

Lessons Learned in Alzheimer's & Dementia Prevention

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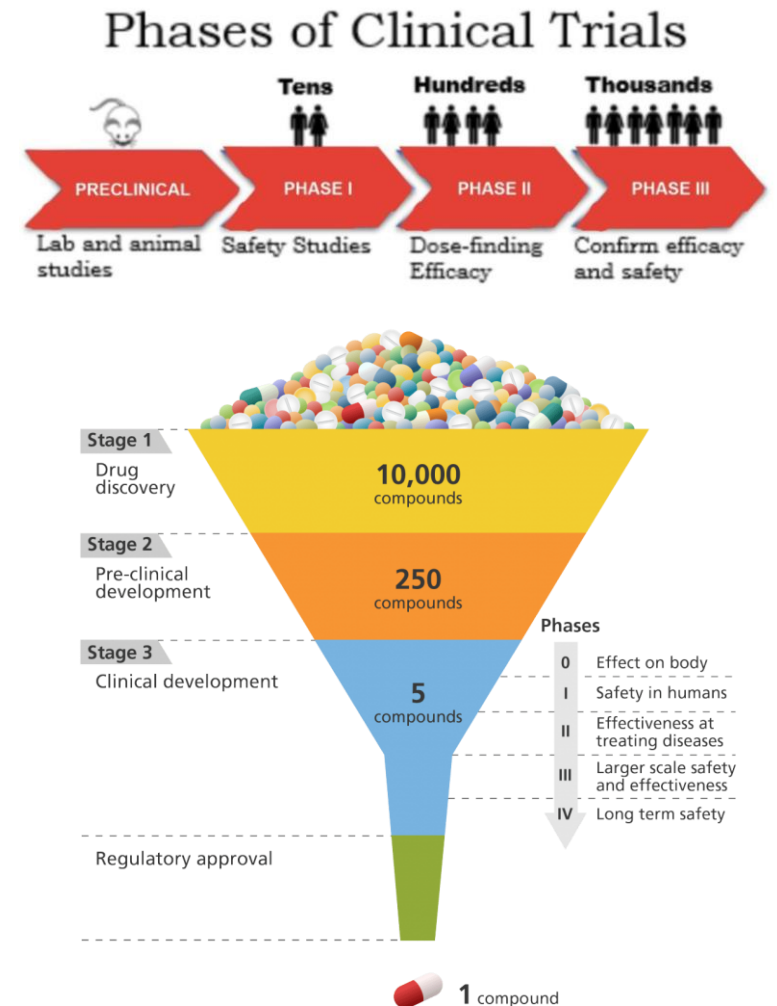
Sometimes you do everything right...

- **But, it still can go wrong!**
- **Alzheimer's and other types of dementia are coming for us all**
- **Please try and develop a brain healthy lifestyle as you learn from the many presentations and exhibitors here at the Mind Matters Brain Health Fair**
- **But, if you are at risk (and we all are), much more may be needed...**

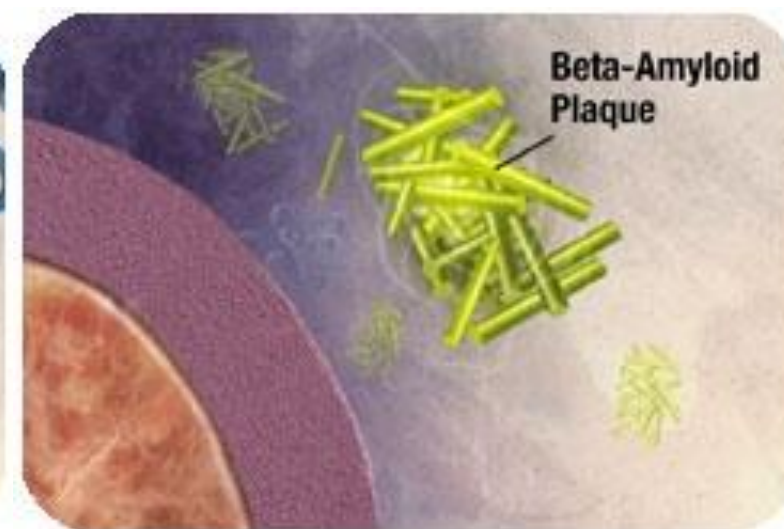
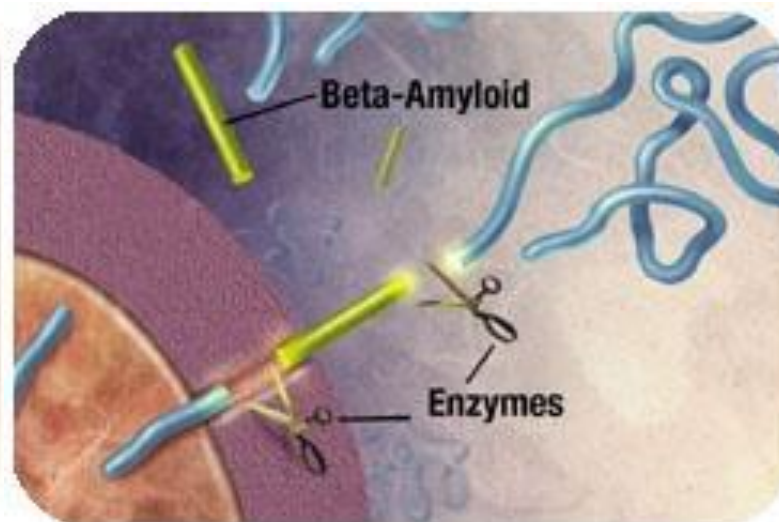
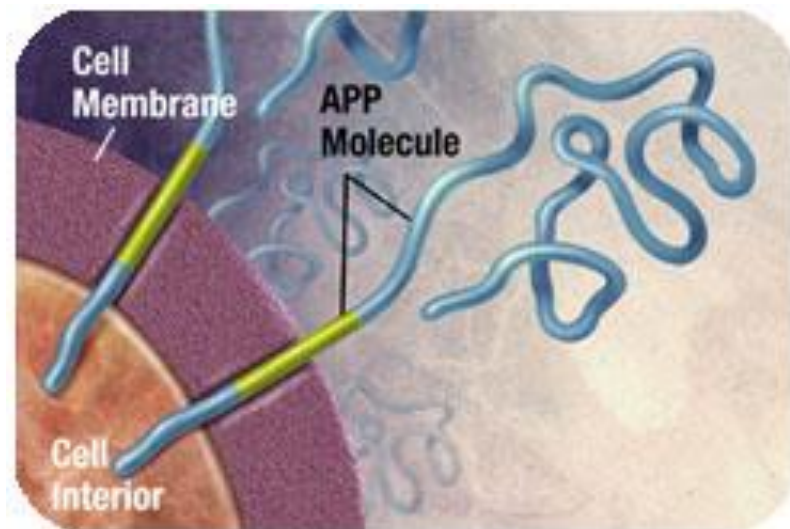


