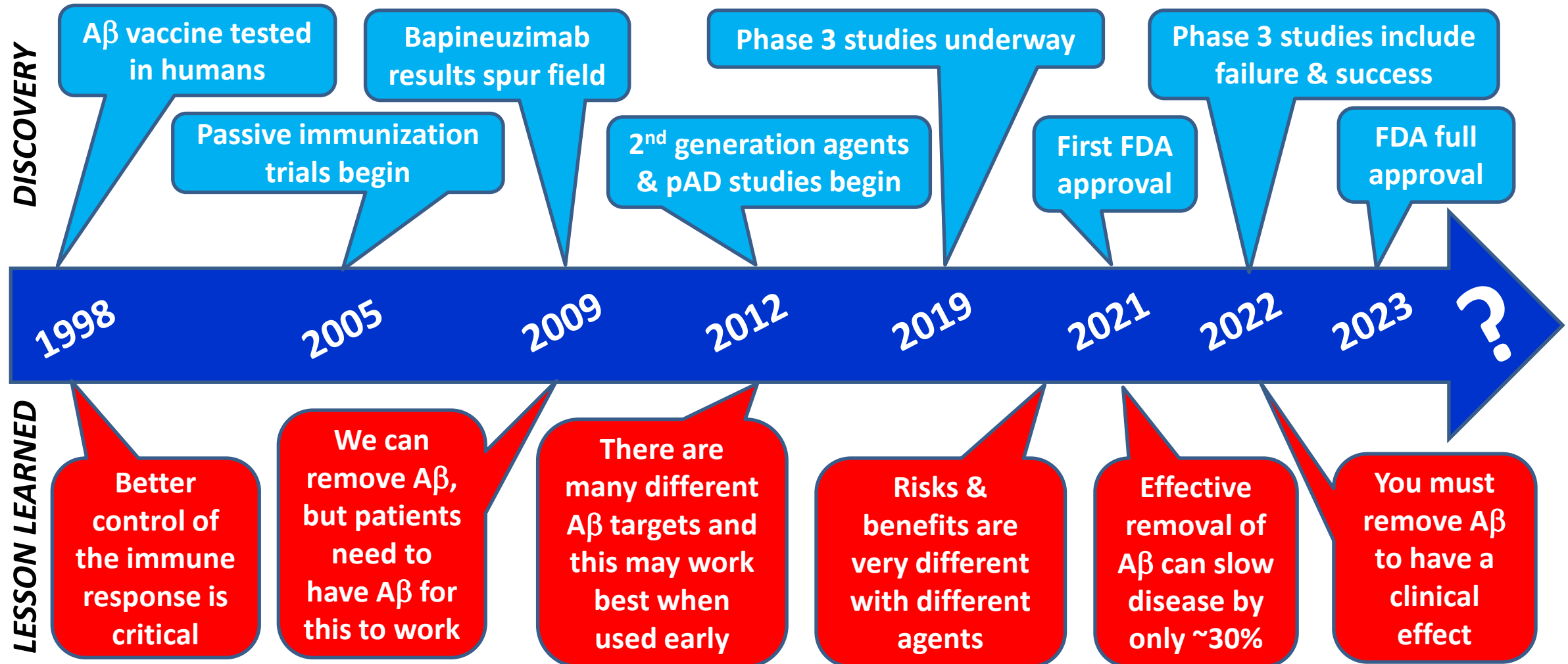


Symptomatic treatment will always be a part of our care

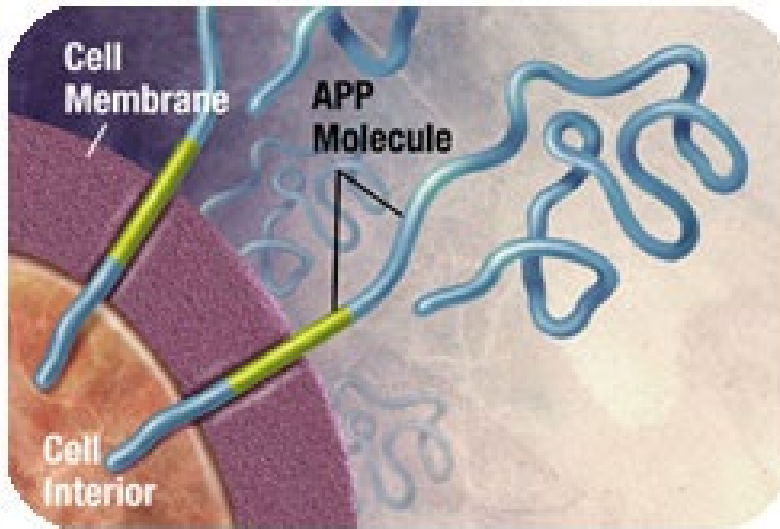
- True, the endgame of mortality appears unchanged
- Still, use of a AChEI alone results in a >1 year delay in reaching a MMSE of 15
- And, a >2 year delay in reaching a MMSE of 10
- Other symptomatic treatments can also help maintain QOL & decreased caregiver burden



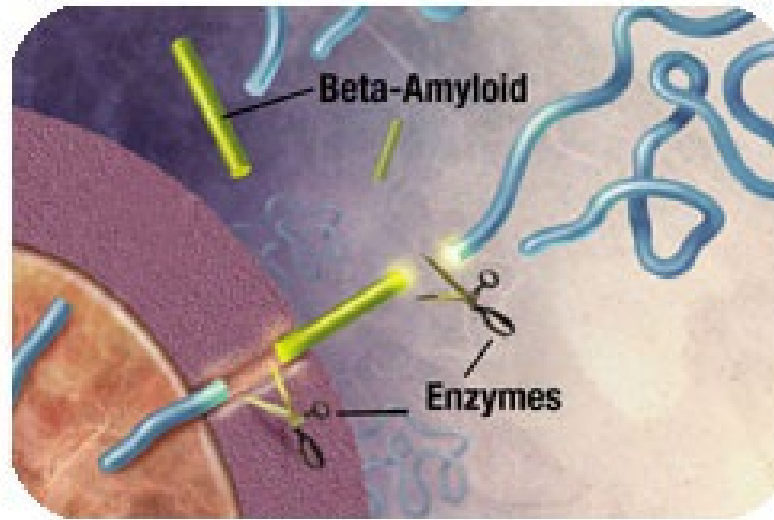
Timeline of anti-A β therapeutic discoveries & advances



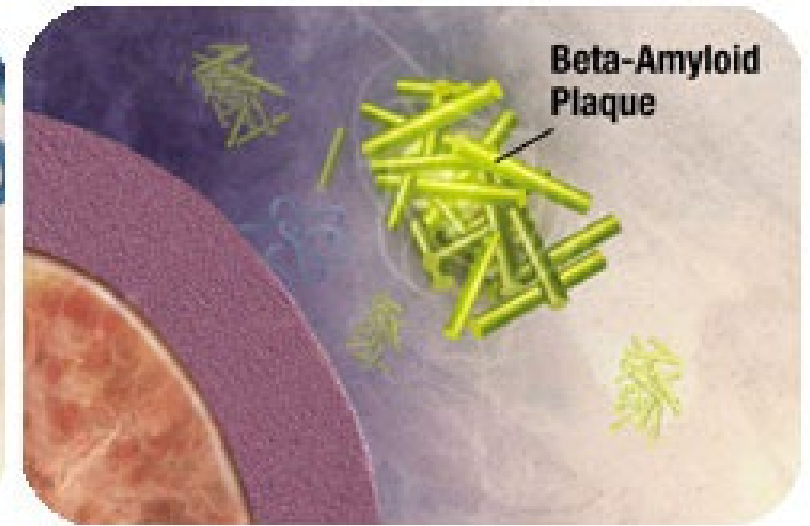
Why is A β a target for drug development?



1) APP is a membrane-bound glycoprotein that may serve as a growth factor in injury and repair



2) APP is normally cleaved by α -secretase and β -secretase, but in AD, γ -secretase is active

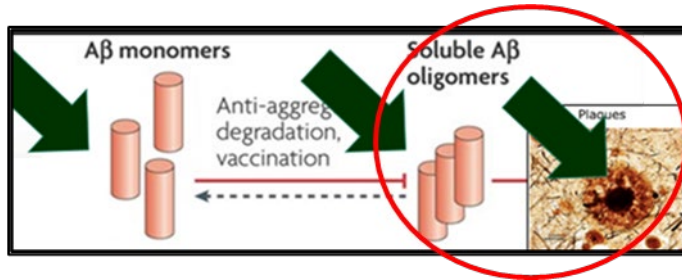


3) β -amyloid is toxic to cells and accumulates in brain tissue as amyloid plaques, a hallmark of AD

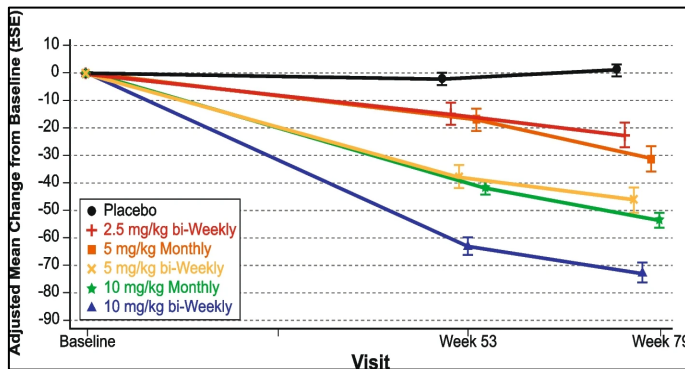
***All dominant genetic mutations leading to AD work by increasing A β**

****A β accumulation is the first step in the development of AD**

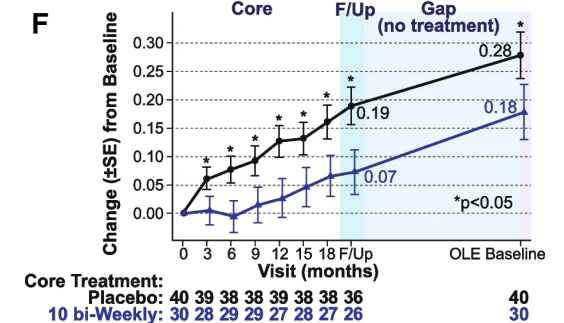
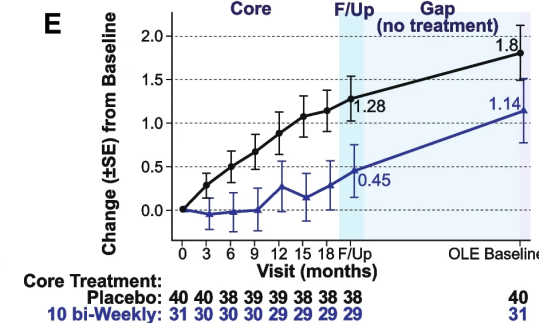
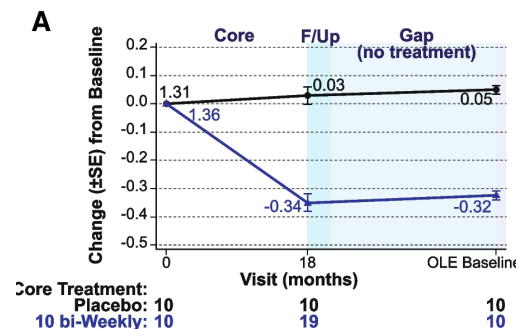
Let's begin the journey with Phase 2 Lecanemab 2012...



Phase 2b/3 study showed removal of Aβ leading to FDA accelerated approval

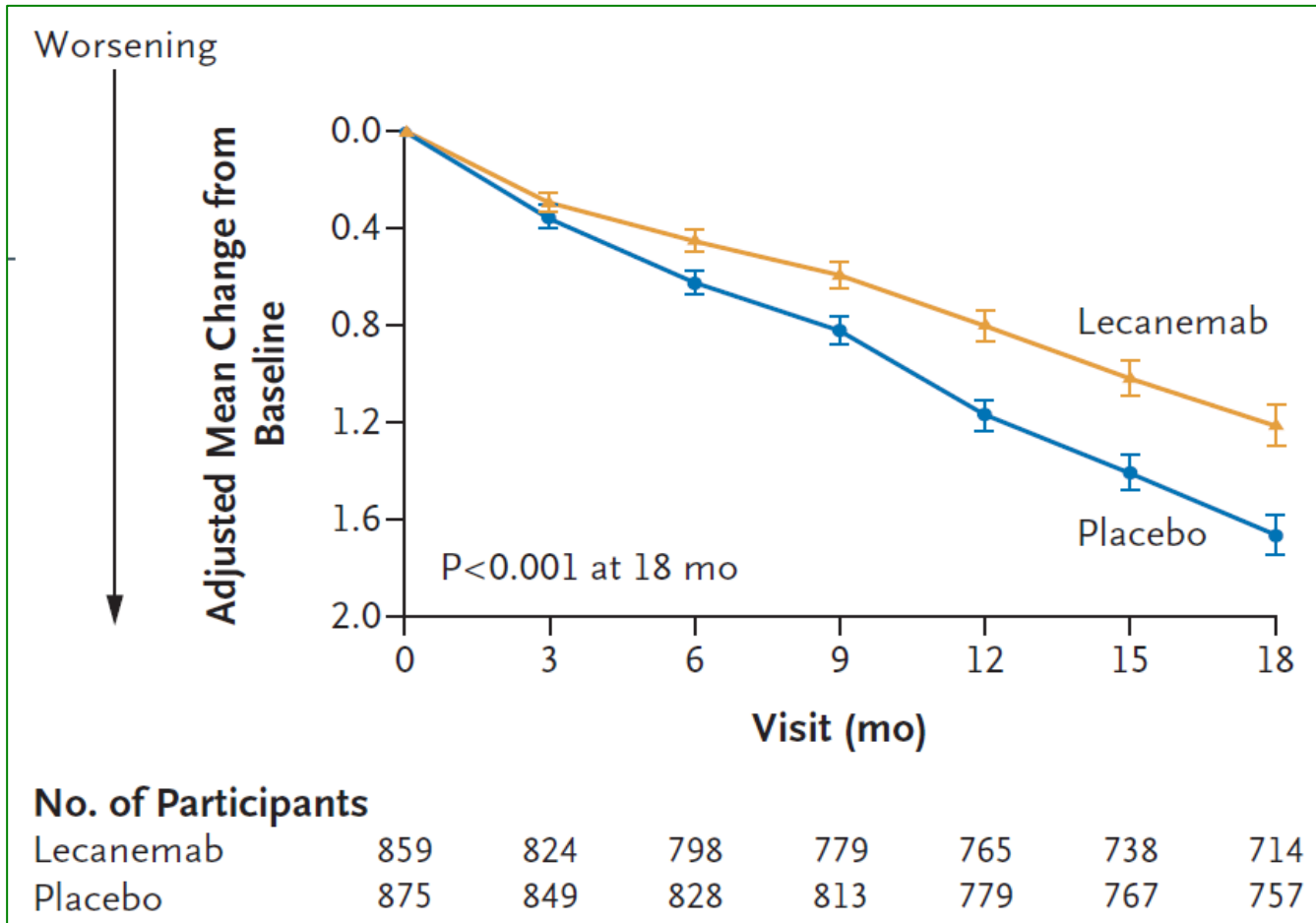


- The trial demonstrated 10 mg/kg biweekly was optimal
 - It eliminated Aβ
 - There was positive clinical benefit
- But the trial ended and all patients went into a gap period before an OLE was started
 - This taught us so much about disease modification and what happens if you stop these medicines



- A slow rise in Ab-PET is seen, but this is really slow
- Cognitive decline continues, but parallel slopes indicate it has changed the disease course permanently

Lecanemab Phase 3 Results...



Clinic OTC Guide

Pharmacy Times

Lecanemab Shows Highly Statistically Significant Reduction of Clinical Decline in Early Alzheimer Disease

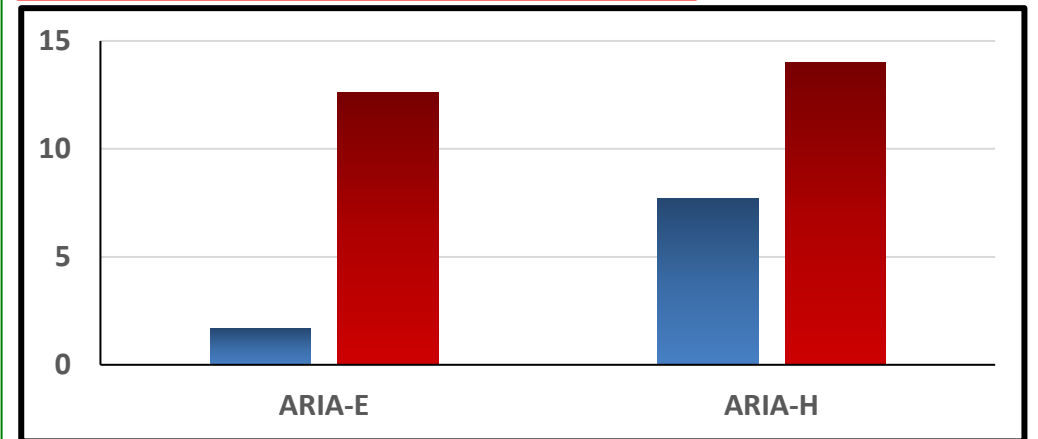
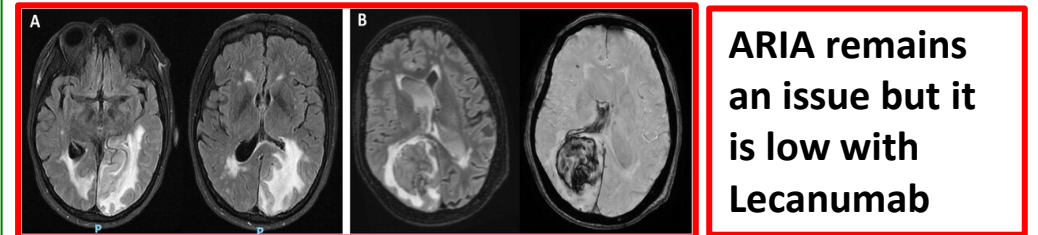
November 3, 2022
Aislinn Antrim, Associate Editor

BioPharma
-Reporter.com

News & analysis on the clinical development

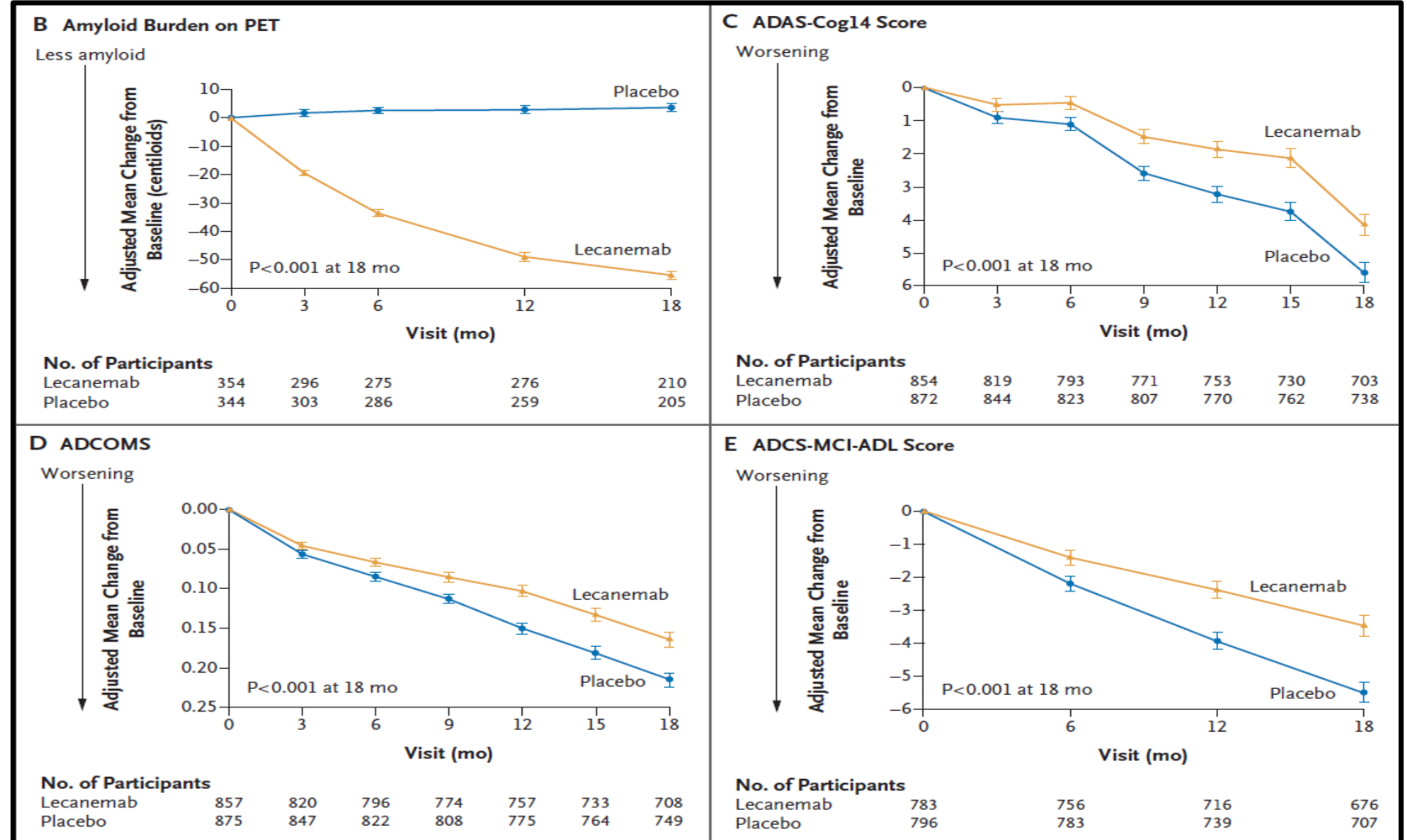
Headlines Hot Topics Resources Events Related Site Search

Alzheimer's disease: Eisai and Biogen release milestone data



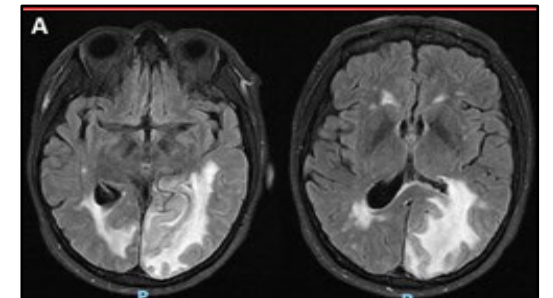
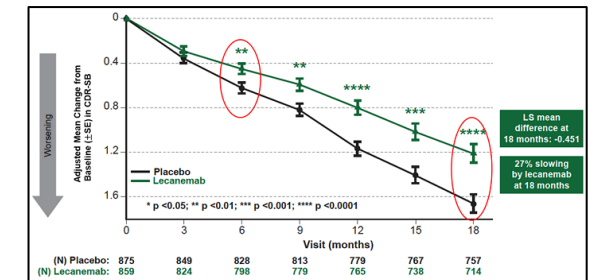
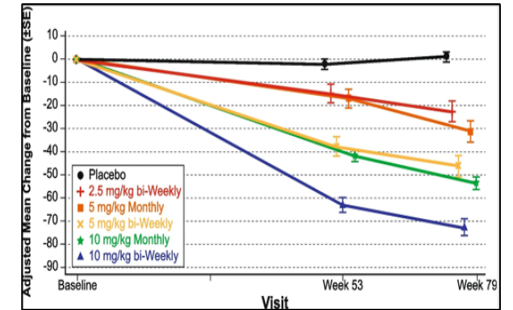
Lecanemab secondary endpoints?