Learning Objectives

1. Learn about key targets for dementia prevention
2. Understand the media buzz around new medicines for Alzheimer's & FDA approval
3. Learn more about ways you can help prevent Alzheimer's disease and other types of dementia through research engagement



Why is A β a target for Alzheimer prevention?



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

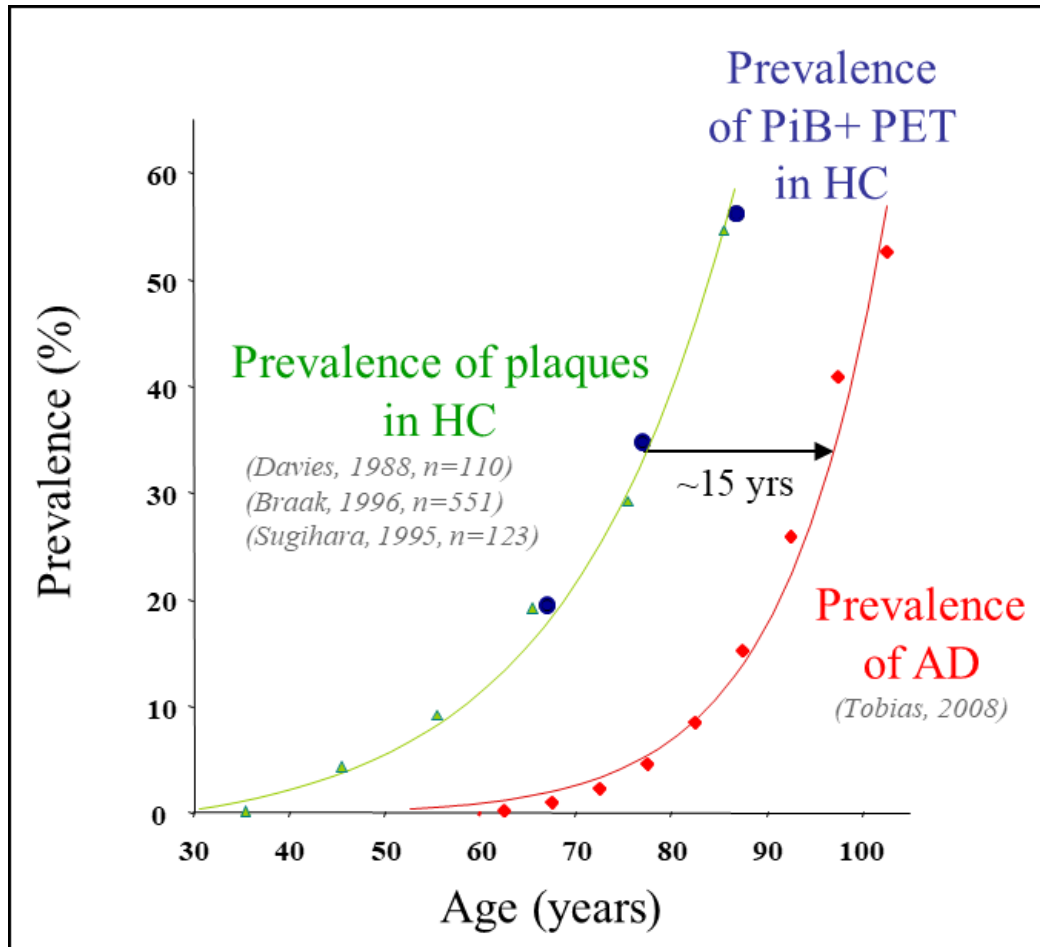
3) β -amyloid is toxic to cells and accumulates in brain tissue as amyloid plaques, a hallmark of AD

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

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

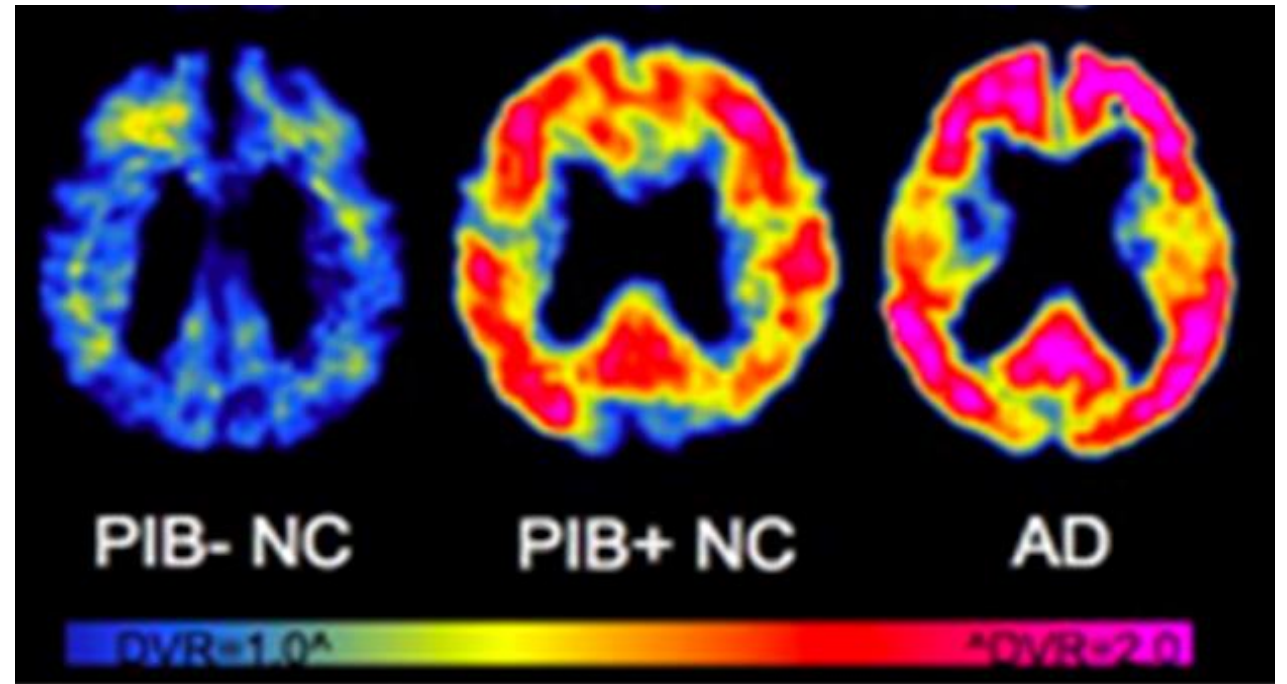


We should all care, because one out of every three persons over the age of 65 years with normal memory and thinking actually has preclinical Alzheimer's



Rowe C et al *Neurobiology of Aging* 2010

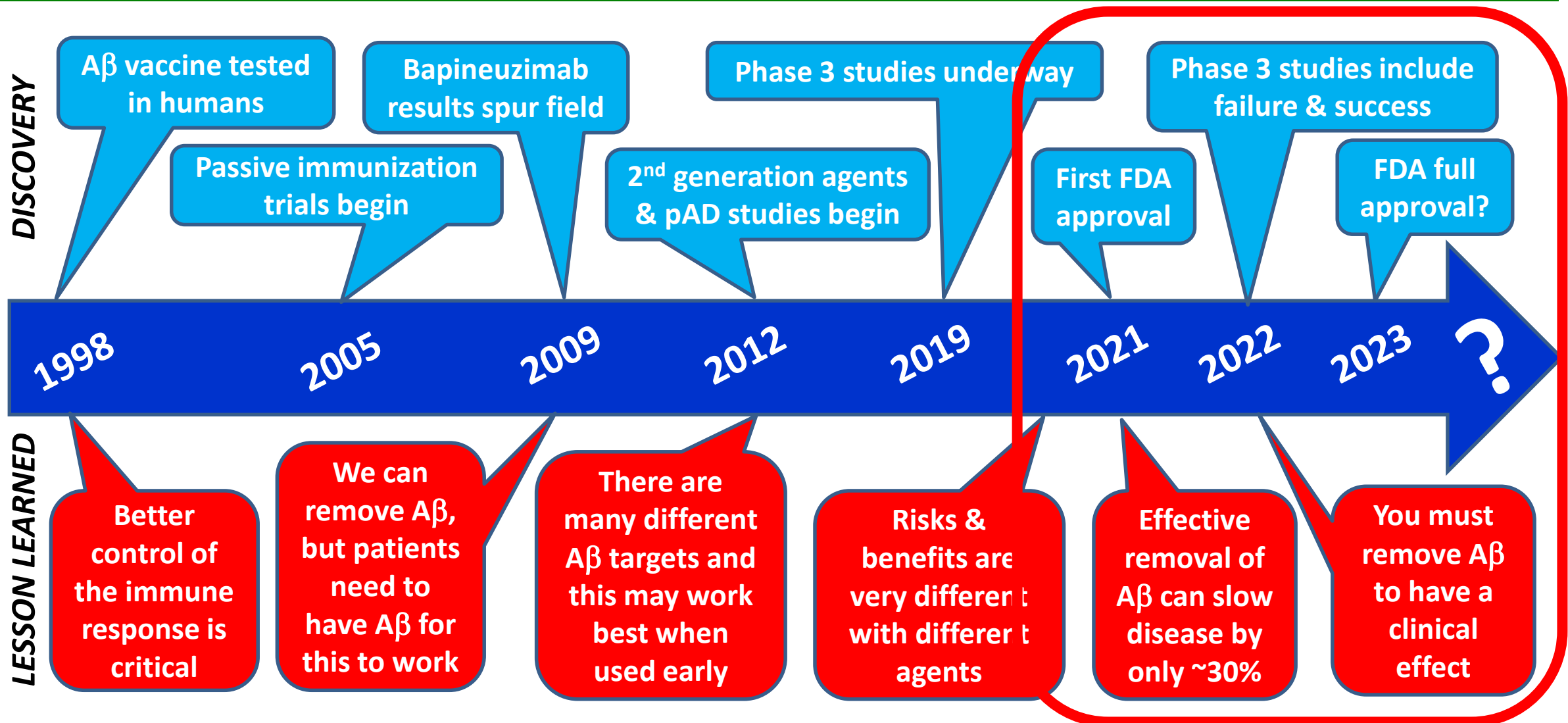
- Amyloid plaques are found in many asymptomatic persons
- Amyloid-PET allows us to see this in living persons
- Amyloid plaques occur ~15 years before clinical AD becomes evident