- Full FDA granted July 6, 2023
- Medicare & the VA have chosen to cover costs
- Infusions starting at UK currently
- Let's get ready...

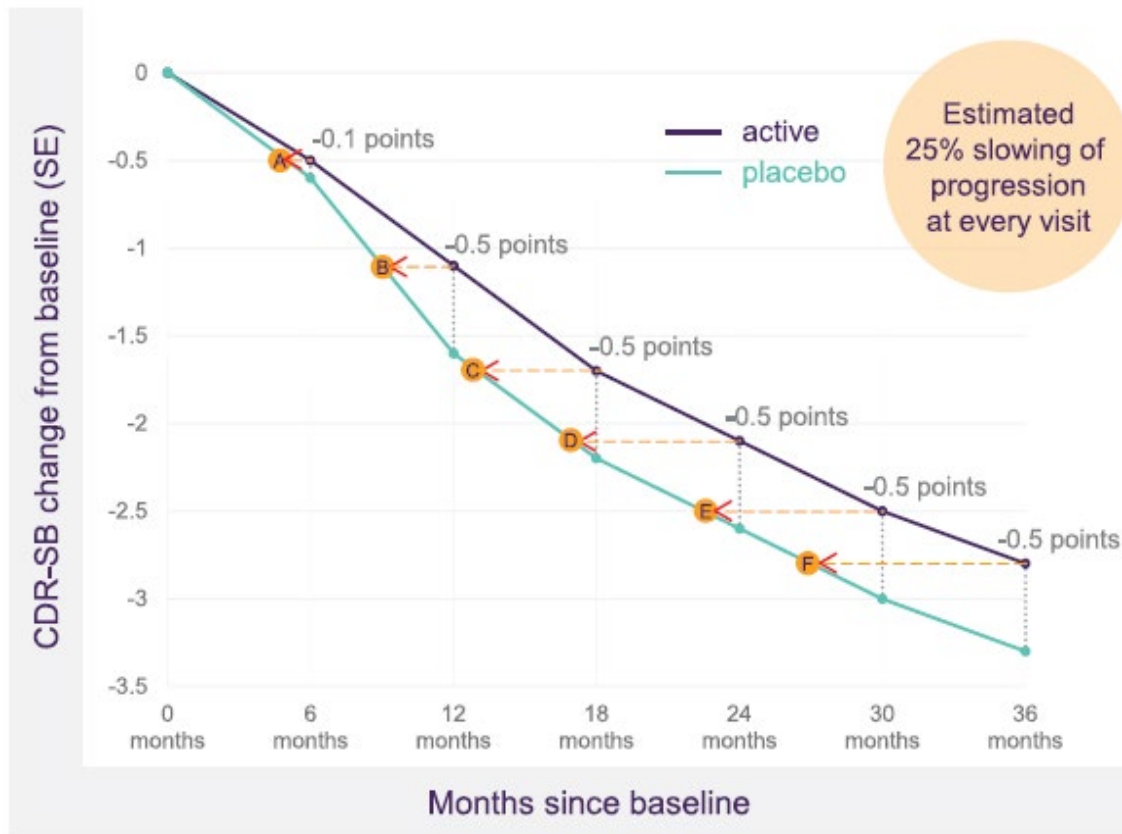


Lecanemab Lessons Learned 2022

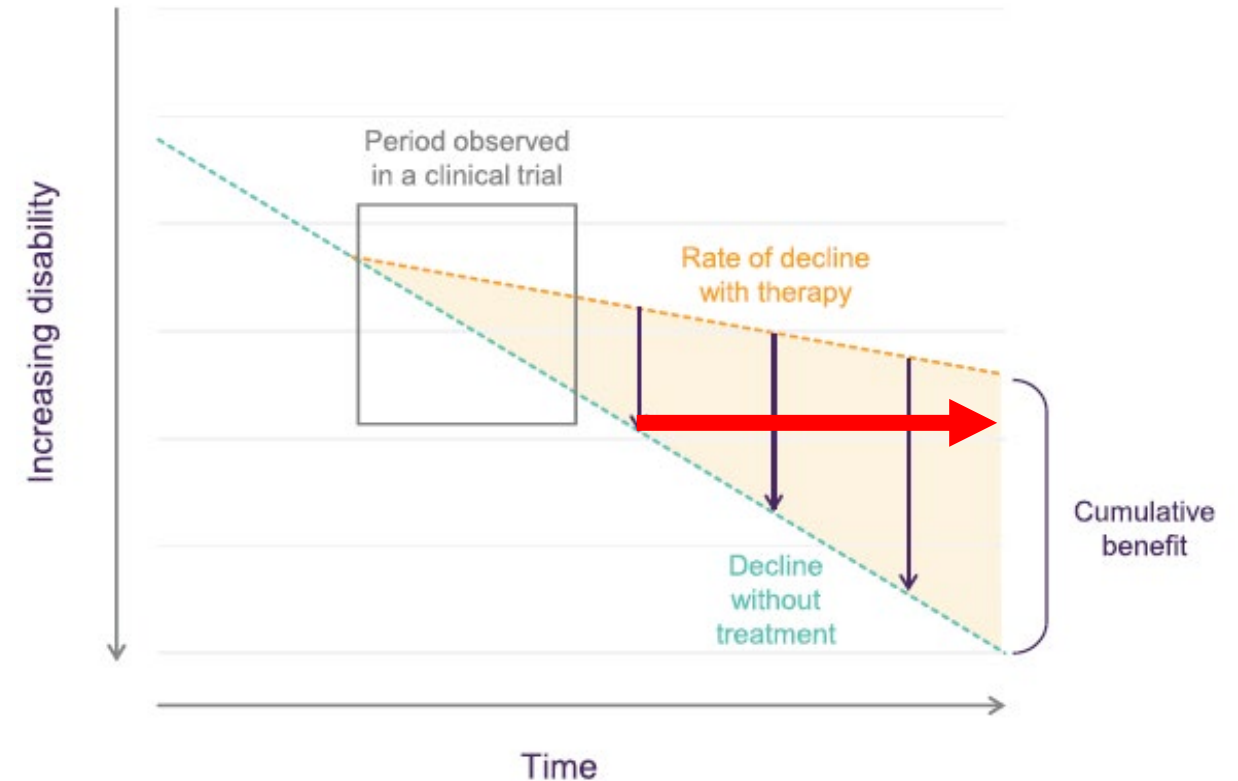
- The Phase 3 CLARITY data is considered by most in the field to be definitive evidence of clinical benefit in addition to the previously accepted demonstration of A β removal
 - The Phase 2b/3 data led to FDA accelerated approval on January 6, 2023 based solely on A β removal
- Clinical benefit ranges from 27% to 40% based on outcomes similar to the many other studies with other agents
 - Eisai immediately filed for full approval based on the Phase 3 CLARITY data which was granted July 6, 2023
- ARIA rates appear low despite full clearance of A β suggesting again a partial dissociation of risk from extent of amyloid removal



How much time will this buy us? Is it clinically meaningful?



	A	B	C	D	E	F
points	-0.1	-0.5	-0.5	-0.5	-0.5	-0.5
months difference vs. placebo	-1.5	-3	-4.5	-6	-7.5	-9

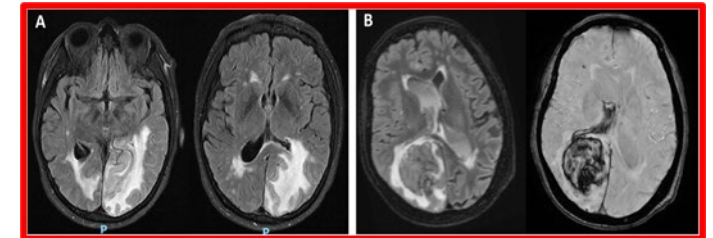
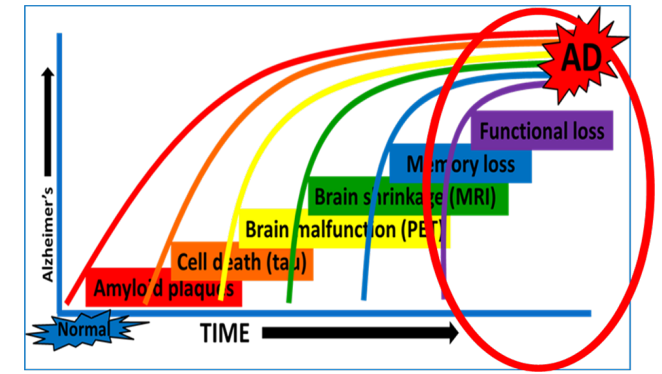


Petersen RC, Aisen PS, Andrews JS, Atri A, Matthews BR, Rentz DM, Siemers ER, Weber CJ, Carrillo MC. Expectations and clinical meaningfulness of randomized controlled trials. *Alzheimers Dement*. 2023 Feb 7. doi: 10.1002/alz.12959. Epub ahead of print. PMID: 36748826.

Imminent practical issues moving forward that we should all know...

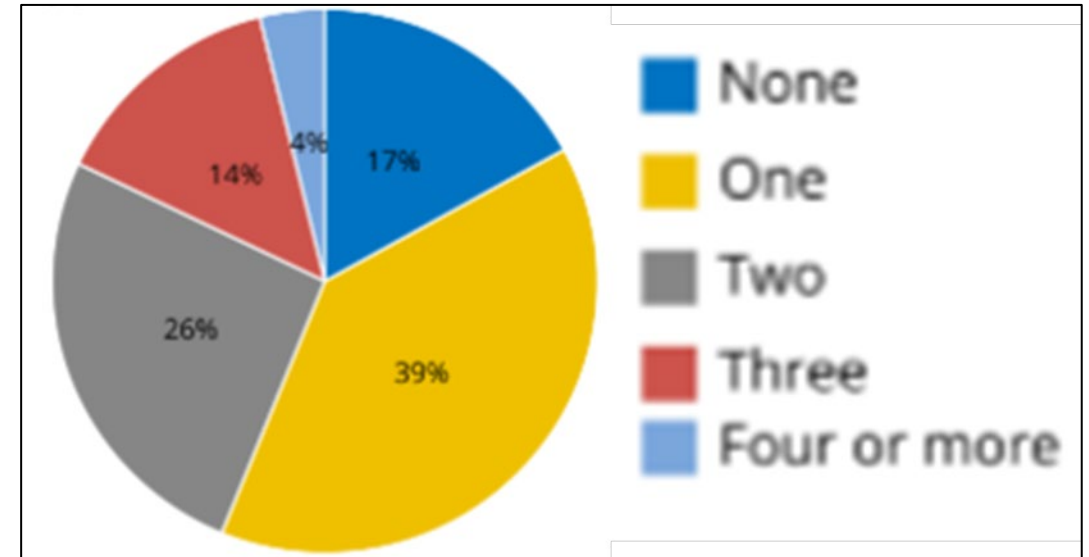
Lecanemab is unfortunately not for everyone...

- *It is only for those with MCI and mild dementia*
- *Patients must be able to have an MRI scan for safety monitoring*
- *Patients cannot have significant past microhemorrhages or other bleeding in the brain*
- *Caution should be used for those on blood thinners (no concerns for anti-platelet blood thinners)*
- *Caution should be used for ApoE e4 homozygotes (e4/e4 carriers)*
- *If a person has only basic Medicare, 20% of the cost (~\$5K) will be a co-pay needed (Eisai has a patient assistance program that may help?)*



How few of our patients may be eligible?

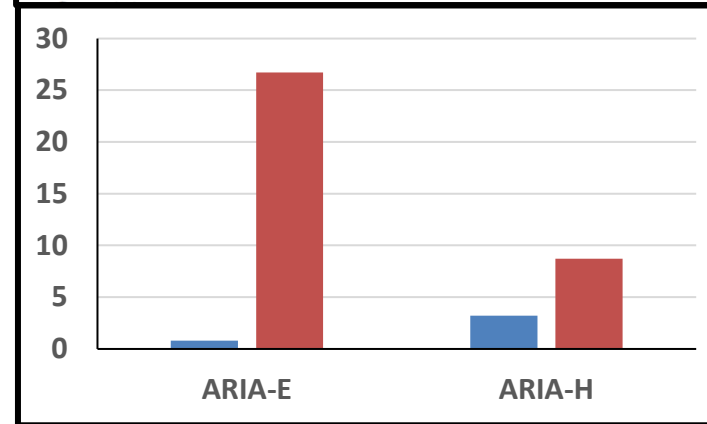
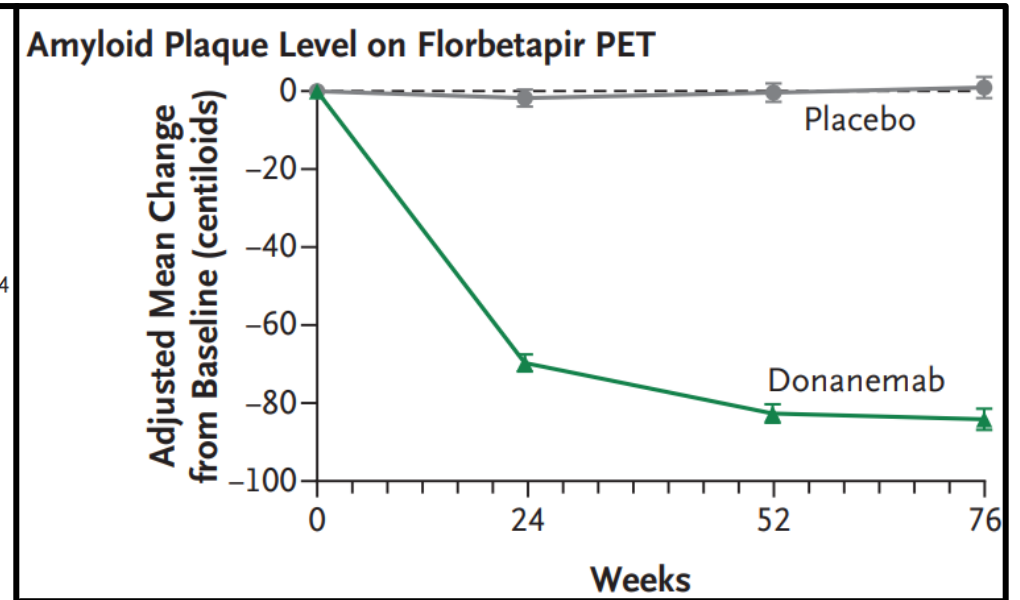
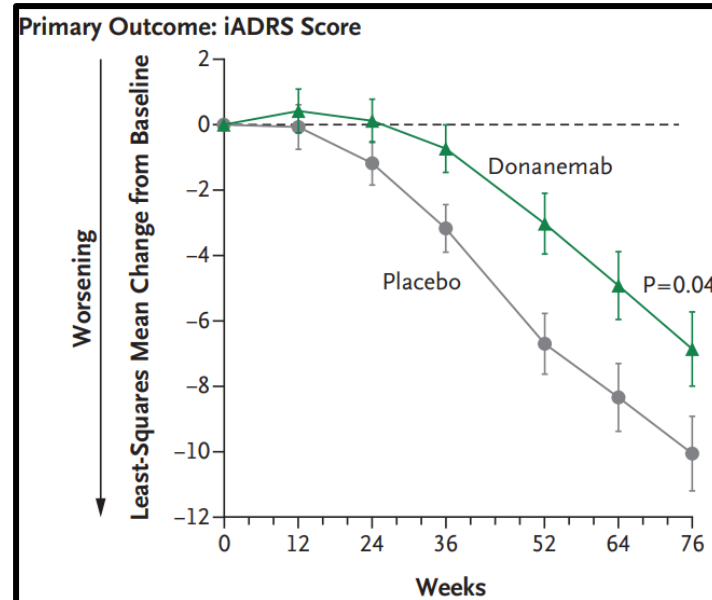
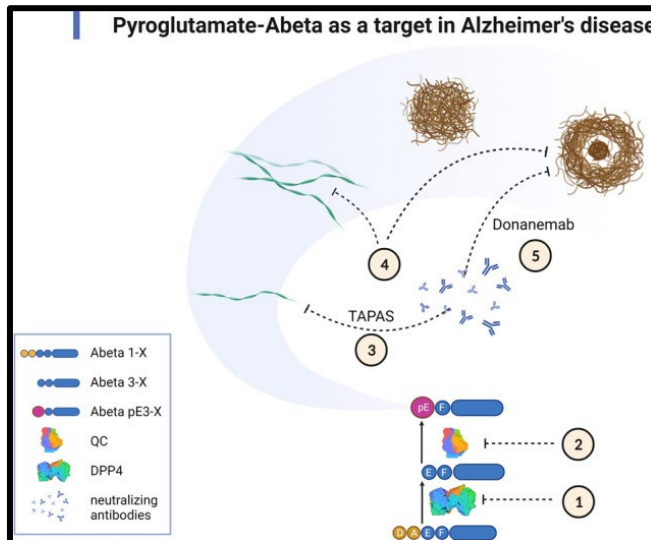
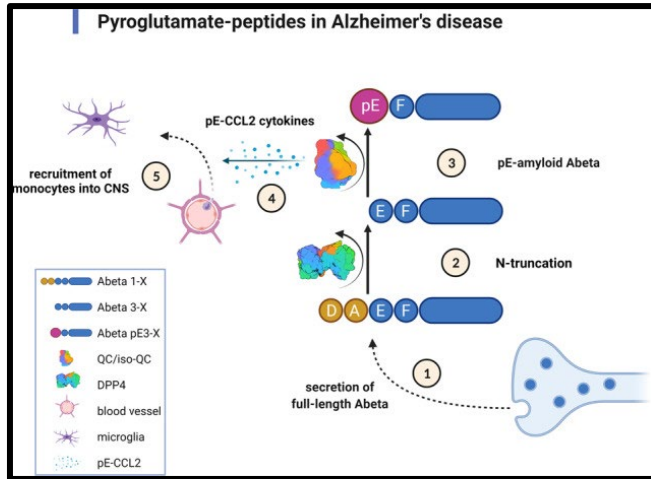
- Only 17% of our patients that appear eligible at first glance may actually be eligible...
- We need to be prepared to tell those that are not eligible why they are not eligible...
- Many may have exclusionary conditions...
- In the worst case scenario, with over 6 million persons on the US with AD, this still allows us to help over a million!!!



COMMON EXCLUSIONARY CONDITIONS:

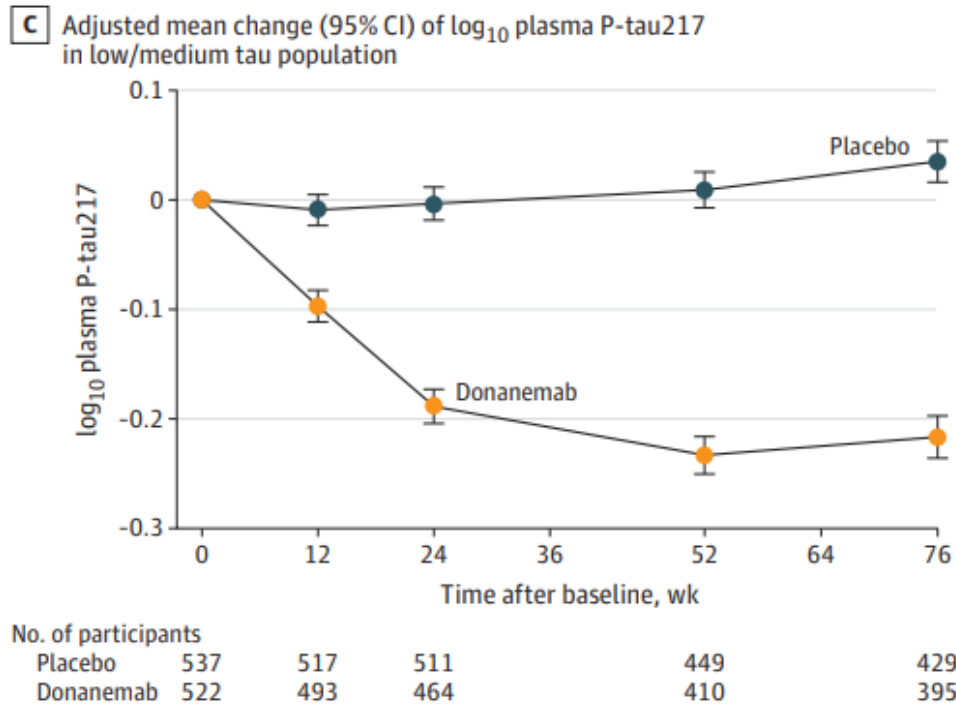
- Imaging exclusion (37.5%) including past ICH
- Cardiac exclusions if not well controlled (36%)
- Renal or liver disease (3.6%)
- Immunologic disease ever (10.7%)
- TIA or stroke in last year (6.3%)

Let's continue the journey with Donanemab 2017...