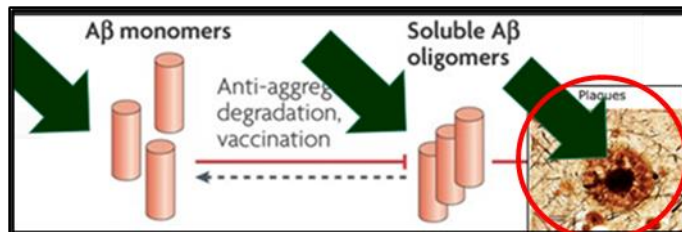
Sperling, Johnson *NeuroMolecular Med* 2010



Timeline of anti-A β therapeutic discoveries & advances

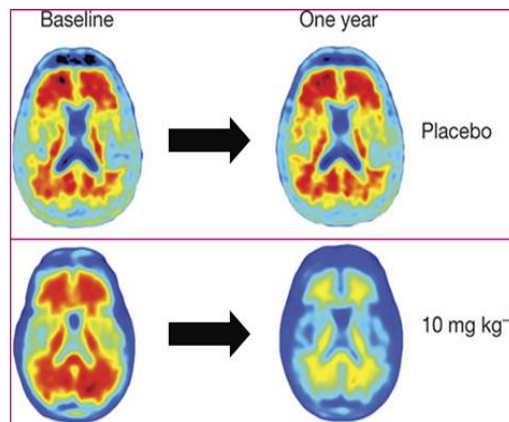


Let's start the journey with Aducanumab 2017...



- This worried me, and we chose not to participate in clinical trials because...
- We didn't know if it would be safe?
- We didn't know if it would be of benefit?
- It has the same target as Bapineuzumab so are we just repeating history's mistakes?

- ENGAGE and EMERGE, tested aducanumab in ~1600 mild AD patients
- The drug removed amyloid plaques from the brain
- The FDA concluded that benefits on slowing cognitive decline were inconclusive and the conditional approval requires an additional study
- ~41% subjects had brain swelling/stroke or bleeding in the brain and 25% of those had symptoms including worsening of cognitive decline



BIOMEDICINE

Doubts persist for claimed Alzheimer's drug

Once declared a failure, Biogen's antibody drug to be submitted for U.S. approval in 2020

By Kelly Servick

ast week, with trading in the company's stock halted for the widely anticipated

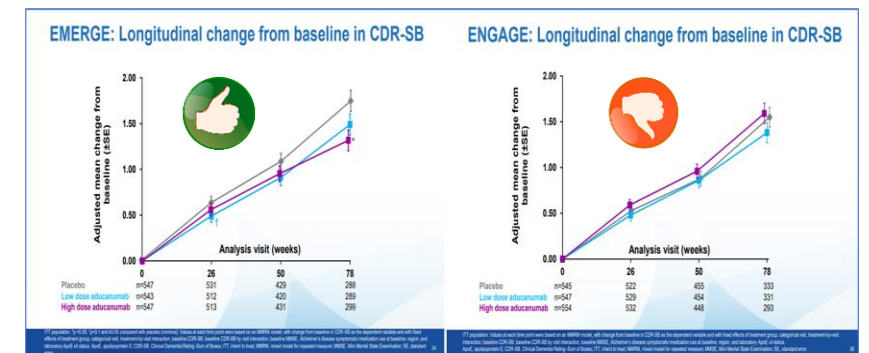
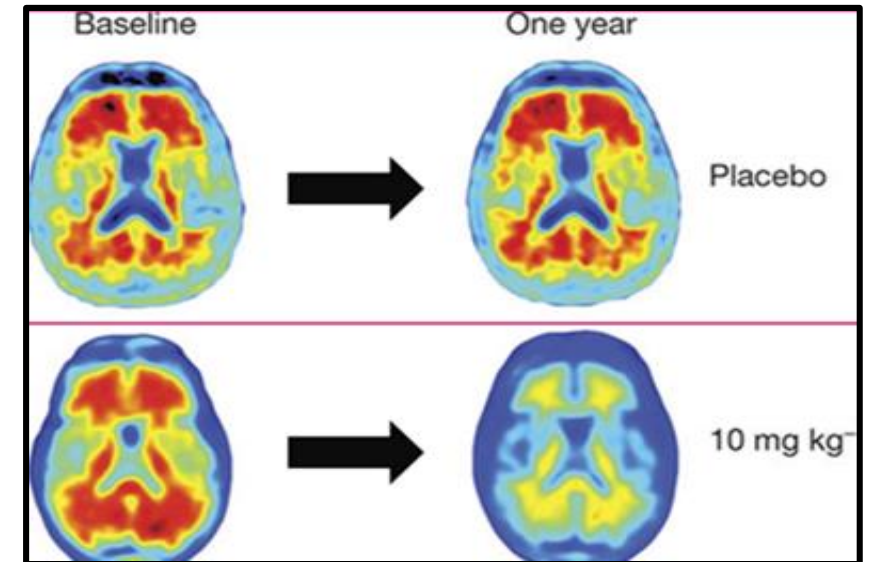
ties that suggest aducanumab helped trial participants retain some independence. "Those of us who know this disease well know what it means to lose yourself, slice

the high-dose group showed less cognitive decline than the placebo group, based on a standard dementia rating scale. But in ENGAGE, the high-dose group declined

<http://science.sciencemag.org/content/366/6471/1298>

Aducanumab Lessons Learned 2021

- **Definitive proof that such agents can fully remove amyloid from the brain!**
 - Removal of A β plaque clearly demonstrated in both Phase 3 studies leading to accelerated FDA approval
- **With one positive and one negative study on clinical outcomes it remained unclear what the benefit might be?**
- **Do another definitive studies was the FDA mandate! (conditional approval)**



Accelerated & or Conditional FDA Approval?

- **“Accelerated” FDA Approval**

- Accelerated means the FDA knows how much we need something
- Approval was based on evidence of removing A β only



- **“Conditional” FDA Approval**

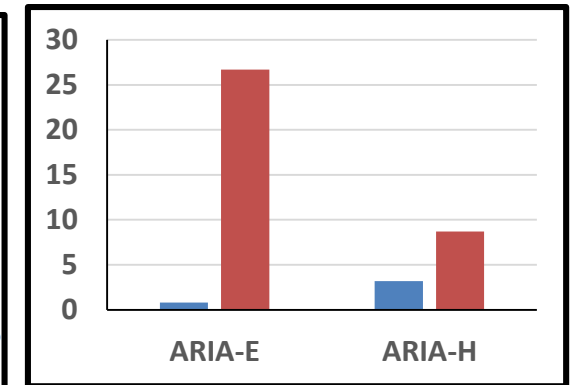
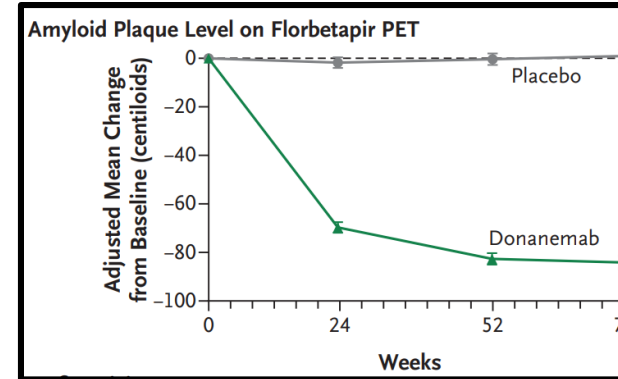
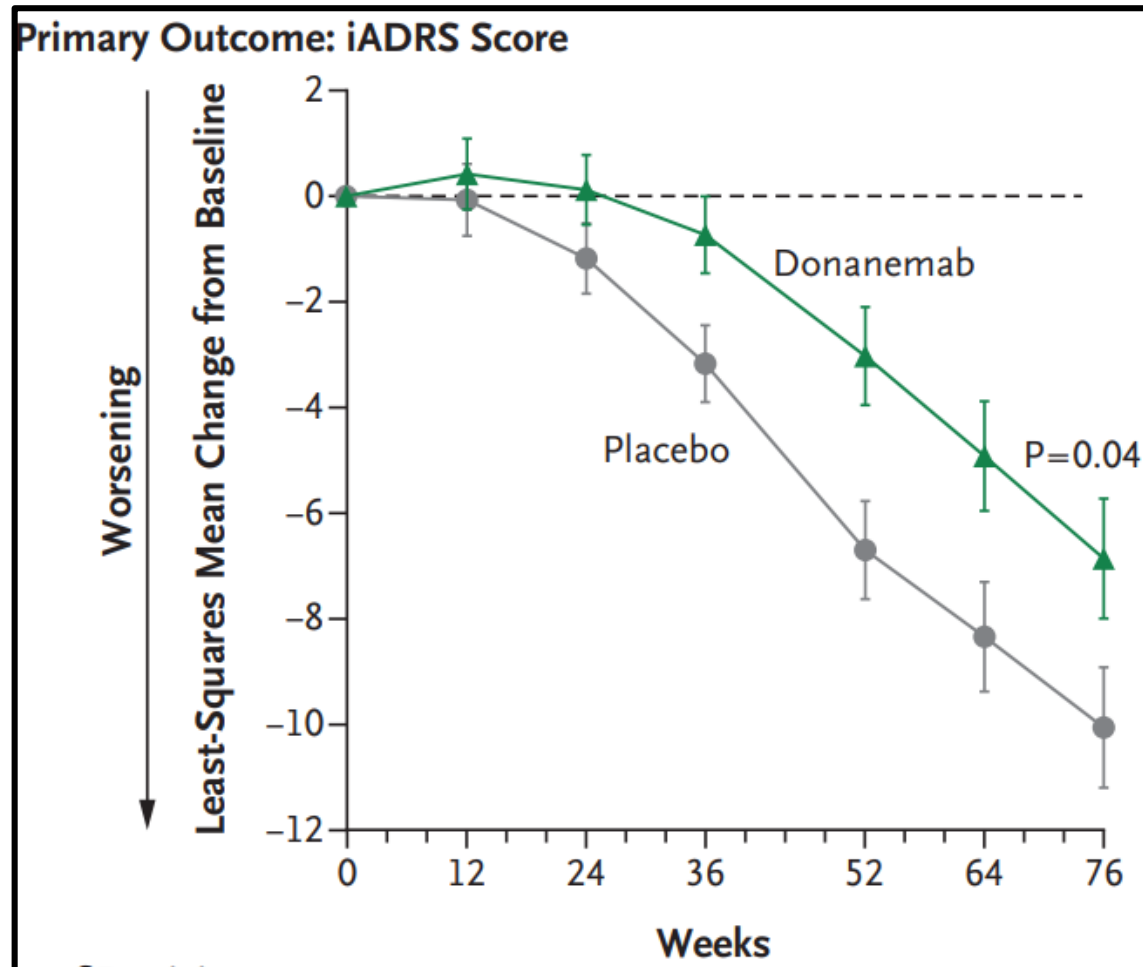
- There is a requirement for an additional study to prove clinical benefit by 2026 or the drug approval will be pulled
- This is really still an experimental research drug, similar to the many others we are working with in the field