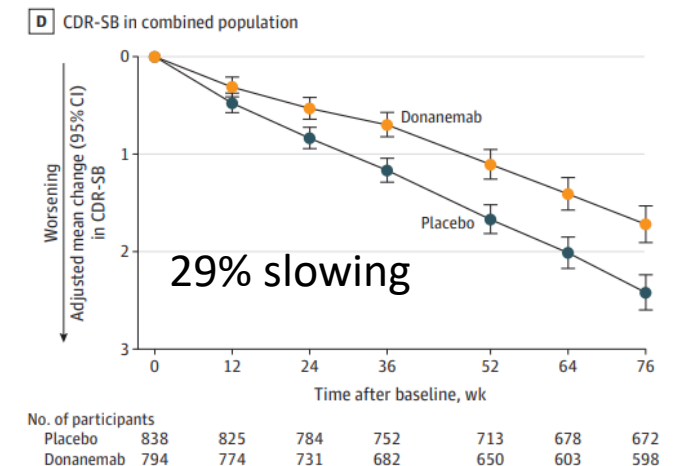
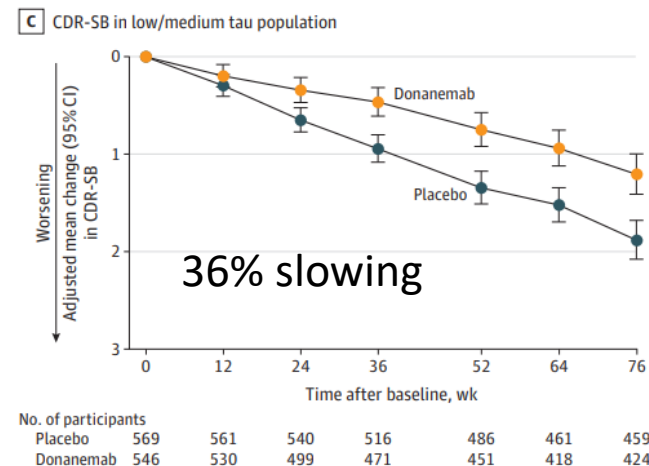
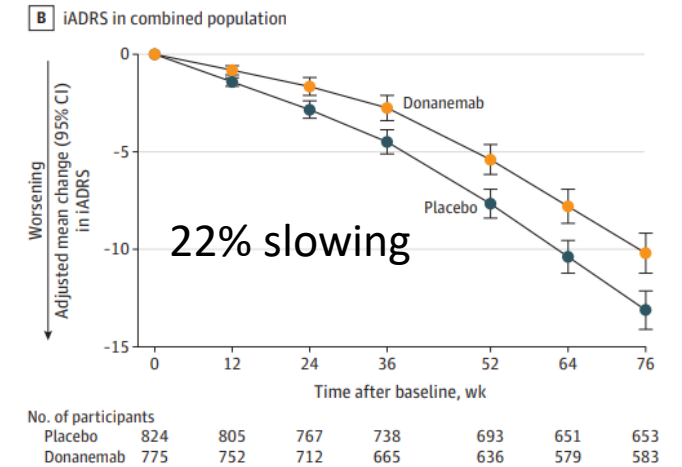
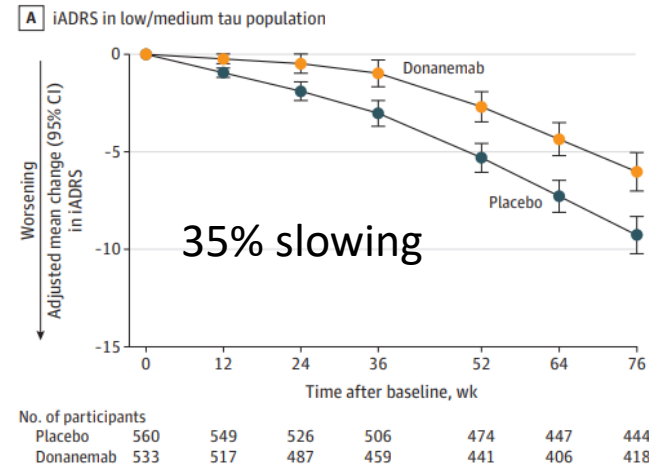


- Results similar to other antibodies that remove Aβ plaques resulting in ~25% slowing of AD
- Complete removal of Aβ plaques demonstrated clearly in a subset of patients
- ARIA risk remains in a midrange

But that's not all, Donanemab full FDA approval is pending 1/24

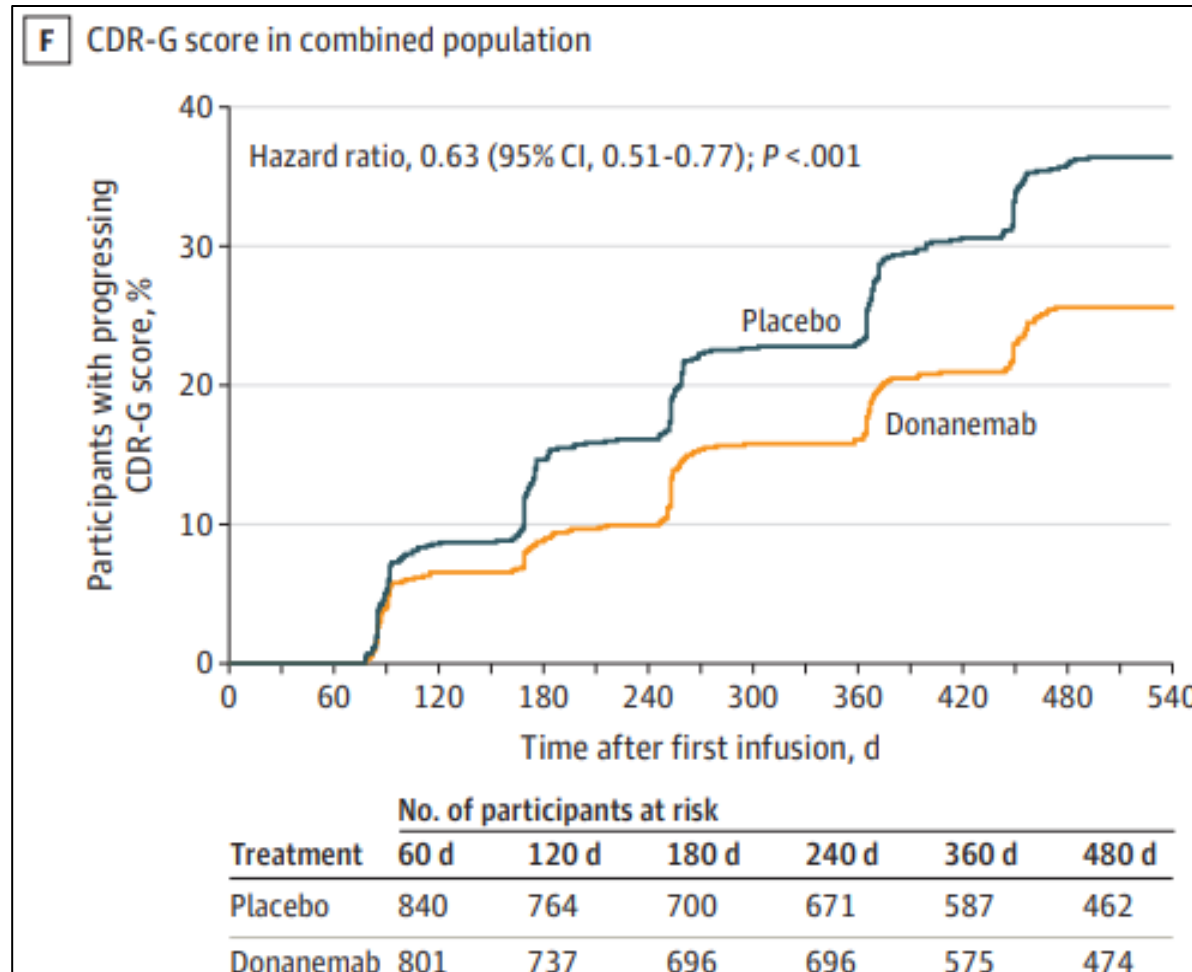
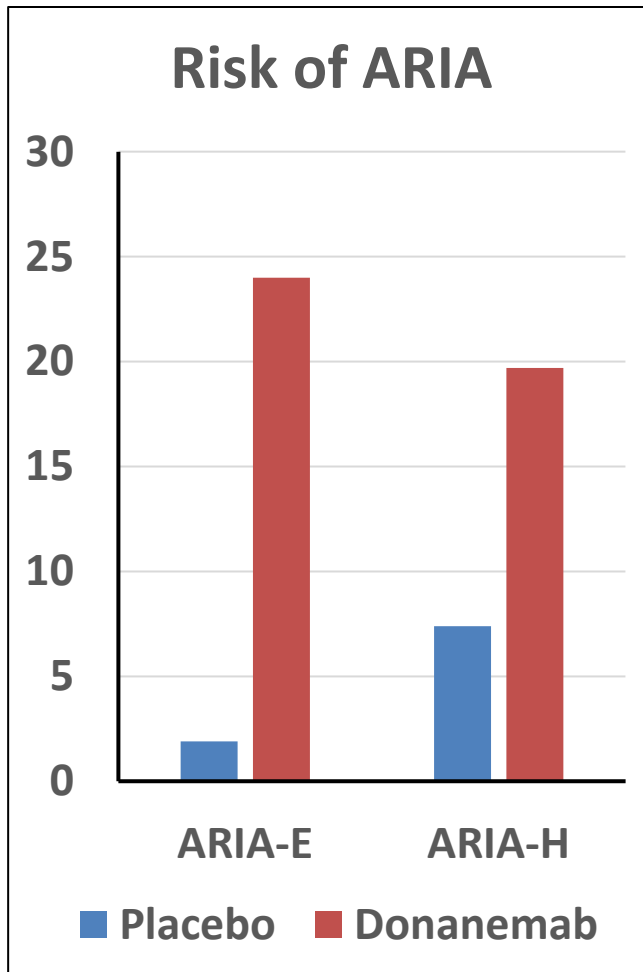


- Removes A β
- Slowing similar to Lecanemab



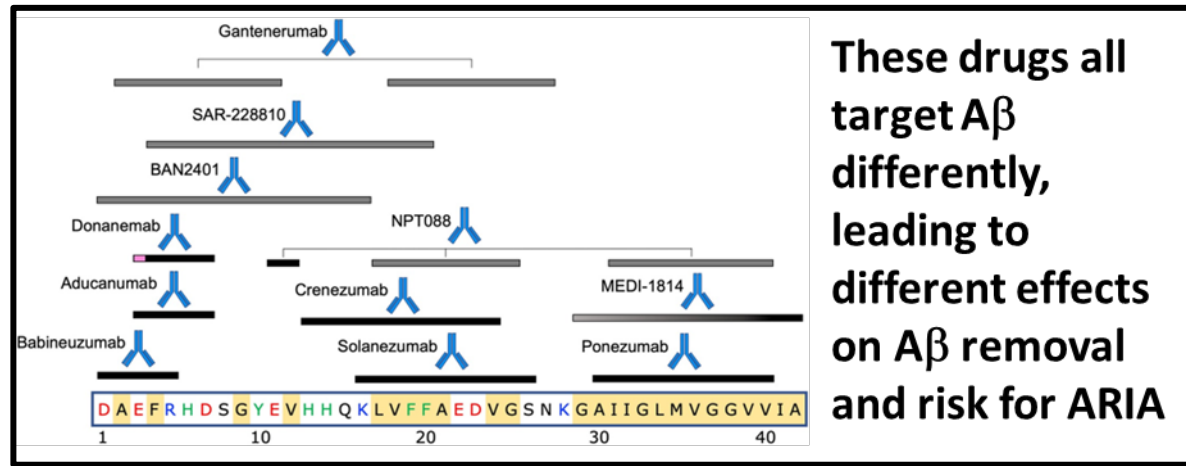
Sims et al. JAMA. 2023 Aug 8;330(6):512-527.

Risks vs. benefits?

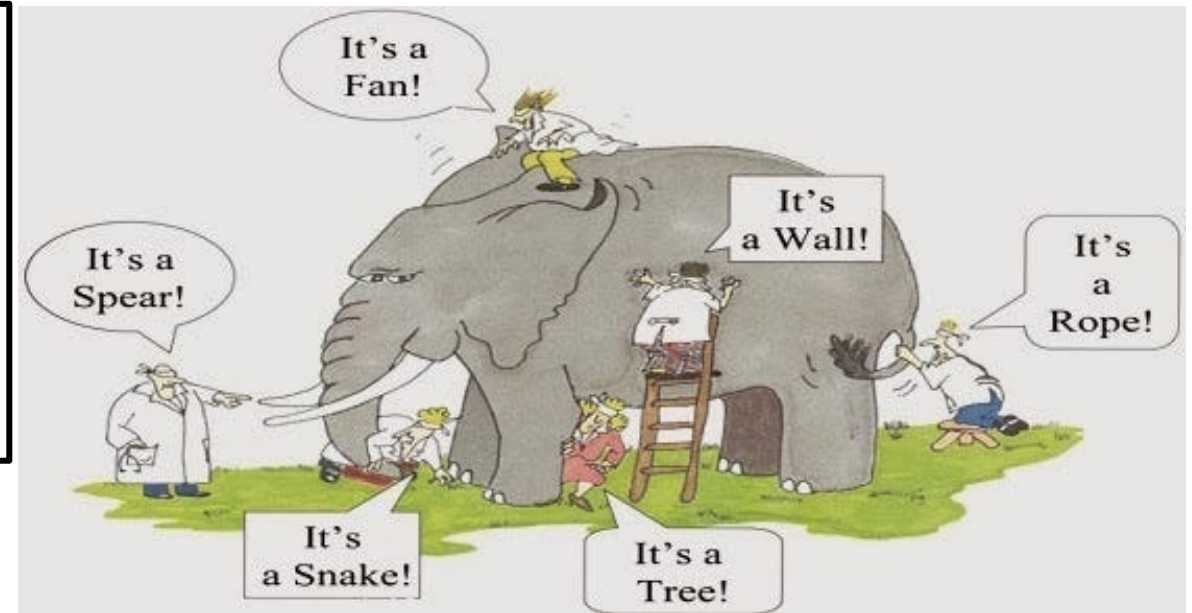


- ARIA risks remain higher than placebo
- 4.4 month delay over the 1.5 year study period
- This difference could be much more significant if continued post-therapy

Are these medicines all the same or are they different?



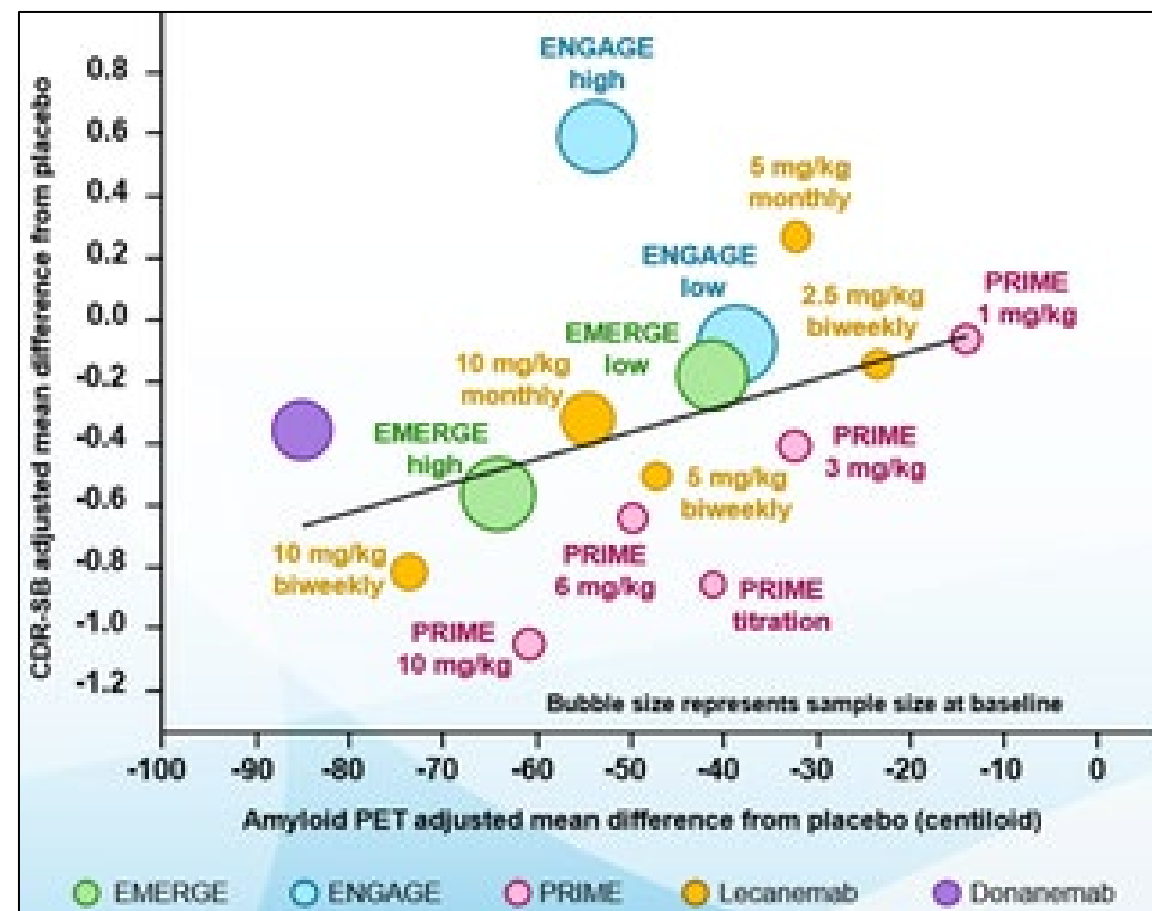
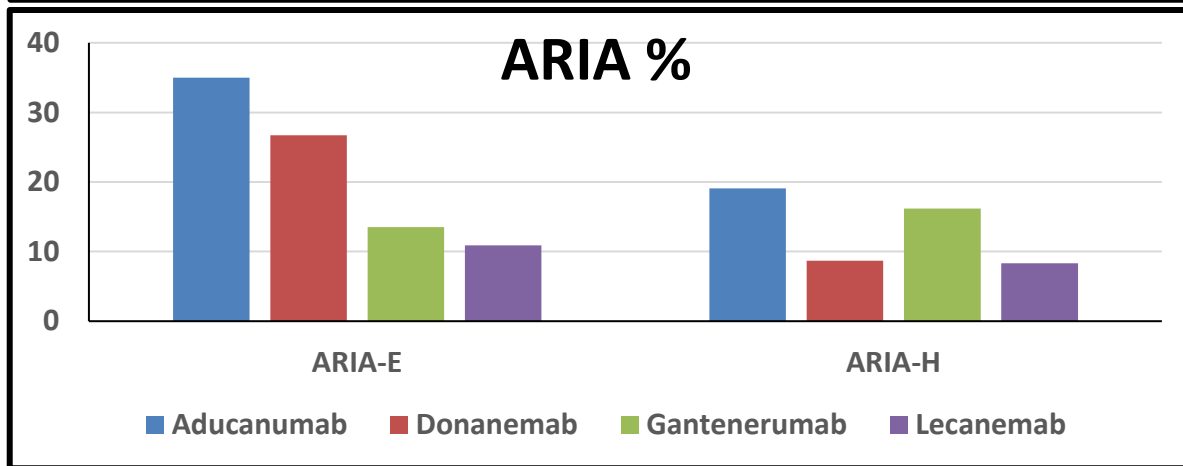
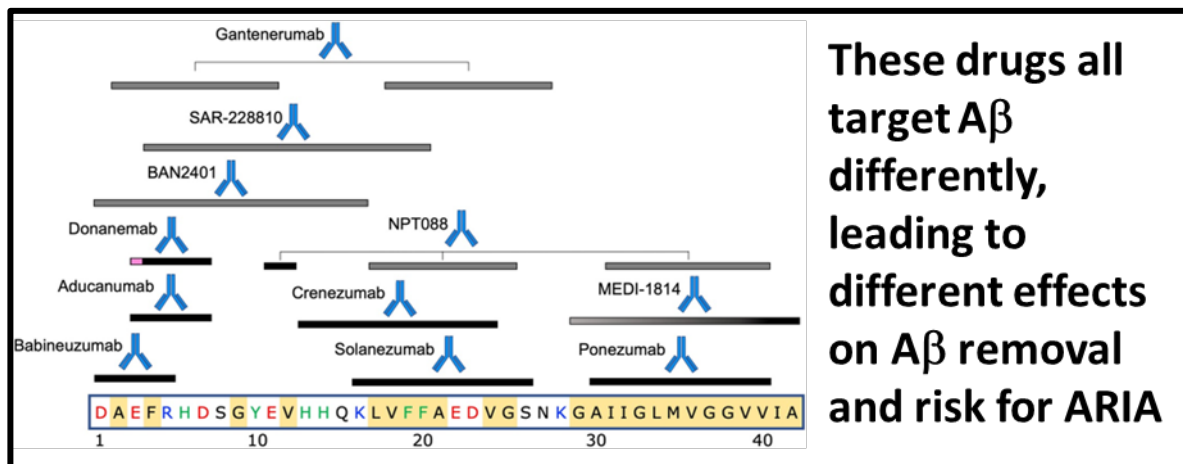
Haass & Selkoe (2022) PLoS Biol 20(7): e3001694.



This conundrum is no different than the story of the blind men and the elephant

- Each part of the elephant is different depending on where you touch!
- These therapies all “touch” amyloid in different areas and are different!

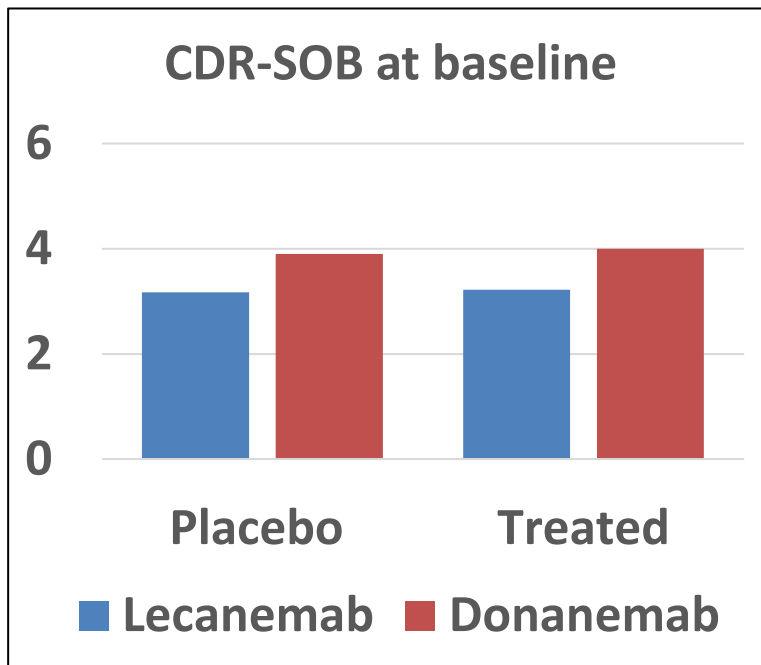
Are these medicines all the same or are they different?



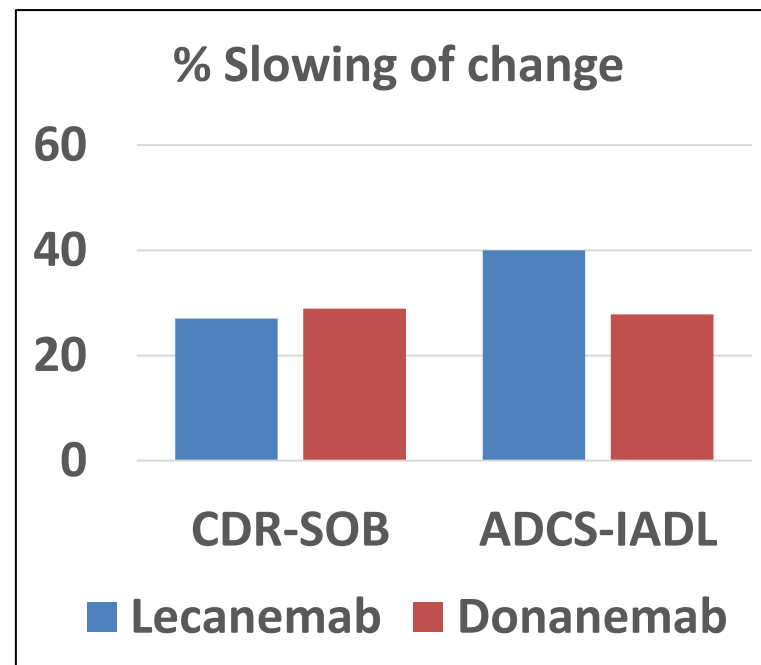
Comparing lecanemab & donanemab...

- Donanemab studies required tau-PET positivity whereas lecanemab studies did not (these populations are different)**

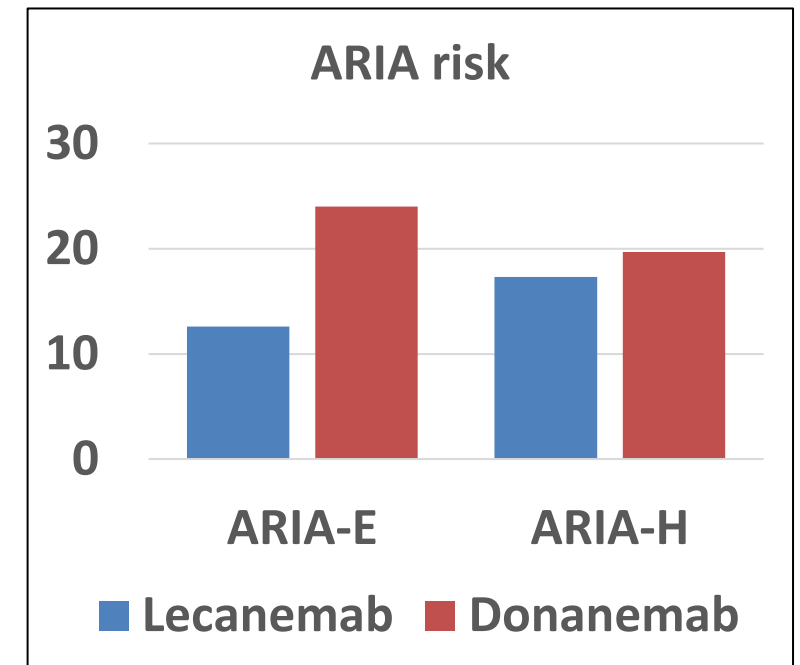
Comparison of subjects enrolled



Comparison of benefits

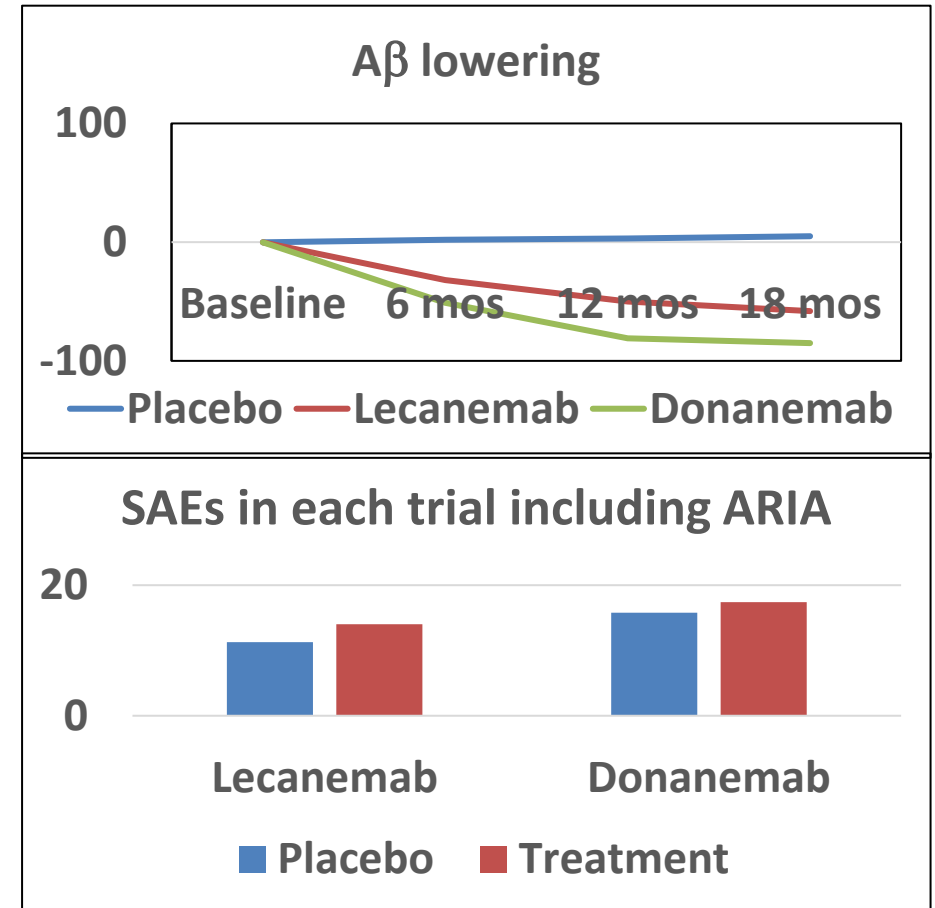


Comparison of risks



How to guide our patients?

- Overall, the data show similar effects and risks
- Donanemab appears to clear amyloid faster
- Donanemab is also associated with slightly greater risk of ARIA & SAEs but this increased risk was also seen in the placebo group...
- These risks are manageable with either agent and SAEs are high irrespective of treatment in our patients with AD



Advice to patients...

-
- **The medications have similar effects and similar safety profiles**
 - **The safest approach may be to go with lecanemab, but the more aggressive approach is to go for donanemab**
 - This is like thinking of your retirement account investments...
 - **Much of this may come down to what your patient's 3rd party payor will cover**
 - **A consideration is that lecanemab is every two weeks and donanemab is only every 4 weeks**
 - With that said, missing an infusion or 2, or 3, or more is not as important as getting that amyloid out of their brains!
 - **Our patients will ultimately have to make the choice for themselves as to whether these are right for them and if so, which one?**
 - We should be prepared to guide and educate on this important decision!

What else do we need to learn to best use these new meds?

- **We still don't know how long we need to treat?**
 - The trials were 1 ½ years & that is sufficient to clear the brain of amyloid plaques!
 - But, we also know that there is a slow buildup of amyloid after stopping the treatment...
- **Post-marketing studies are needed!**

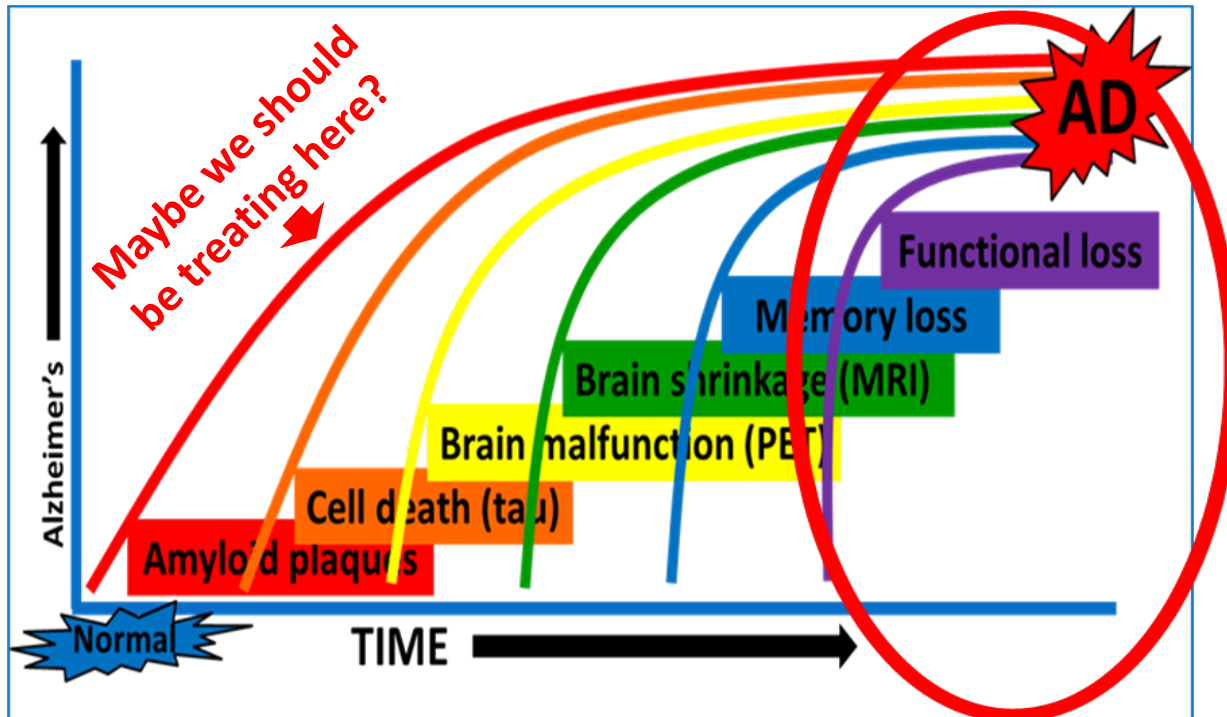


- **Infusions are not convenient and add significant costs**
- **Can SQ at home injections work as well?**

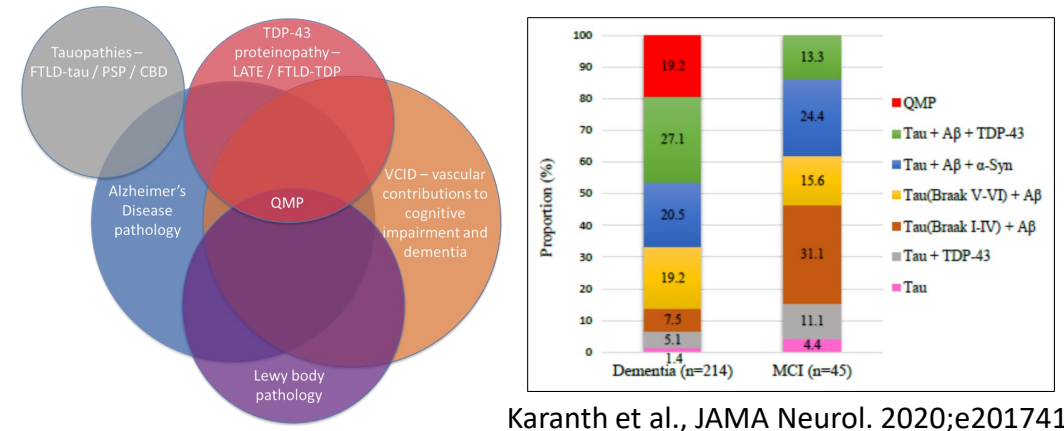
Why only ~30% clinical benefit despite full A β removal?

Two major possibilities exist...

#1 We are treating way too late in the disease and there is so much more injury this won't reverse



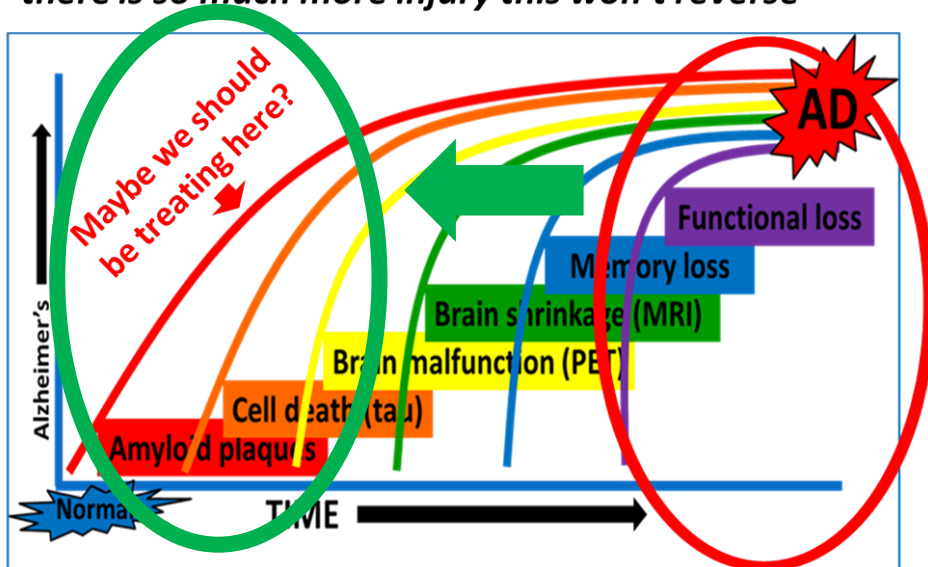
#2 We are only treating the A β & most cases of MCI and dementia are mixed disease states



"Pure" AD is only 27% to 40% of the pathology found in most MCI and or dementia cases at autopsy

What about earlier treatment? Even at the asymptomatic phase?

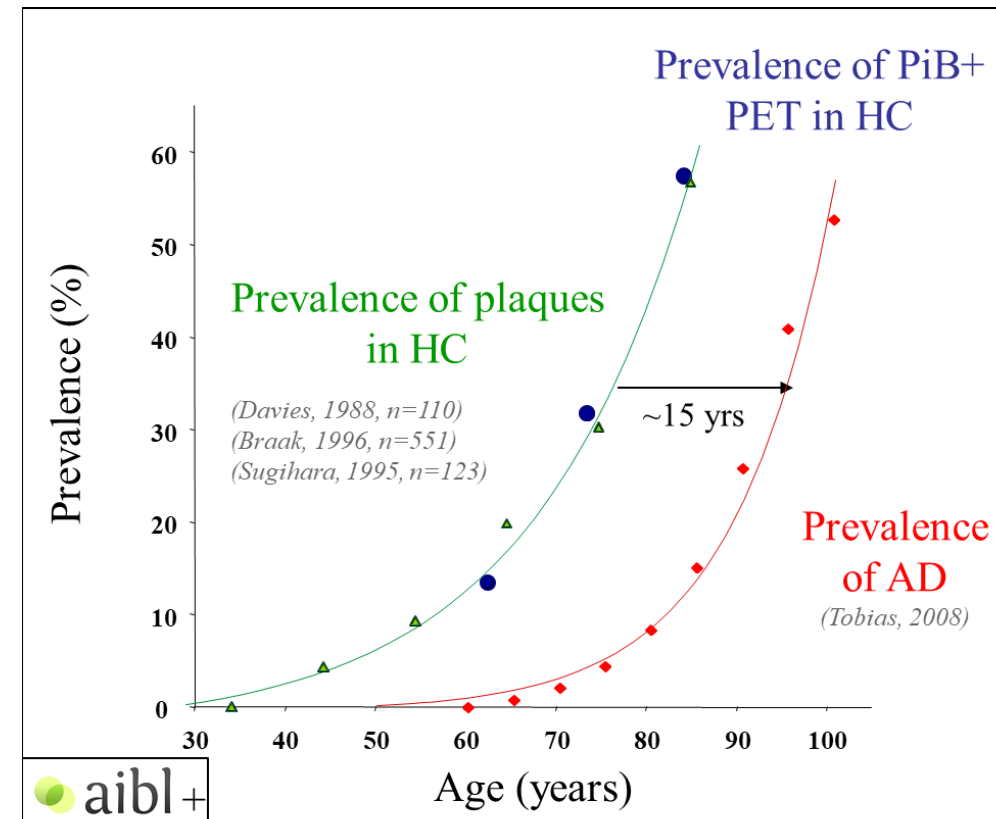
#1 We are treating way too late in the disease and there is so much more injury this won't reverse



- We know that the buildup of amyloid plaques precedes memory decline by 10 to 20 years

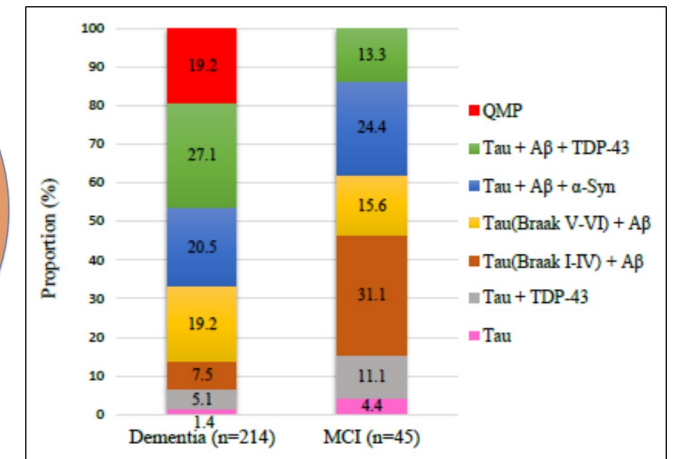
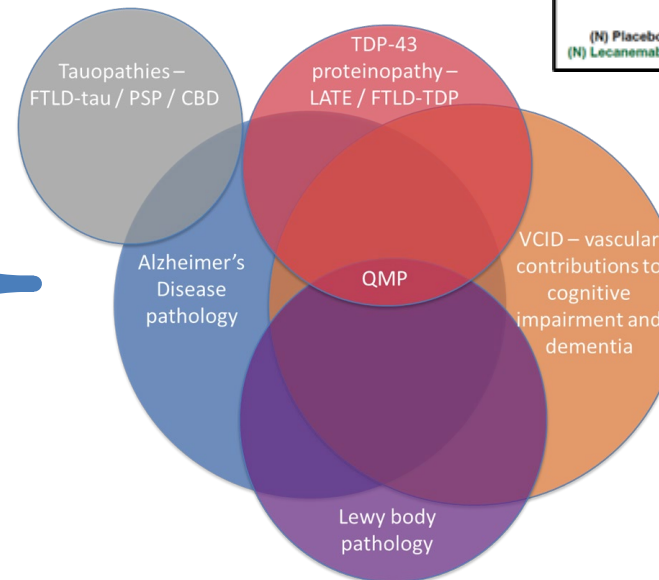
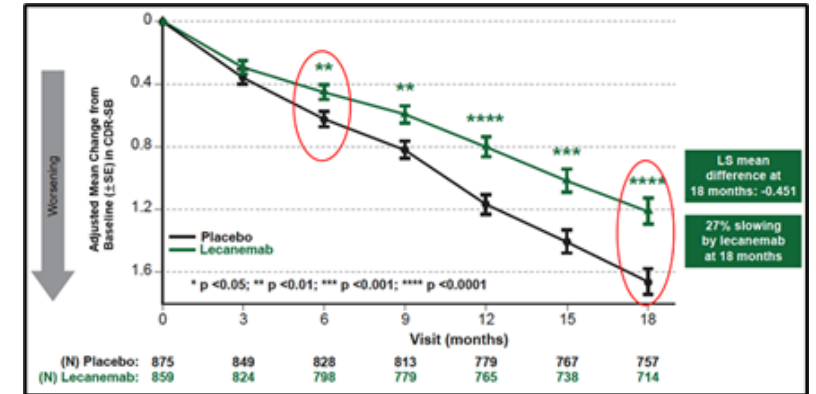
AHEAD
STUDY

Enrolling
now at UK
and across
the globe!