- **What it takes for “Full” FDA Approval?**

- Definitive evidence for significant clinical benefit, not just A β brain removal



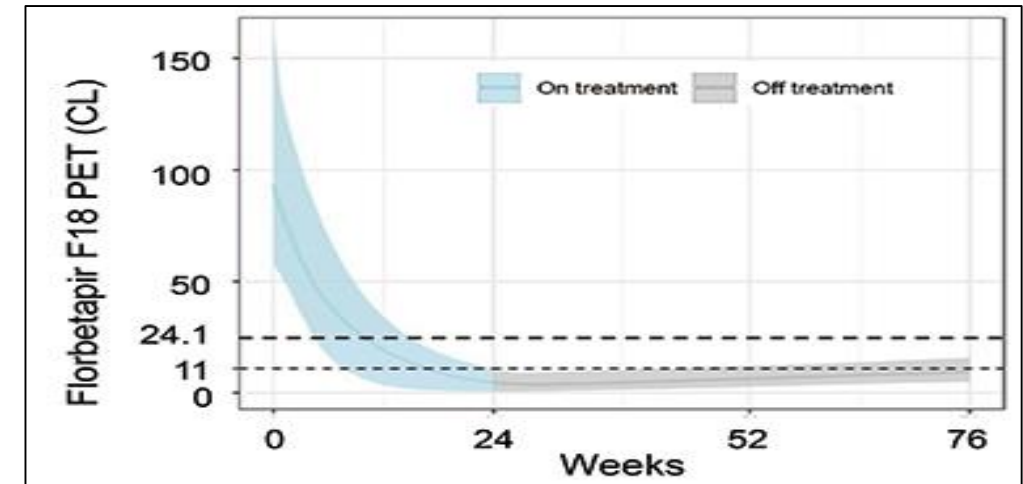
Let's continue the journey with Donanemab 2017...



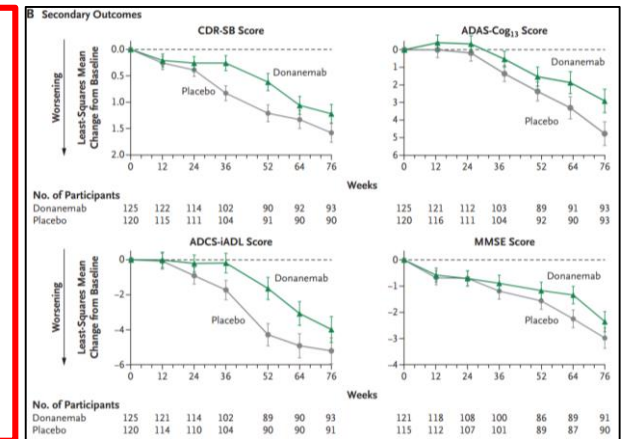
- Results similar to other antibodies that remove A β plaques with a ~32% slowing of full-blown Alzheimer's disease
- Complete removal of A β plaques demonstrated clearly
- ARIA risk remains in a midrange