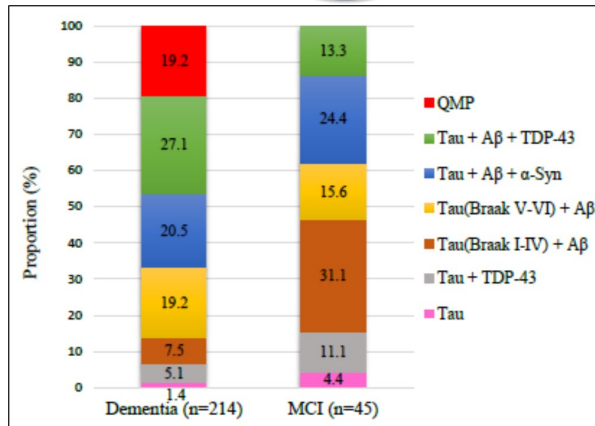
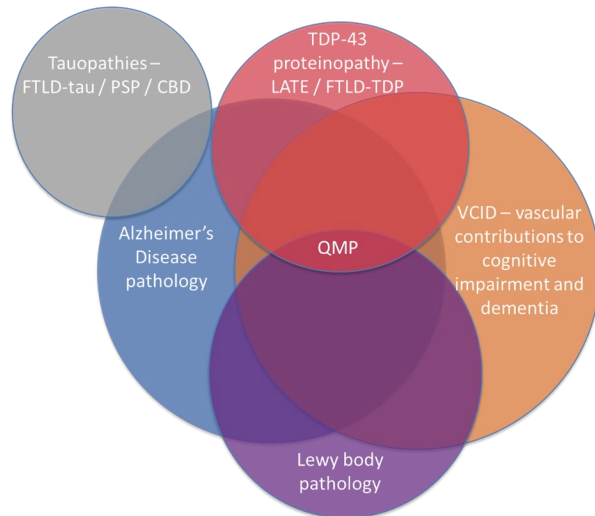


Why do we need to have targets other than A β ?

1. Treating only A β only slows AD by ~30% and that is not enough
2. We are only treating the A β & most cases of MCI and dementia are mixed disease states
3. *"Pure" AD is only 27% to 40% of the pathology found in most MCI and or dementia cases at autopsy*

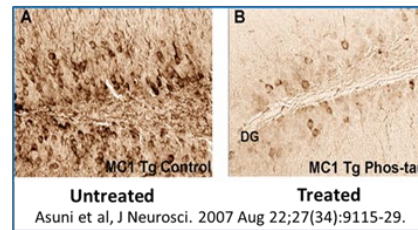


What other medicines can we potentially add to A β agents?



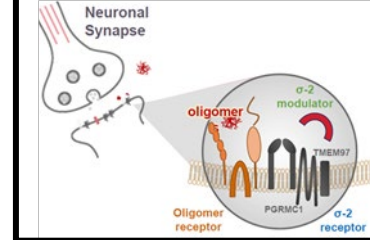
Karanth et al., JAMA Neurol. 2020;e201741

Targeting tau and tangles?

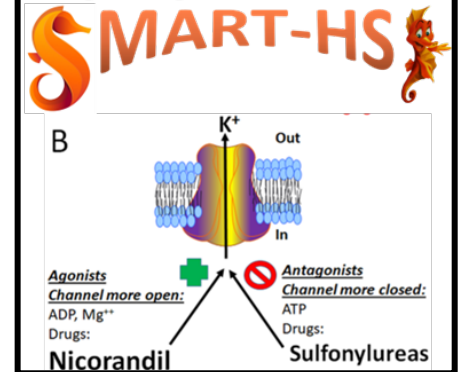


It works in mouseheimer's disease!

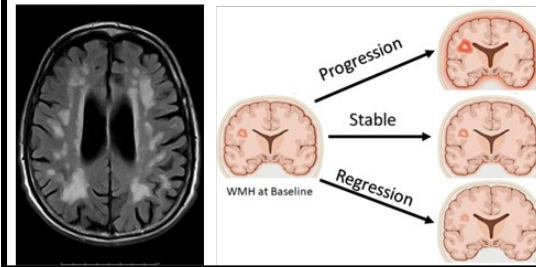
Targeting DLB?



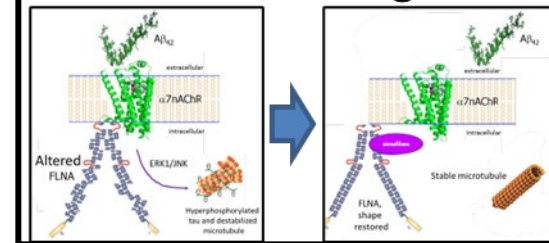
Targeting TDP-43/LATE?



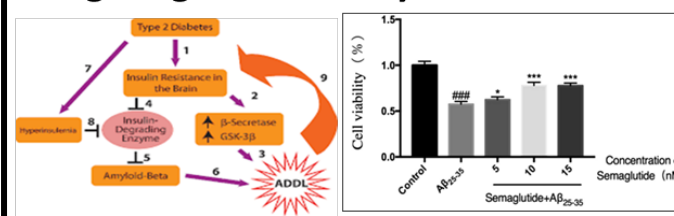
Targeting vascular disease?



Protein misfolding?



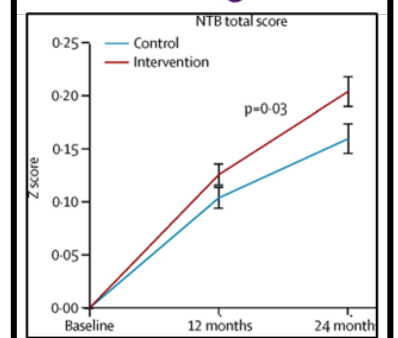
Targeting metabolic dysfunction?



As these are developed it is likely we will enter an age of "precision medicine" where treatment is unique for every individual person!

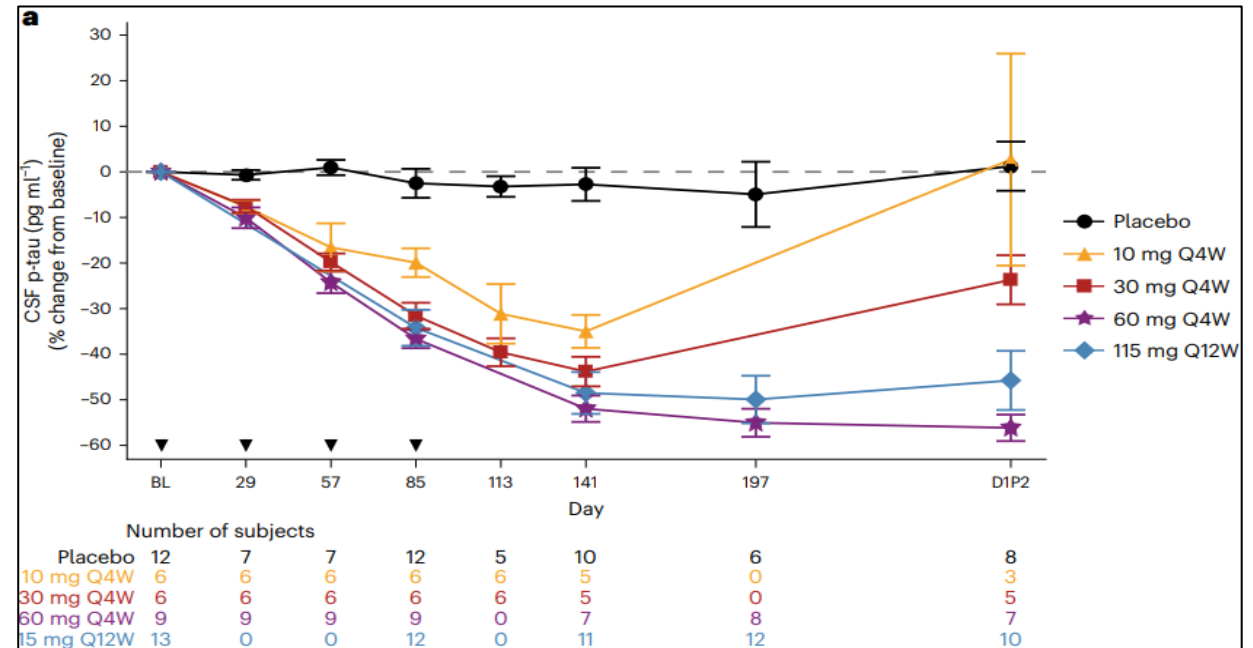
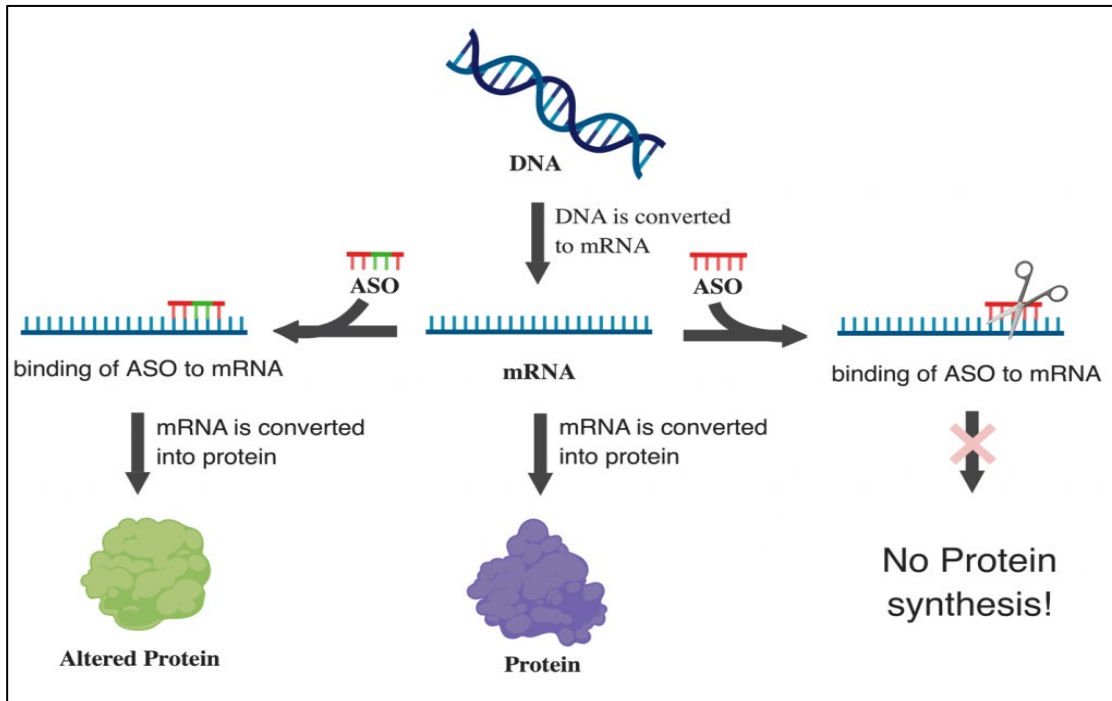
Targeting lifestyle?

U.S. POINTER
alzheimer's association



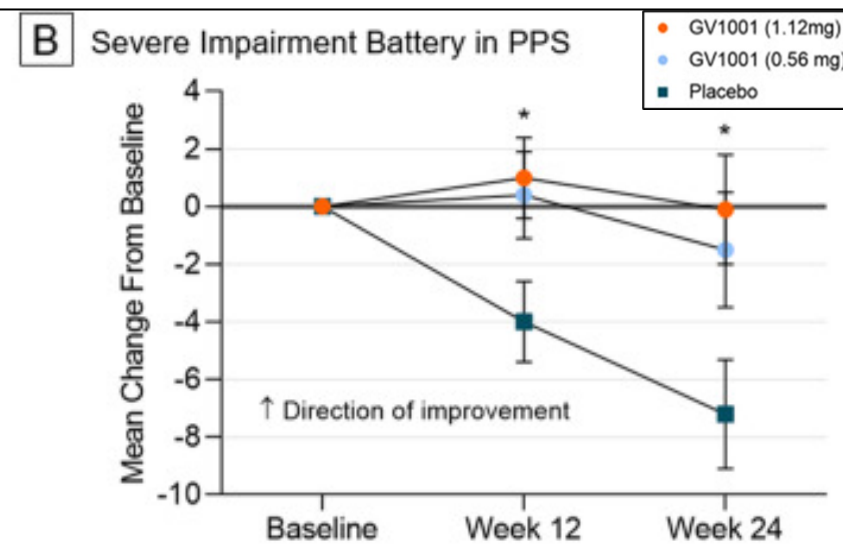
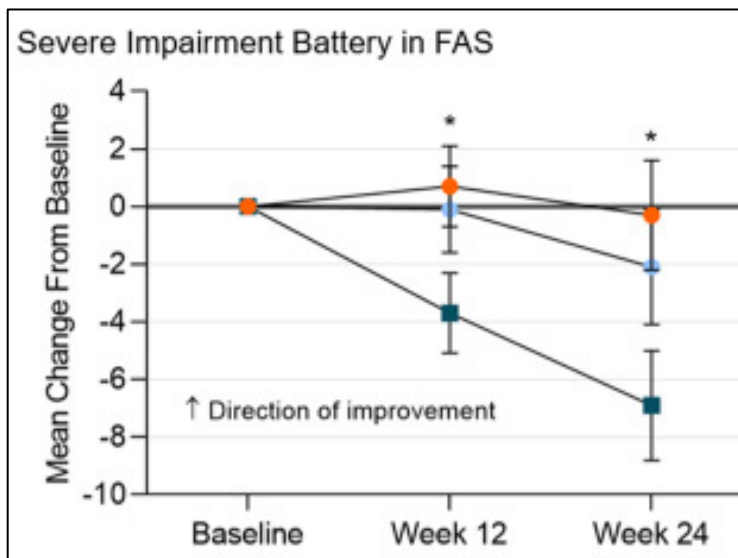
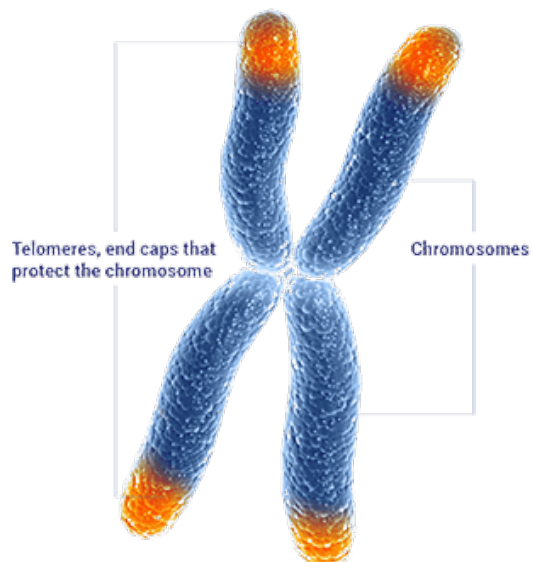
Tau antisense oligonucleotides?

- This study sought to inhibit MAPT expression with a tau-targeting antisense oligonucleotide (MAPTRx) and reduce tau levels in patients with mild AD
- A randomized, double-blind, placebo-controlled, multiple-ascending dose phase 1b trial evaluated the safety, pharmacokinetics and target engagement of MAPTRx



Mummery et al. Nat Med. 2023 Jun;29(6):1437-1447.

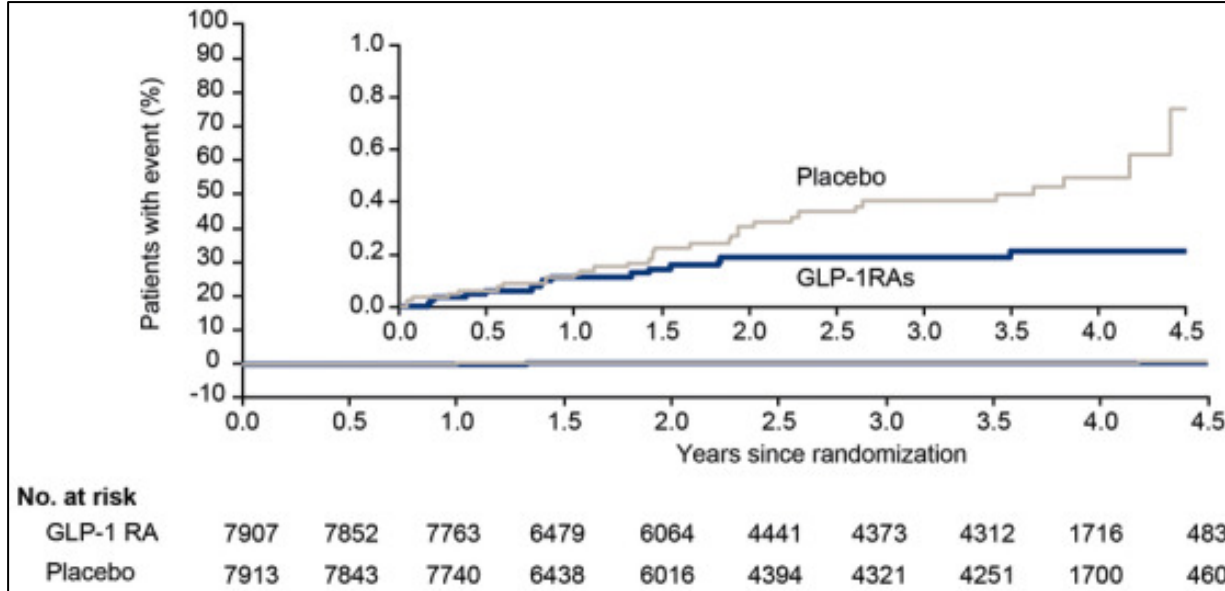
Anti-brain aging with GEM-VAX effects on telomeres?



- GV1001 is a vaccine targeting telomere effects that protects neural cells against neurotoxicity, apoptosis, and reactive oxygen species (ROS) induced by $A\beta$ and oxidative stress
- Phase 2, double-blind, parallel-group, placebo-controlled, 6-month randomized clinical trial (n=96)

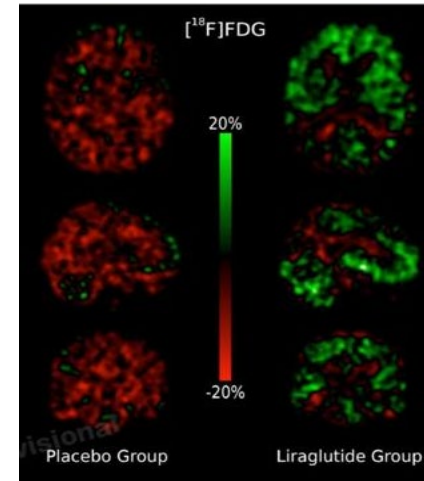
GLP1 agonists may be able to power up the brain in just 26 weeks & slow AD progression

Epidemiologic data from across the globe show reduced rates of dementia in those on a GLP-1 agonist



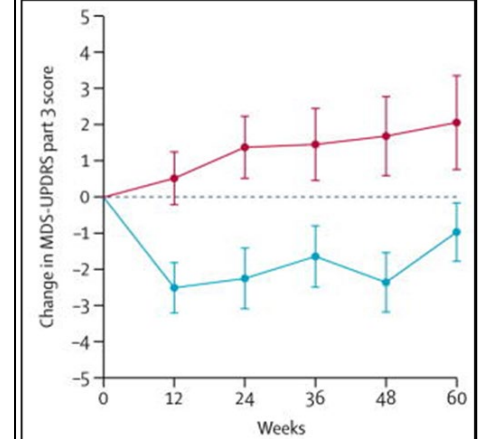
Nørgaard et al. *Alzheimers Dement* (N Y). 2022 Feb 23;8(1):e12268

- Prevents insulin resistance that lowers A β through better IDE clearance
- Reduces A β through inhibition of BACE (key enzyme that produces A β)
- Prevents tau/tangle pathology through inhibition of GSK-3 β induced hyperphosphorylation of tau



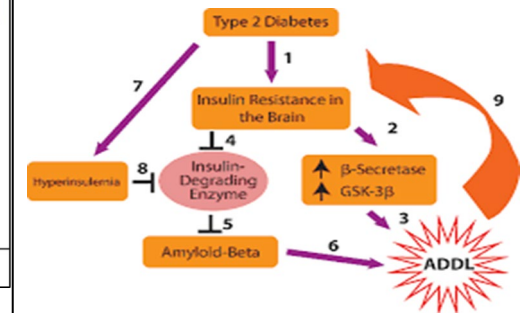
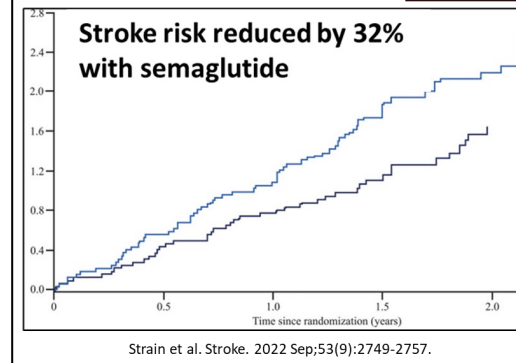
Gejl et al. *Front Aging Neurosci.* 2016 May 24;8:108.

- May also benefit Parkinson's disease
– 12 week clinical trial (n=62)



Athauda et al. *Lancet.* 2017 Oct 7;390(10103):1664-1675.

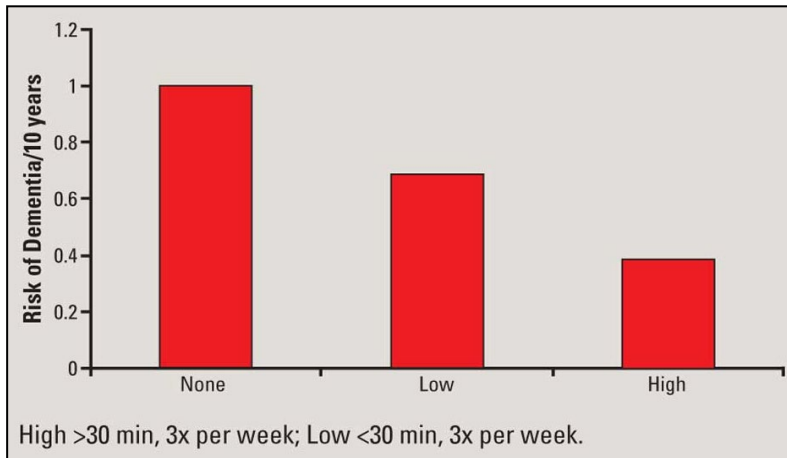
- Also reduces cerebrovascular disease risk



Exercise to prevent dementia?

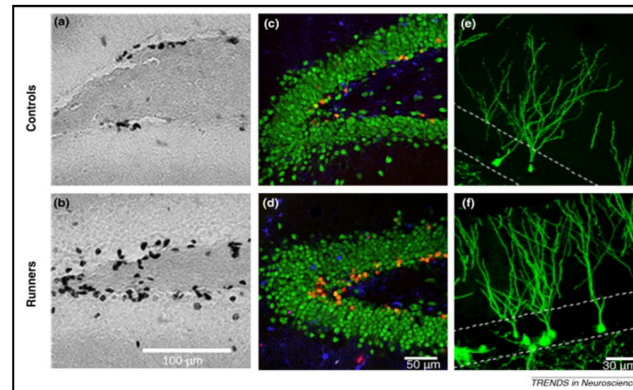


Exercise reduces risk of dementia!

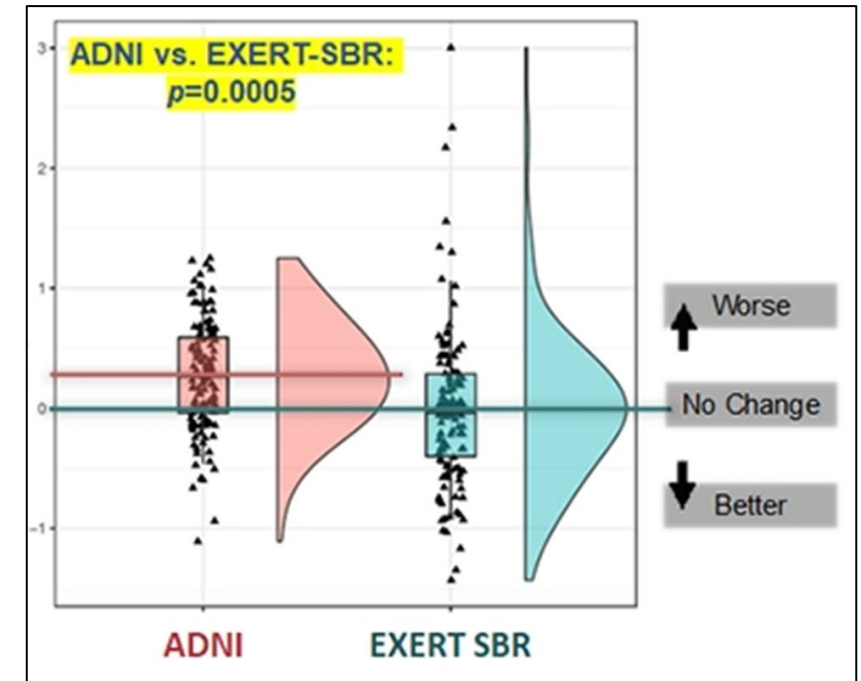


Cummings et al., Primary Psychiatry. 2008;15:2: 1-24

BDNF released by exercise can grow your brain!



Lazarov et al, Trends Neurosci. 2010;33(12):569-79

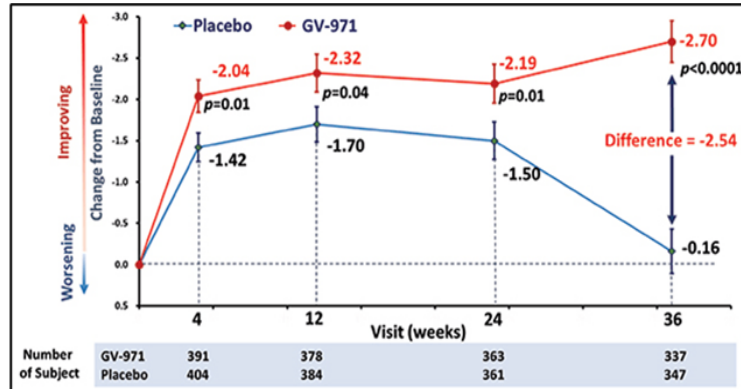
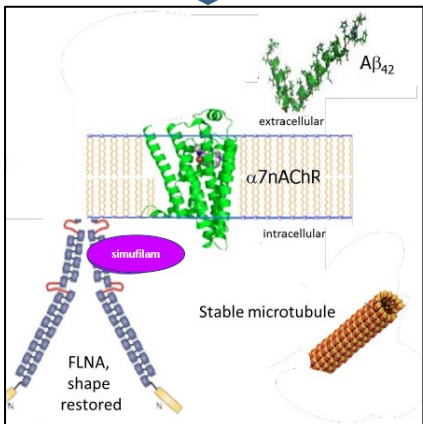
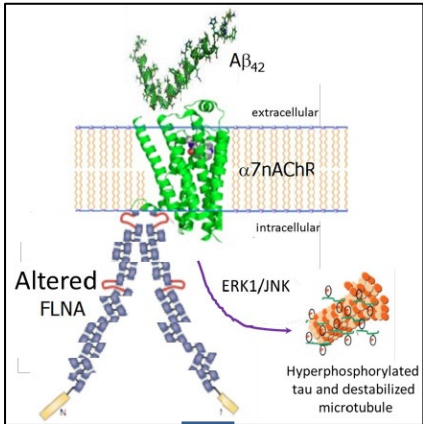


Baker et al., (2022), Alzheimer's Dement., 18: e069700.

- **Exercise trial for MCI: Aerobic exercise vs. stretching-breathing**
- **No between group differences seen over 2 years study**
- **ADNI comparison showed that stretching/breathing was most effective in reducing decline**
- **First off, this was a clearly negative trial**
- **Second, it shows that any kind of exercise is what is really important, it does not have to be high intensity aerobic workouts!**

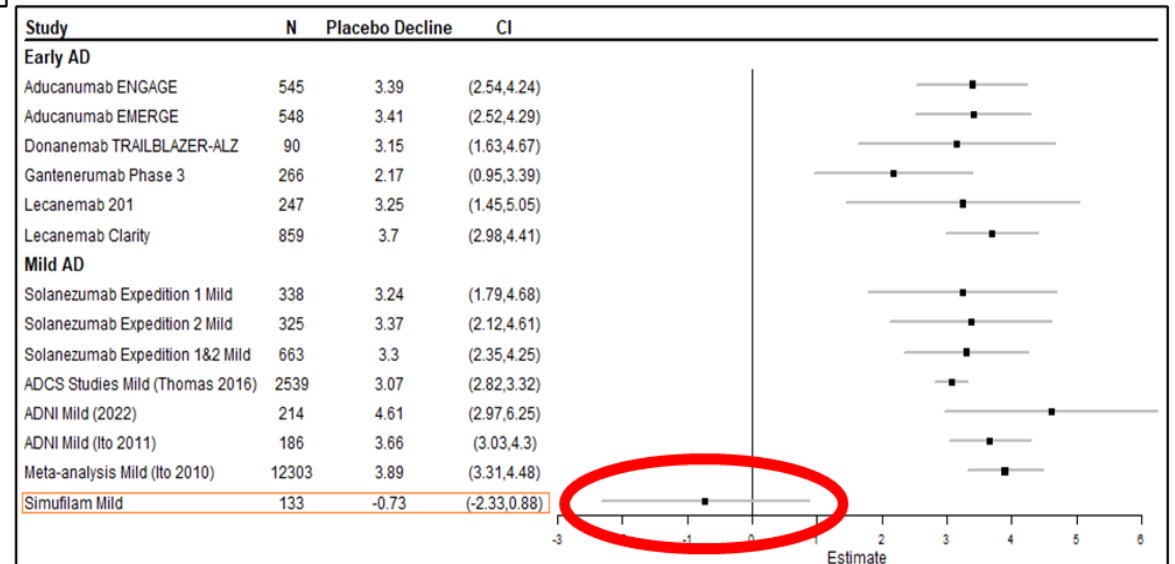
Targeting abnormal protein folding: Cassava's simufilam

Focused on correcting
altered Filamin A to
treat MCI/AD



- Phase 2 OLE data promising compared to historical data of other drugs
- No placebo group

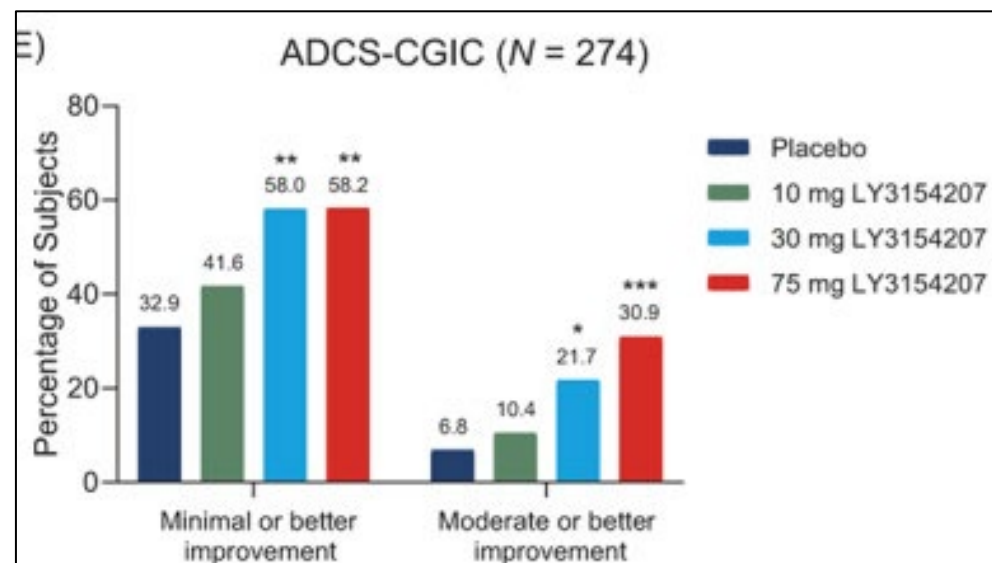
- Phase 2 data looks promising
- Major differences seen after 24 weeks of treatment



Other approaches for DLB...

PRESENCE Study (n=344)

- Mevidalen (LY3154207) is a novel modulator of the dopamine D1 receptor
- While negative results were seen overall, there was a positive dose-effect relationship



Biglan et al. Mov Disord. 2022 Mar;37(3):513-524.

AscenD-LB study (n=91)

- Neflamapimod (NFMD) is a specific p38 α kinase inhibitor, that can restore cholinergic function
- CDR-SB and TUGO test results suggest cognitive and motor benefit

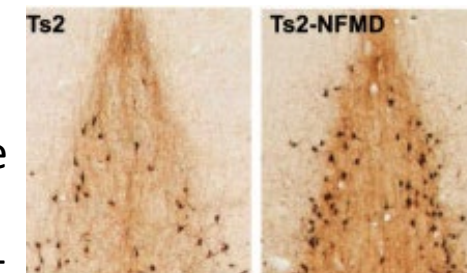


Table 2 | Efficacy outcome measures in the clinical study

Outcome measure	All Neflamapimod (NFMD; includes 40 mg BID and 40 mg TID participants) vs. All Placebo						
	Number of participants		Mean baseline values		Change from baseline		
	NFMD	Placebo	NFMD	Placebo	Drug-Placebo Difference On-Study (95% CI)	p-value	Cohen's d Effect Size for Improvement - <i>d</i>
NTB* Composite	39	37	0.04	0.05	0.04 (-0.11, 0.19)	>0.2	0.10
Attention Composite	39	36	0.04	-0.02	0.14 (-0.06, 0.35)	0.17	0.18
Clinical Dementia Rating Sum of Boxes (CDR-SB)	41	42	4.9	5.1	-0.45 (-0.83, -0.06)	0.023	0.31
International Shopping List Test (ISLT)	42	42	14.3	13.6	-0.17 (-1.61, 0.87)	>0.2	-0.02
Timed Up and Go (TUG)	39	38	12.7	13.5	-1.4 (-2.7, -0.1)	0.044	0.22

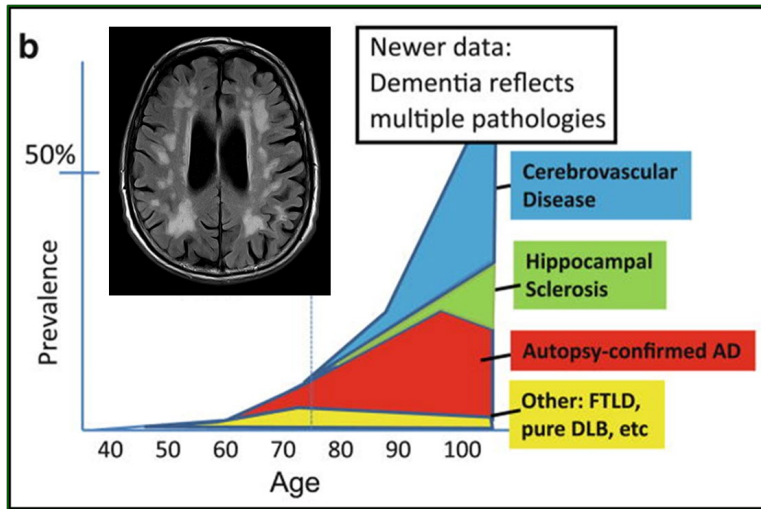
*NTB: Neuropsychological Test Battery evaluating attention, executive function, and visual learning.

The NTB was the primary outcome measure. NTB and Attention composites reported as z-scores.

Note: Difference (95% confidence interval, CI) shown is from MMRM (mixed model for repeated measures) analysis. Improvement is reflected as increases in NTB, Attention Composite and the ISLT and as decreases in CDR-SB and TUG test. Positive d indicates improvement relative to placebo, and negative d indicates worsening relative to placebo.

Jiang Yet al. Nat Commun. 2022 Sep 21;13(1):5308.

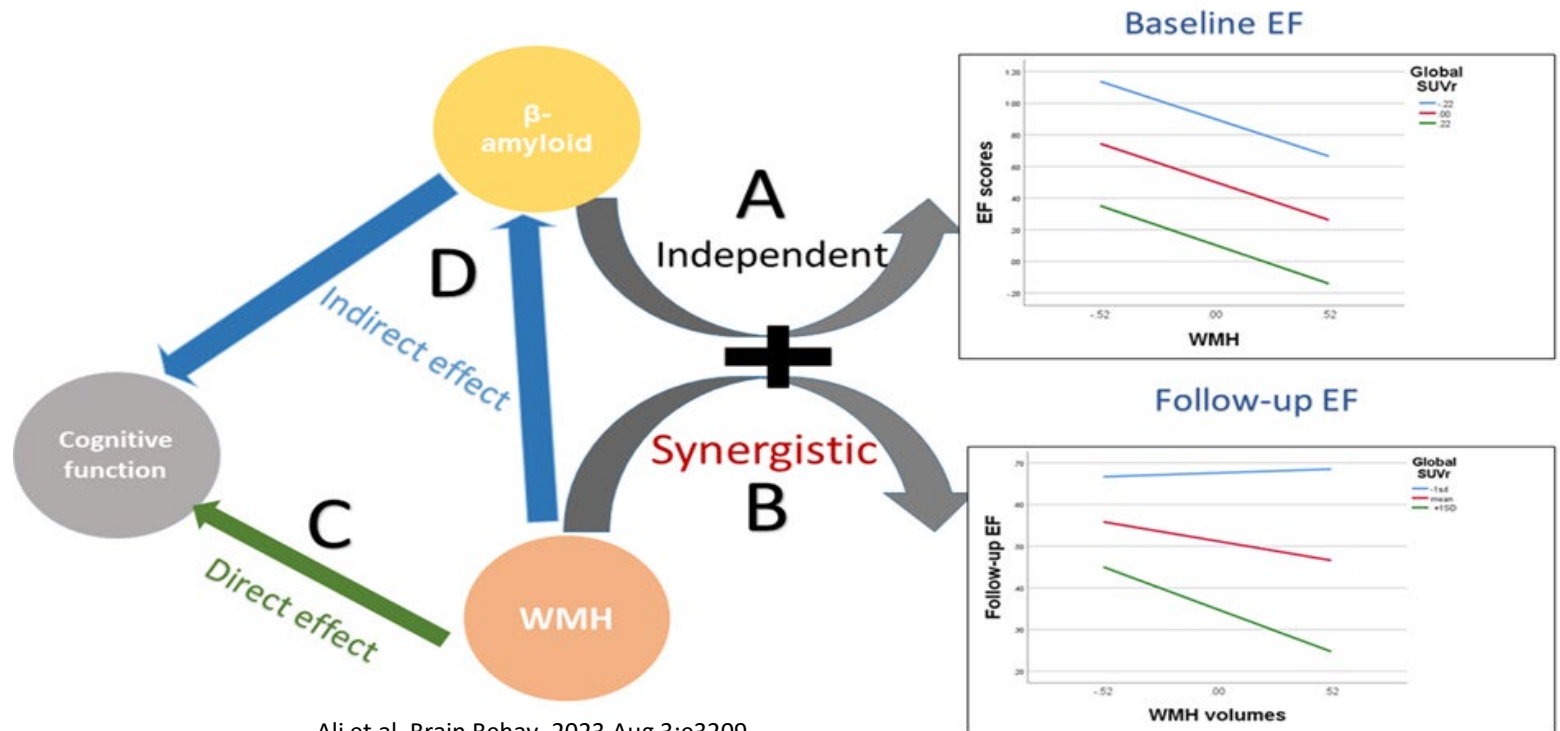
Vascular Cognitive Impairment & Dementia: “Hardening of the arteries”



Nelson et al., J Neuropathol Exp Neurol. 2012
May;71(5):362-81

We know that:

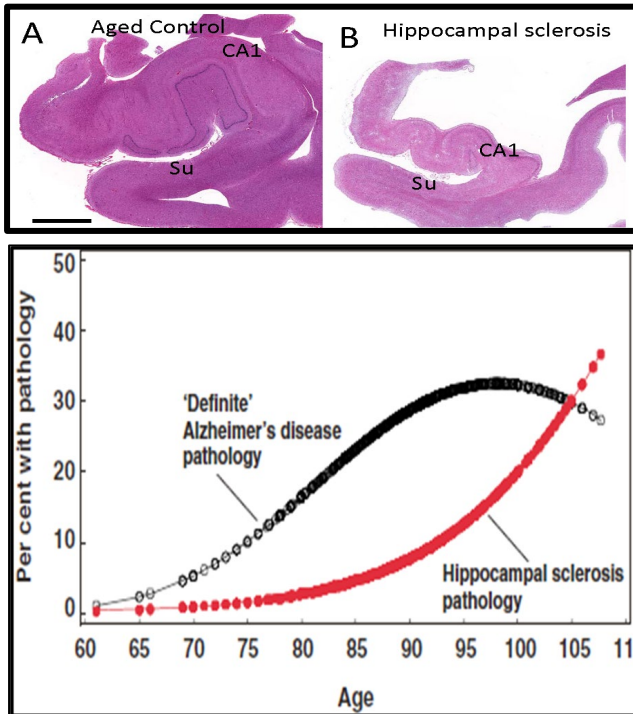
- Hypertension is the #1 risk for this hardening of the arteries
- It is just as devastating as Alzheimer's disease



Ali et al. Brain Behav. 2023 Aug 3:e3209.

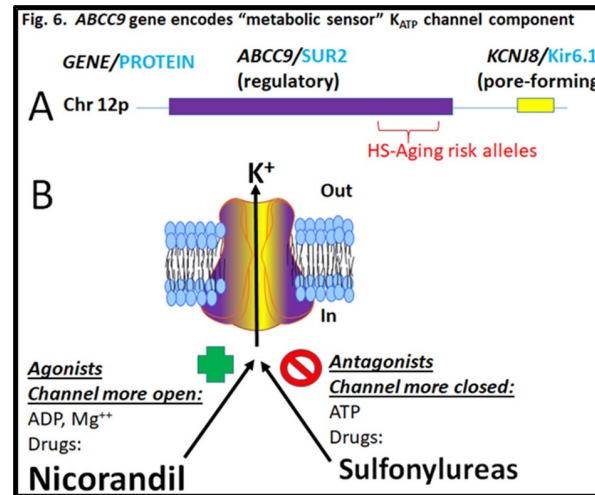
- WMH & AD affect cognition independently in the early stages of disease when VCID & AD are found in isolation
- But, WMH axonal injury increases A β as the disease progresses fueling an AD storm!

LATE Disease (TDP-43) is a major mimic & contributing pathology in AD for advanced aging



Nelson et al., Brain. 2011 May;134(Pt 5):1506-18

- 1 in 5 cases of AD are actually LATE, not AD path
- LATE is comorbid with AD in nearly 50% of cases



- LATE is linked to defects in a potassium channel
- Nicorandil is an available medication that can turn these channels back on!
- While not available in the US, the FDA has granted an IND to study this!