Donanemab Lessons Learned 2022

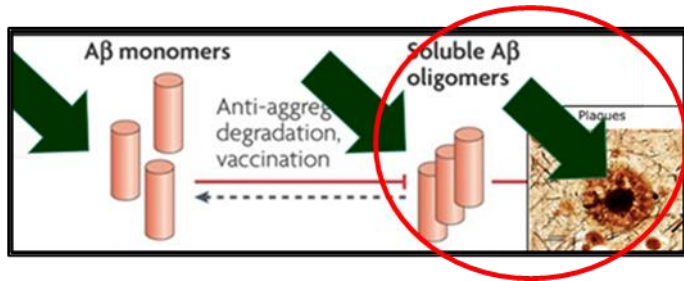
- **Clearly reduces $A\beta$, but the protocol stopped $A\beta$ -PET once clear of $A\beta$, and so not all patients had EOS $A\beta$ -PET**
 - This led the FDA to not grant accelerated approval given the disparate timelines for establishing $A\beta$ clearance
- **A clinical benefit of ~32% was seen in the Phase 2 study, similar to other studies using agents that reduced $A\beta$**
 - A similar clinical benefit was seen across all secondary clinical measures in the study



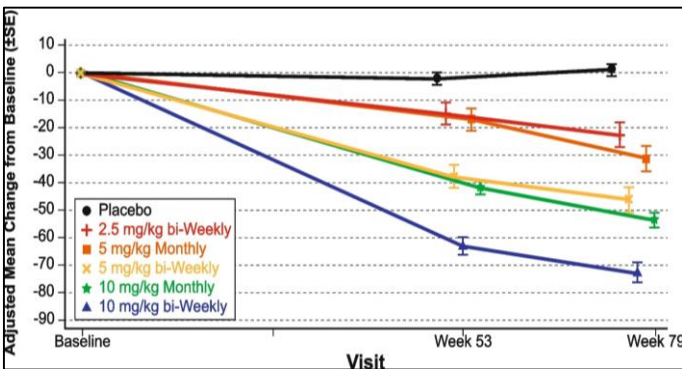
ARIA rate was intermediate between that seen with Aducanumab and that seen with Lecanumab



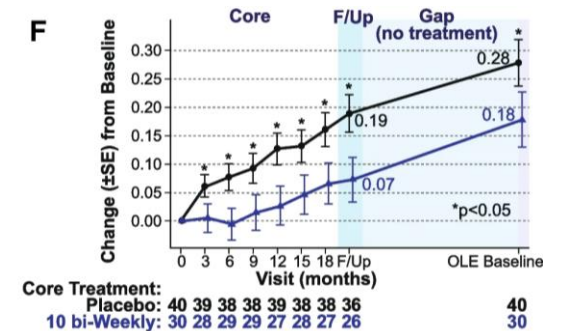
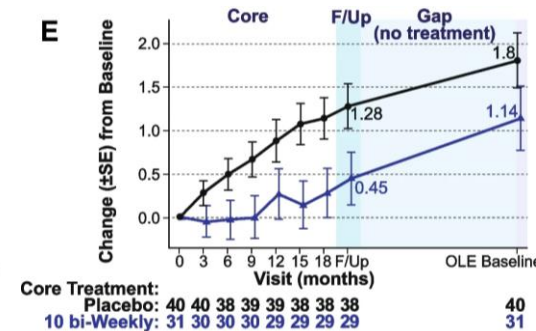
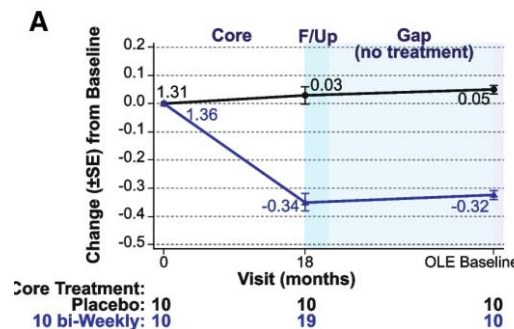
Let's continue the journey with Phase 2 Lecanemab 2012...