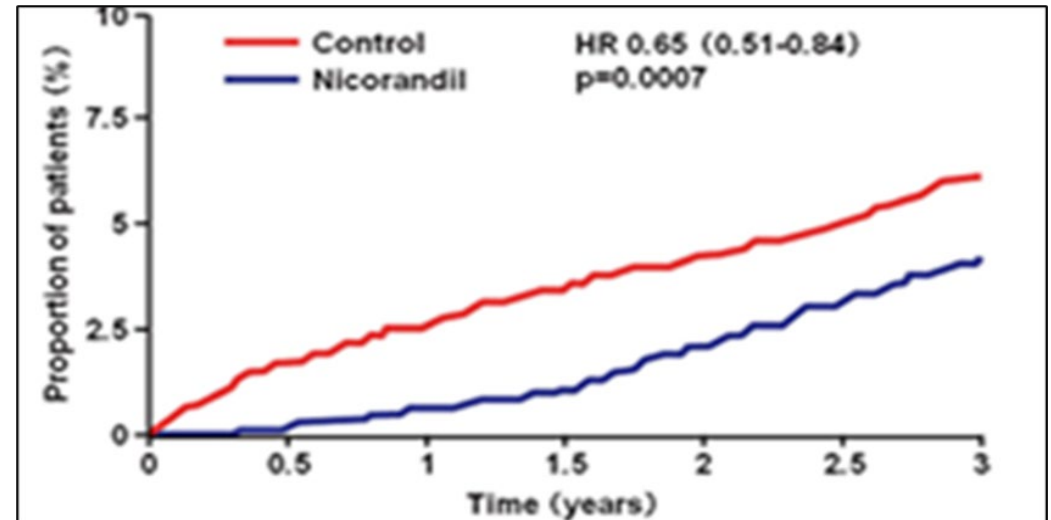
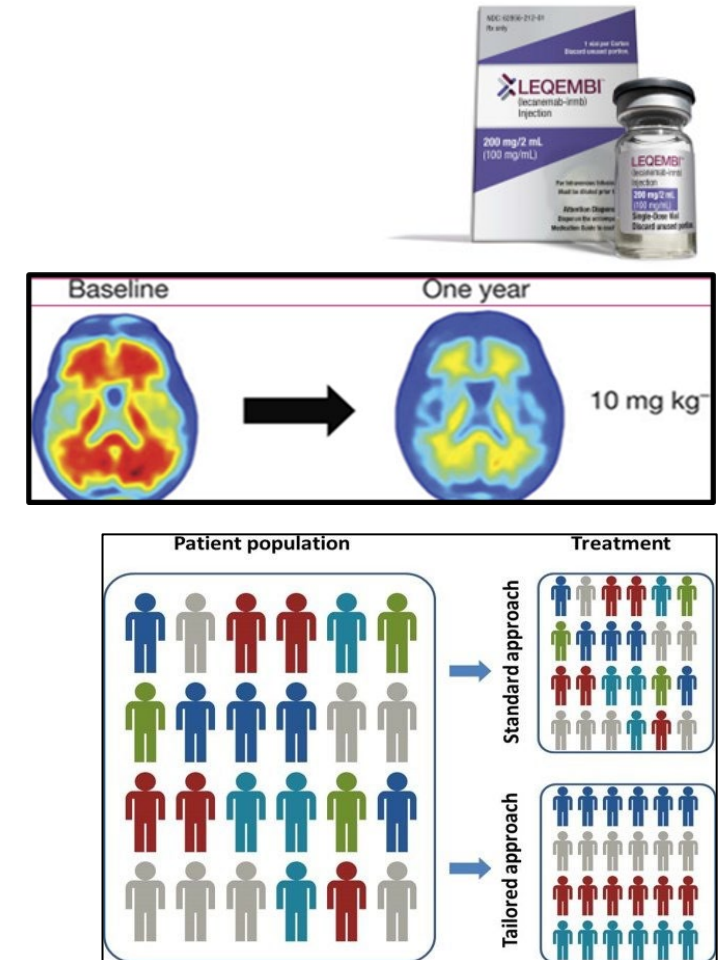


Fig. 13. Fig. 1 from Horinaka et al (24), Cumulative incidence of the primary endpoint, deaths from all causes. HR, hazard ratio. N=5,116.



So, what impact do the new anti-amyloid therapies have on current & future clinical trials & care?

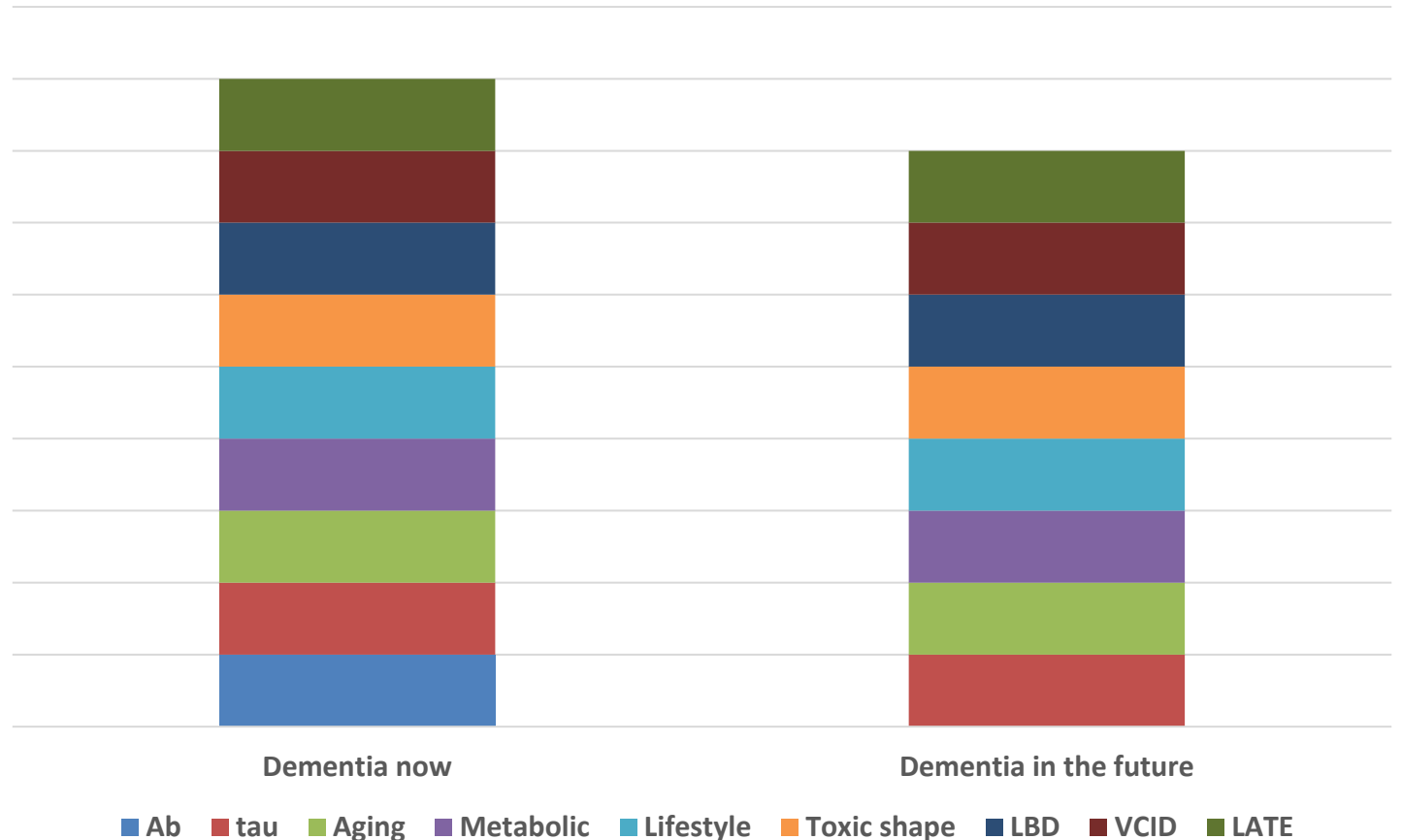
- We have dozens of patients on lecanemab already, many for over 7 years now
- “The first person to be cured of Alzheimer’s disease will be in a clinical trial” *Dr. J 2012*
- We still need to do better, and as we have seen, each successive generation of new experimental medicines brings us safer medicines that move us closer to the cure we are looking for!
- Many that are not eligible for Lecanemab or donanemab may still be eligible for these treatments
- It remains unclear how the field will begin to adapt to combination therapy with experimental medicines that are needed as we move towards precision medicine!



What if we slow or stop A β ?

If we can slow or stop:

- A β
- Tau
- Aging
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43

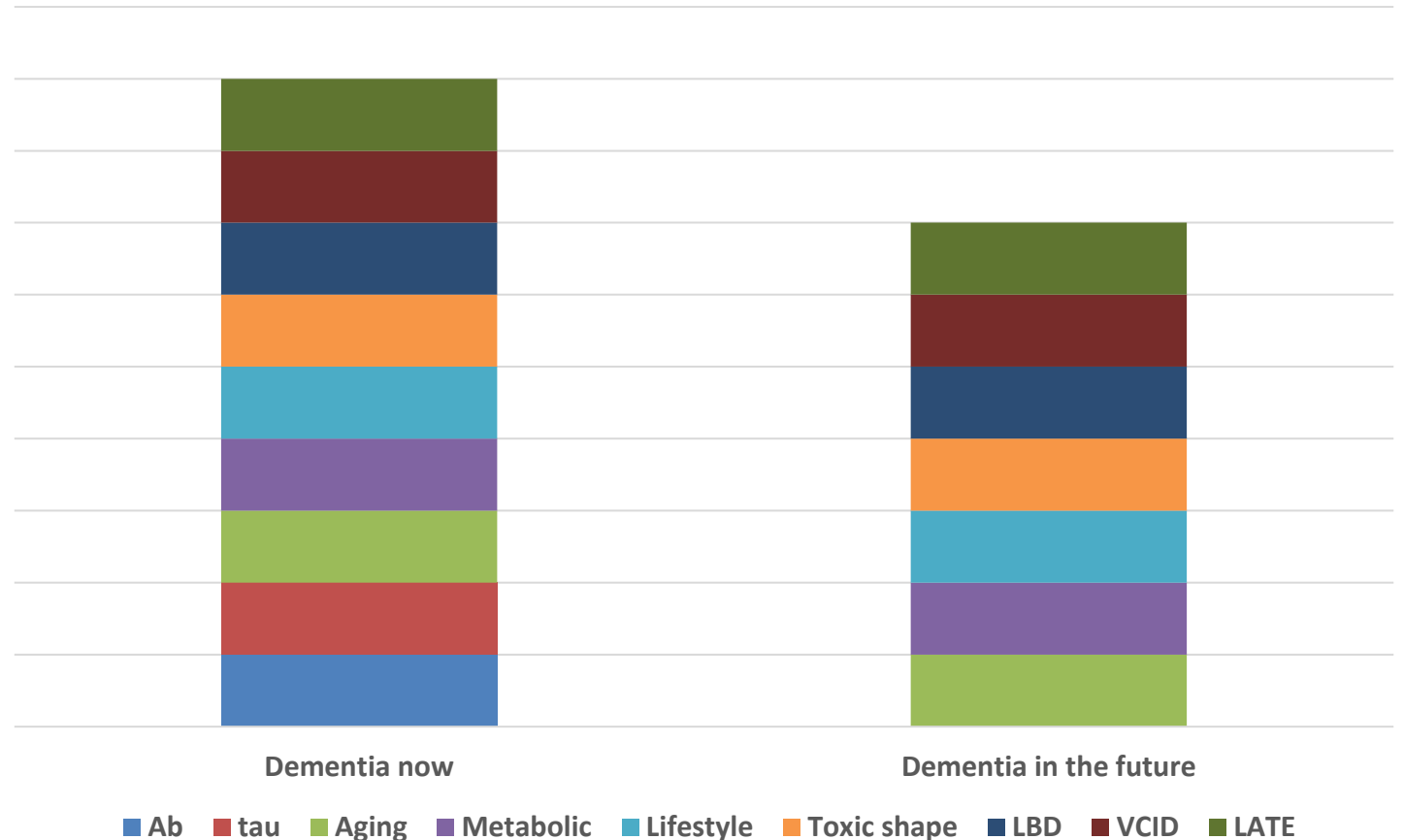


What if we could slow or stop tau too?

If we can slow or stop:

~~• A β~~

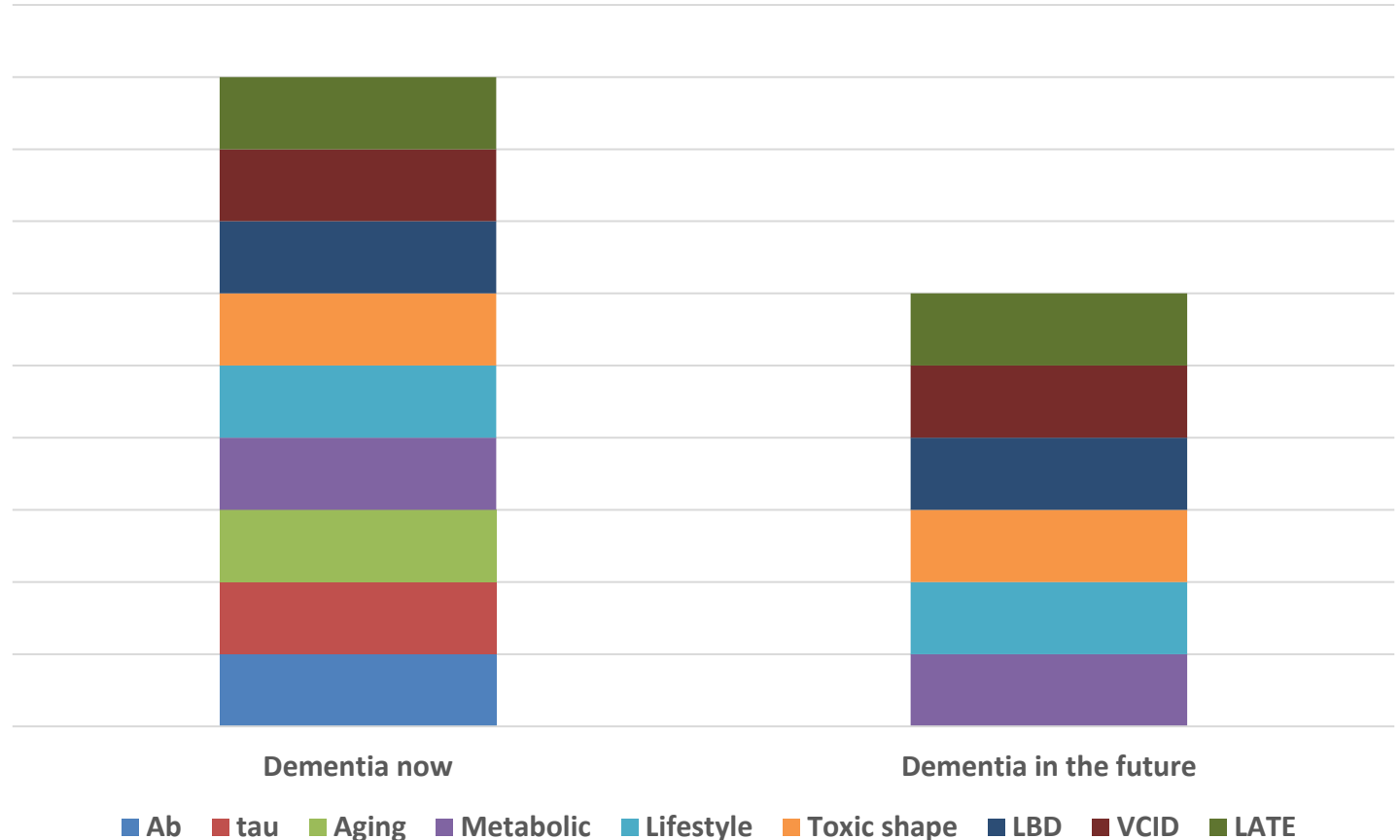
- Tau
- Aging
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



What if we could slow or stop aging too?

If we can slow or stop:

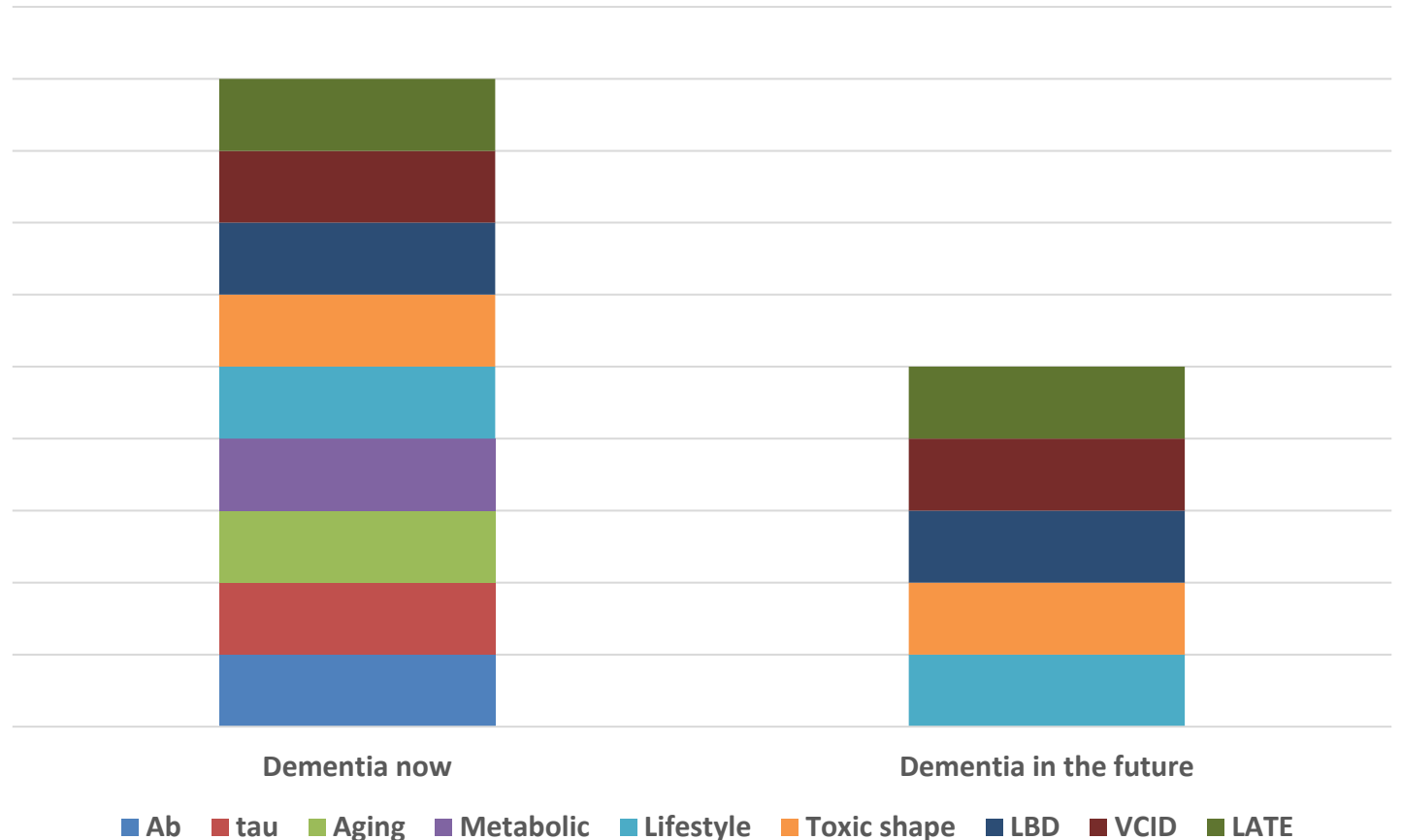
- ~~• A β~~
- ~~• Tau~~
- Aging
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



What if we could slow or stop metabolic dysfunction too?

If we can slow or stop:

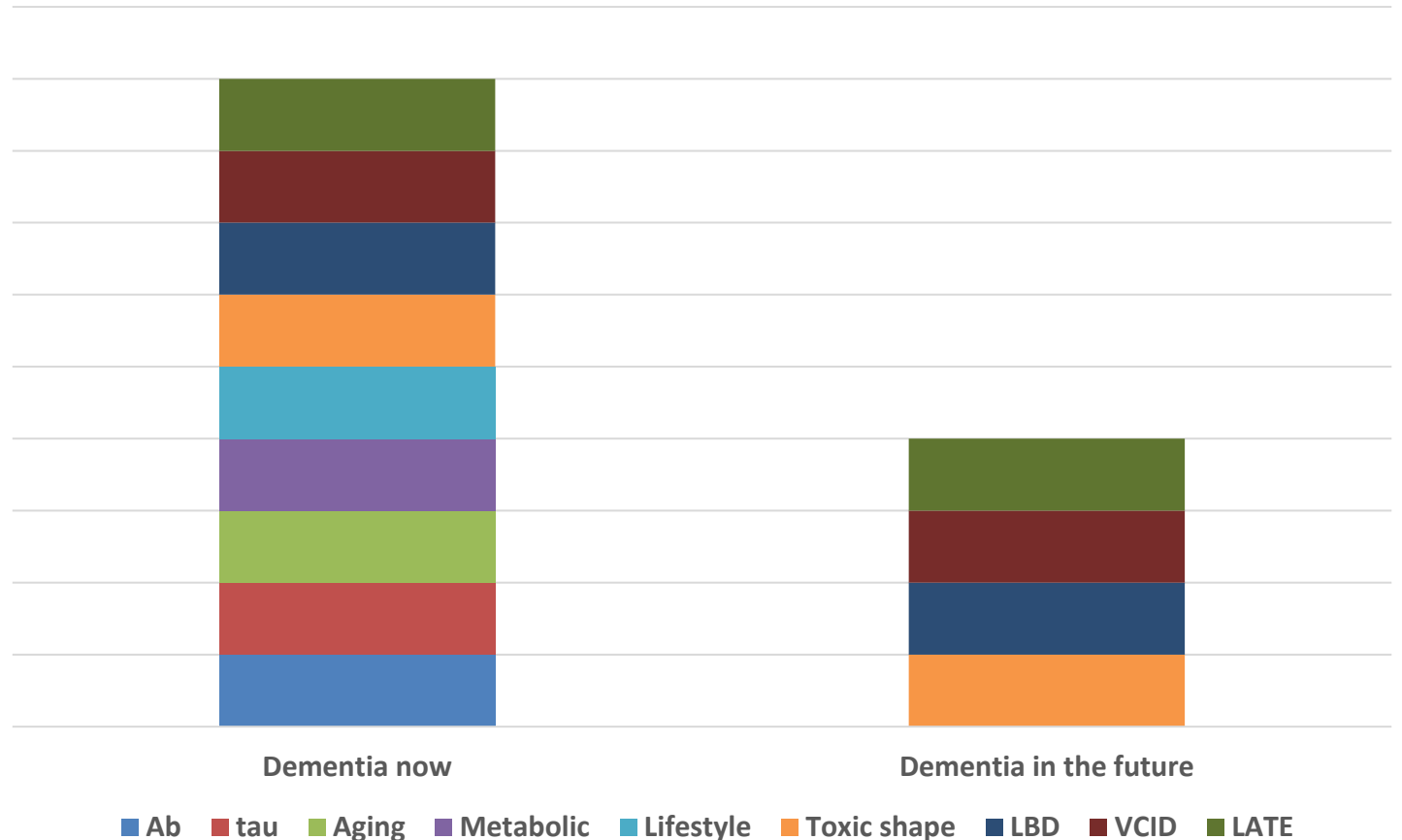
- ~~• A β~~
- ~~• Tau~~
- ~~• Aging~~
- Metabolic dysfunction
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



What if we could slow or stop negative lifestyle impacts too?

If we can slow or stop:

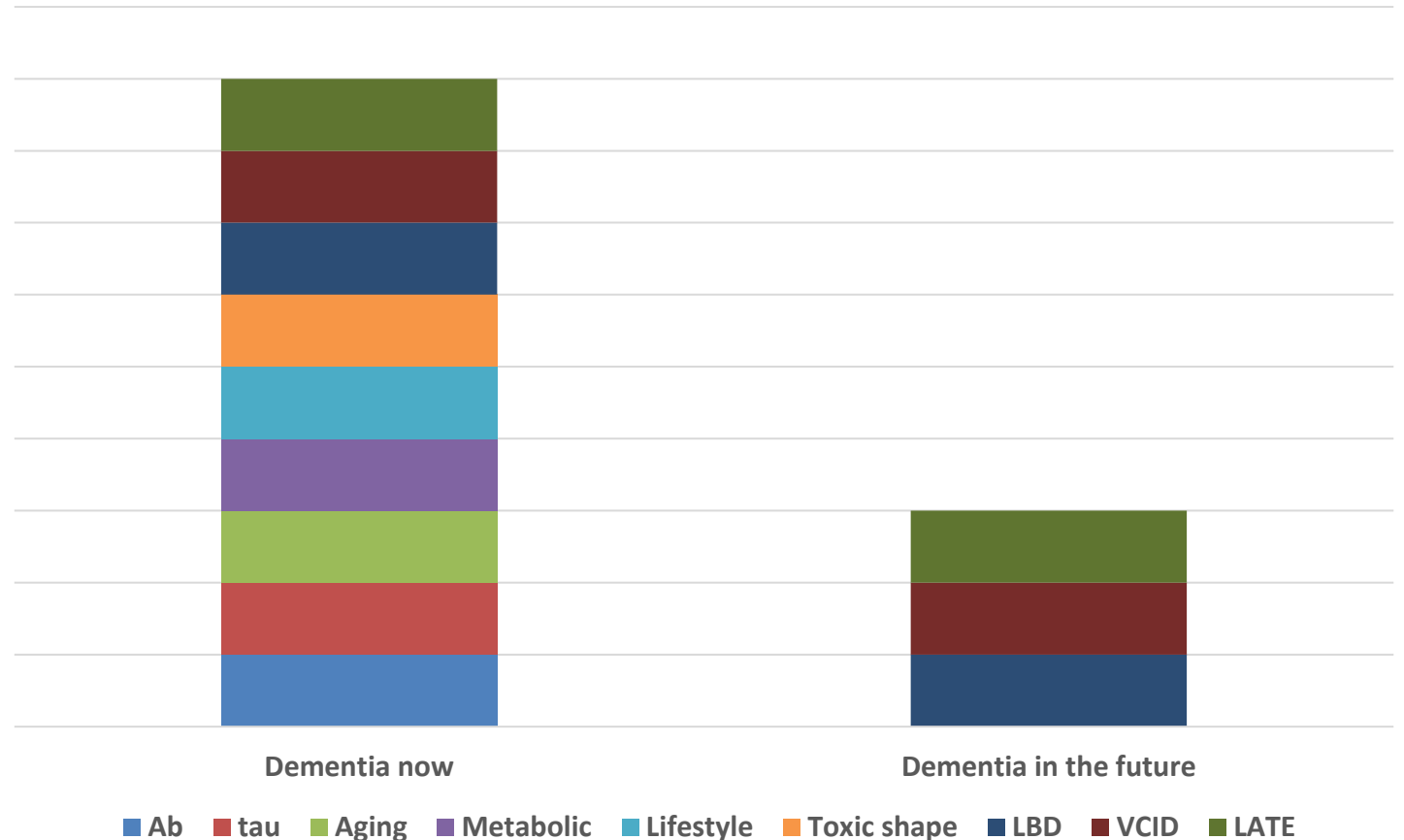
- ~~• A β~~
- ~~• Tau~~
- ~~• Aging~~
- ~~• Metabolic dysfunction~~
- Lifestyle impacts
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



What if we could slow or stop toxic protein shapes too?

If we can slow or stop:

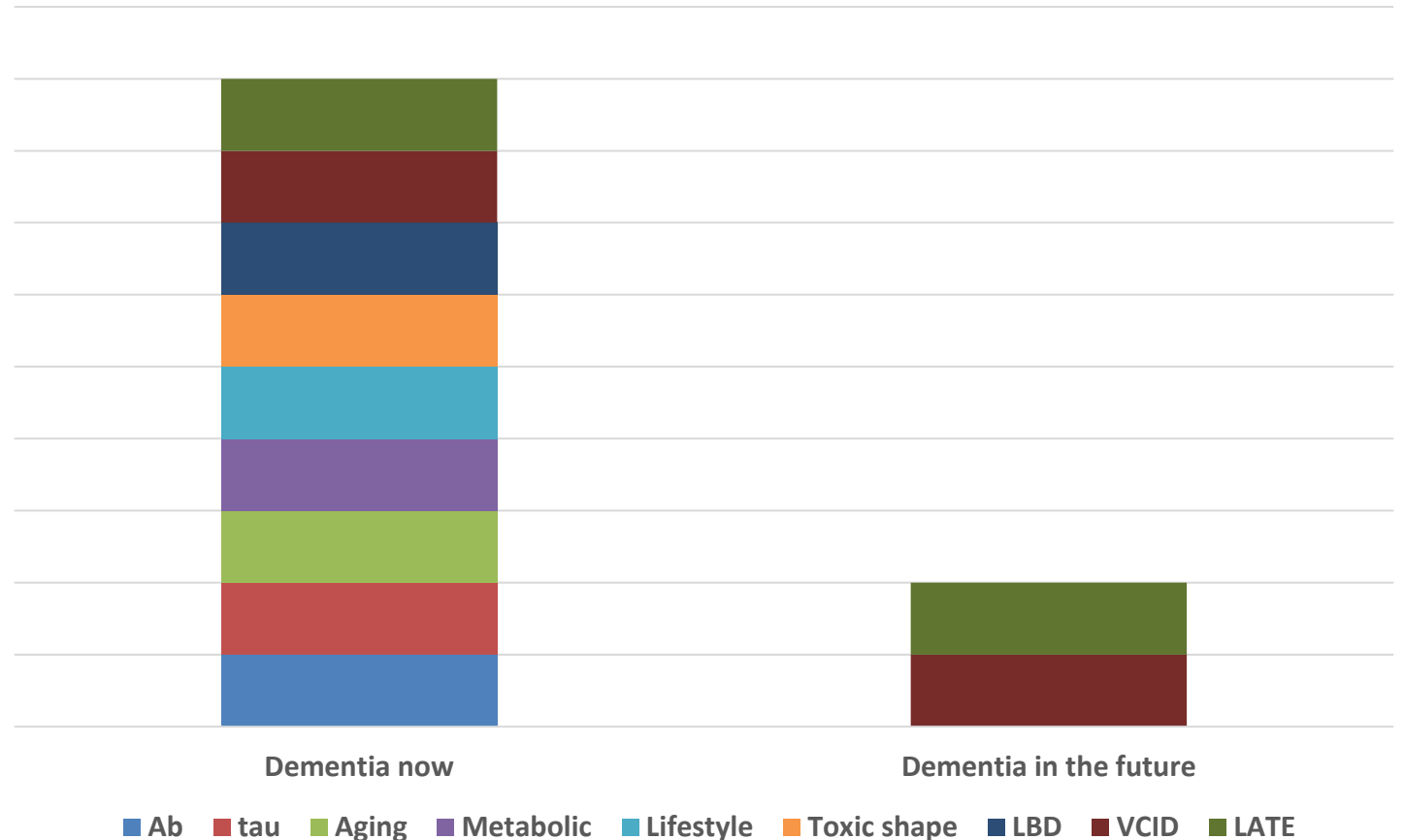
- ~~• A β~~
- ~~• Tau~~
- ~~• Aging~~
- ~~• Metabolic dysfunction~~
- ~~• Lifestyle impacts~~
- Toxic protein shapes
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



What if we could slow or stop Lewy bodies too?

If we can slow or stop:

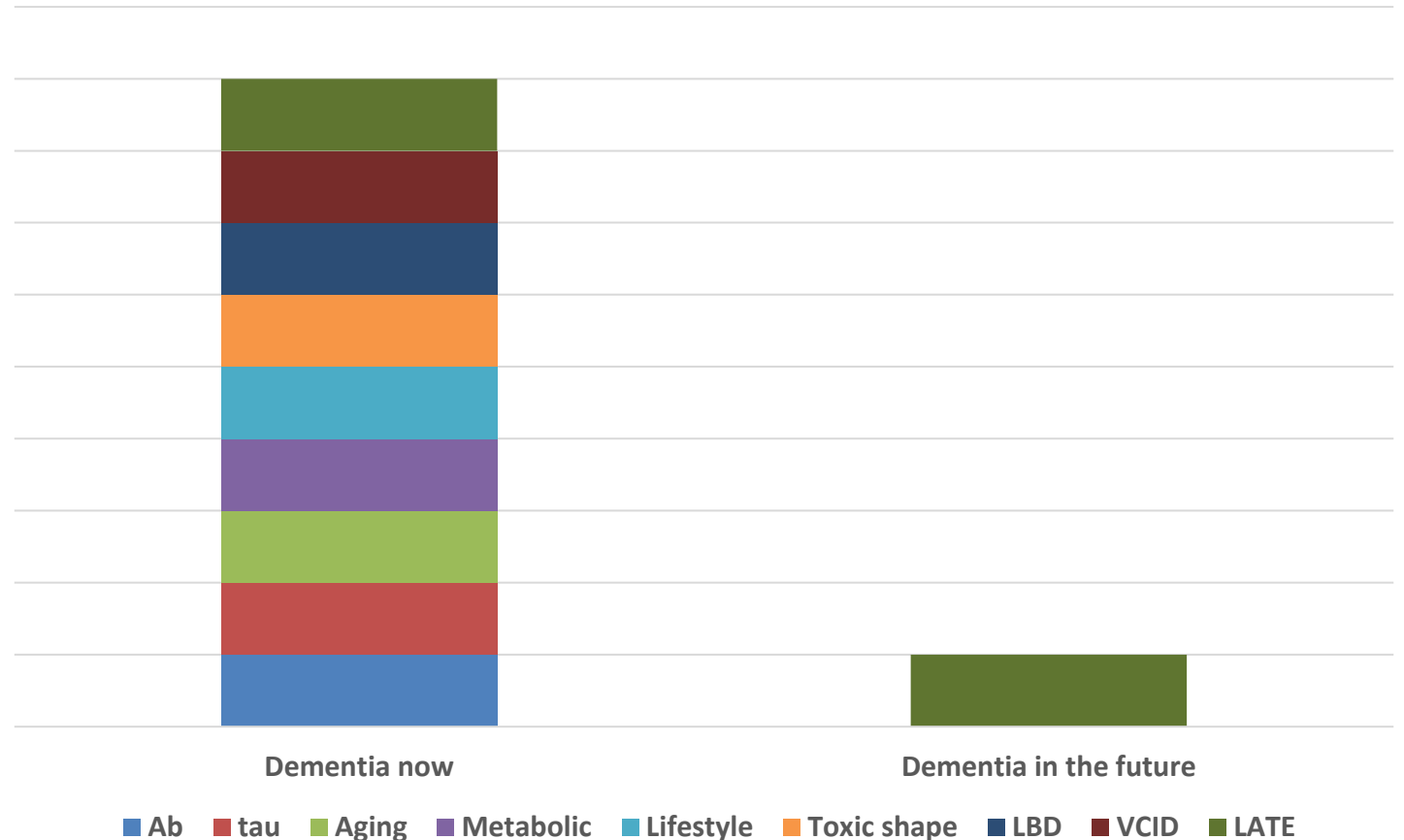
- ~~• A β~~
- ~~• Tau~~
- ~~• Aging~~
- ~~• Metabolic dysfunction~~
- ~~• Lifestyle impacts~~
- ~~• Toxic protein shapes~~
- Lewy Bodies
- Cerebrovascular disease
- LATE/TDP-43



What if we could slow or stop VCID too?

If we can slow or stop:

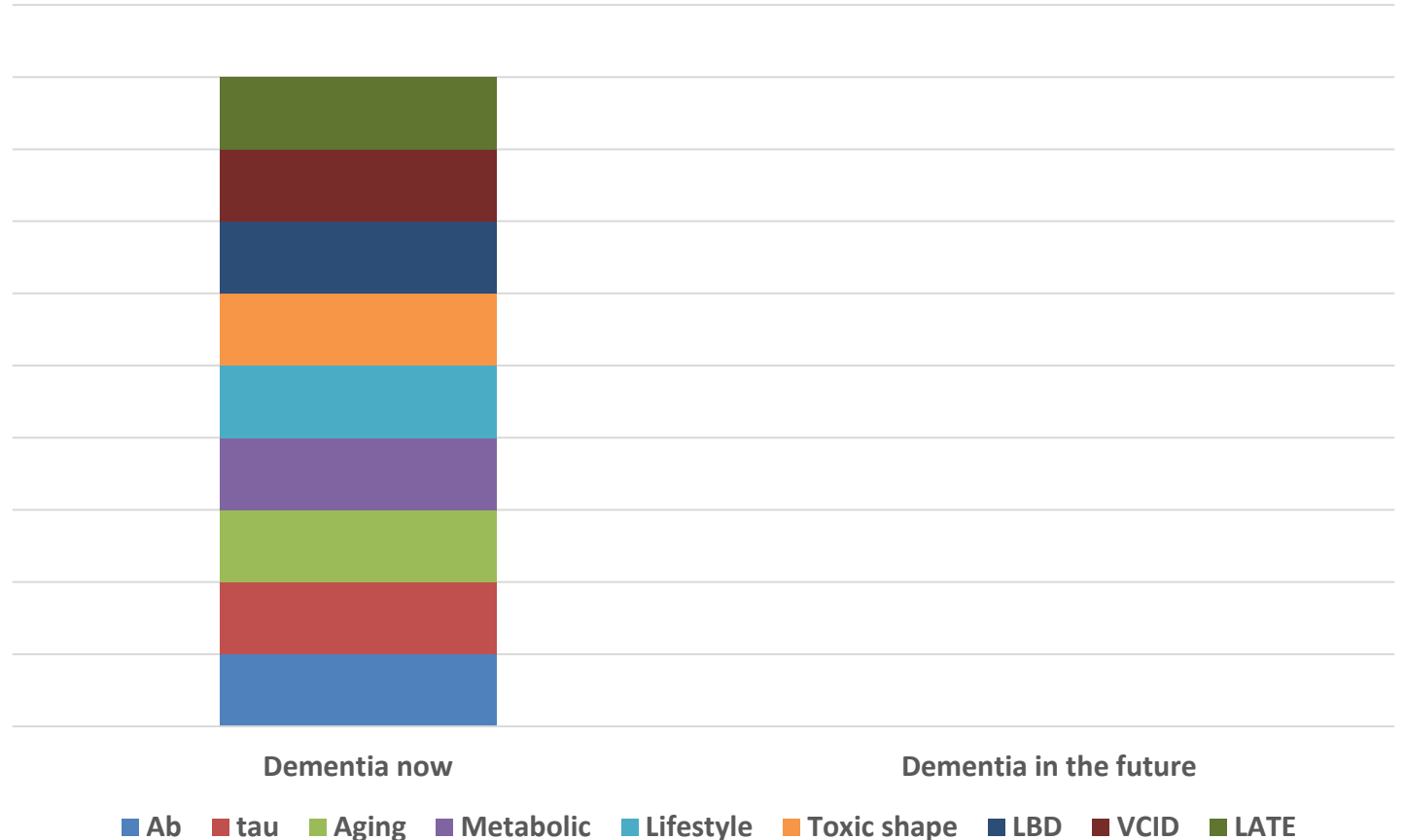
- ~~• A β~~
- ~~• Tau~~
- ~~• Aging~~
- ~~• Metabolic dysfunction~~
- ~~• Lifestyle impacts~~
- ~~• Toxic protein shapes~~
- ~~• Lewy Bodies~~
- Cerebrovascular disease
- LATE/TDP-43



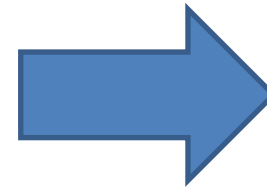
What if we could slow or stop LATE/TDP-43 too?

If we can slow or stop:

- ~~• A β~~
- ~~• Tau~~
- ~~• Aging~~
- ~~• Metabolic dysfunction~~
- ~~• Lifestyle impacts~~
- ~~• Toxic protein shapes~~
- ~~• Lewy Bodies~~
- ~~• Cerebrovascular disease~~
- LATE/TDP-43



Hey wait a minute...



On the other hand, this is worth it!

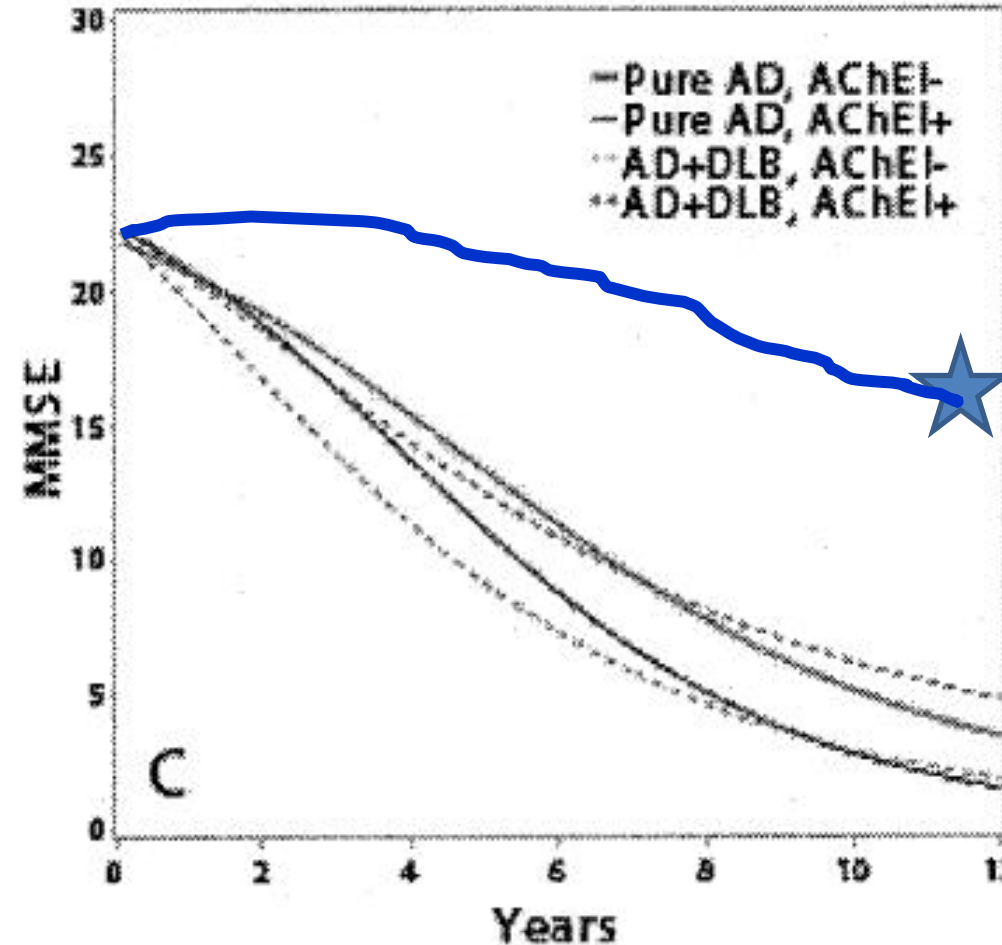
So why would you, or your patients/friends/family want to get involved?

- **Most of these are still experimental**
- **There is always the chance that:**
 - They won't work...
 - That you could get the placebo...
 - That this could make things worse...



Why indeed?

- These medicines are based on state-of-the-art science
- Even in the placebo arm there is benefit of enhanced care & patients do better
- Safety is always first and foremost



- My patient X has been receiving lecanumab for 10 years now
- Let's look at where he is now?
- He did this for himself!
- He did this for his children!
- Where would he be if he had waited for drug approval?
- Maybe its just a fluke?

What's next?

Other experimental therapies?

- There are over 100 potential new treatments including possible cures being investigated
- The Wisconsin ADRC is at the leading edge of this research
- Right here! Right now!
- The time to get involved is now!