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

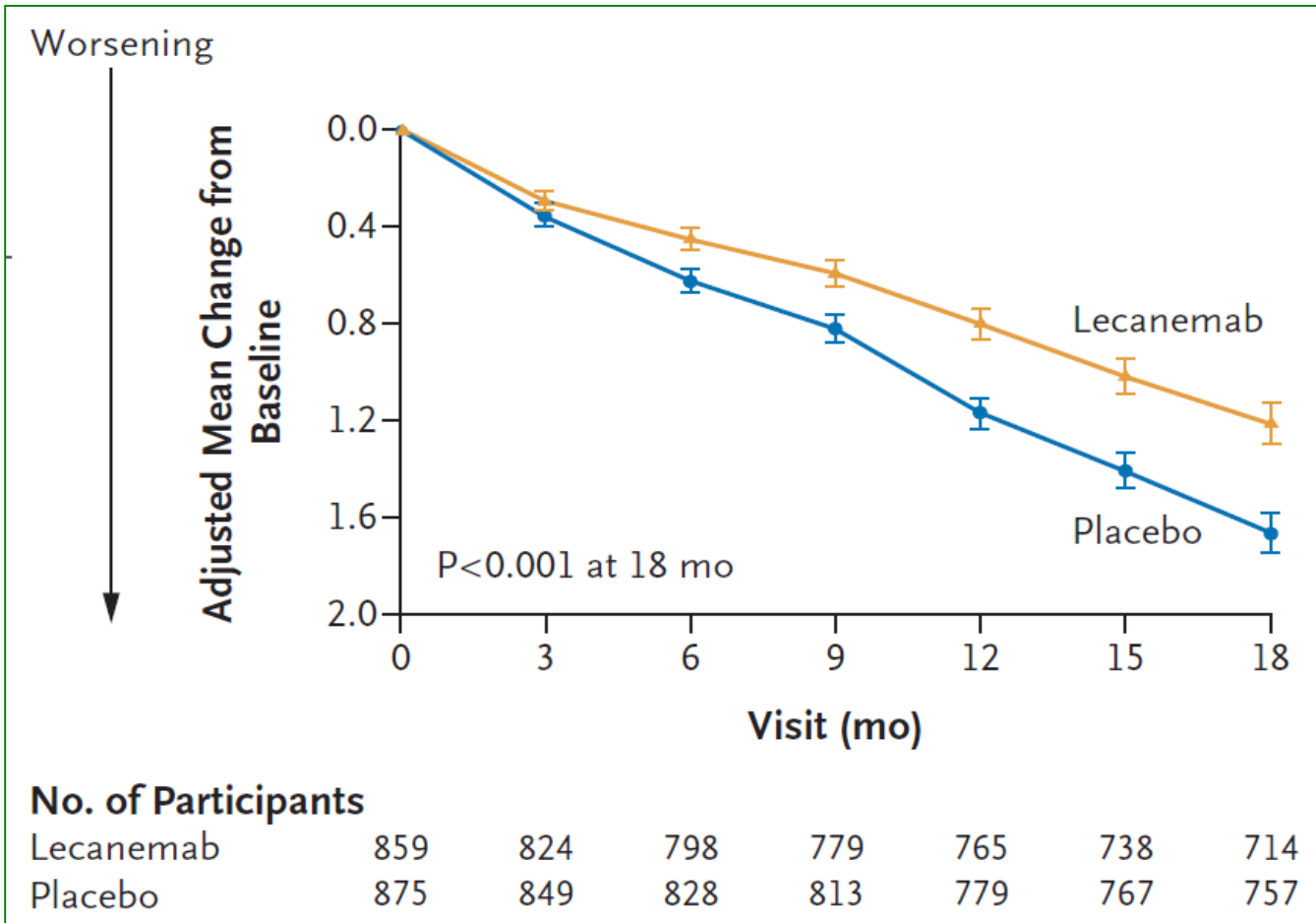


- The trial demonstrated 10 mg/kg biweekly was optimal
 - It eliminated Aβ
 - There was positive clinical benefit
- But the trial ended and all patients went into a gap period before an OLE was started
 - This taught us so much about disease modification and what happens if you stop these medicines



- A slow rise in Aβ-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...



van Dyck et al. N Engl J Med. 2023 Jan 5;388(1):9-21

Pharmacy Times

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

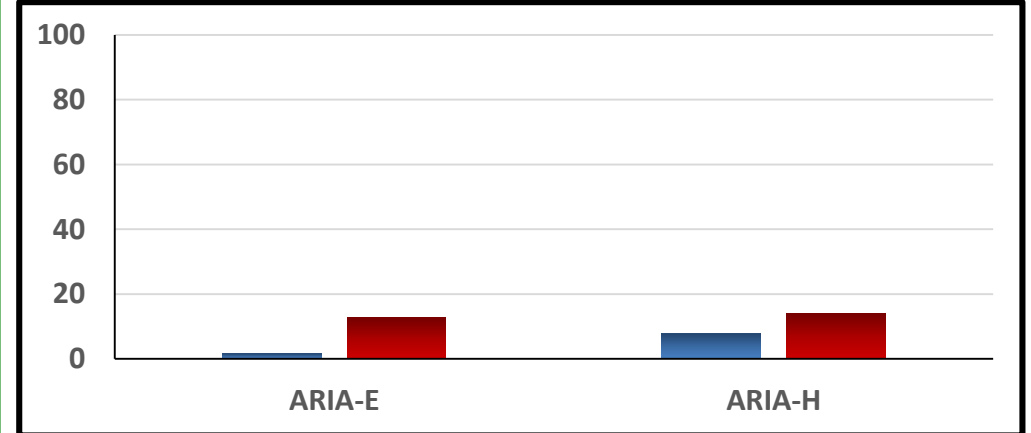
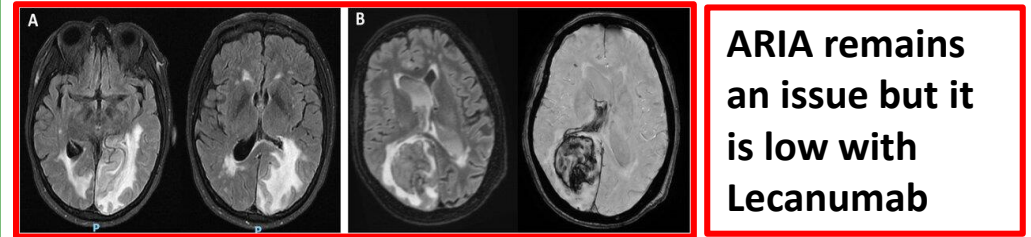
November 3, 2022
Aislinn Antrim, Associate Editor

BioPharma
-Reporter.com

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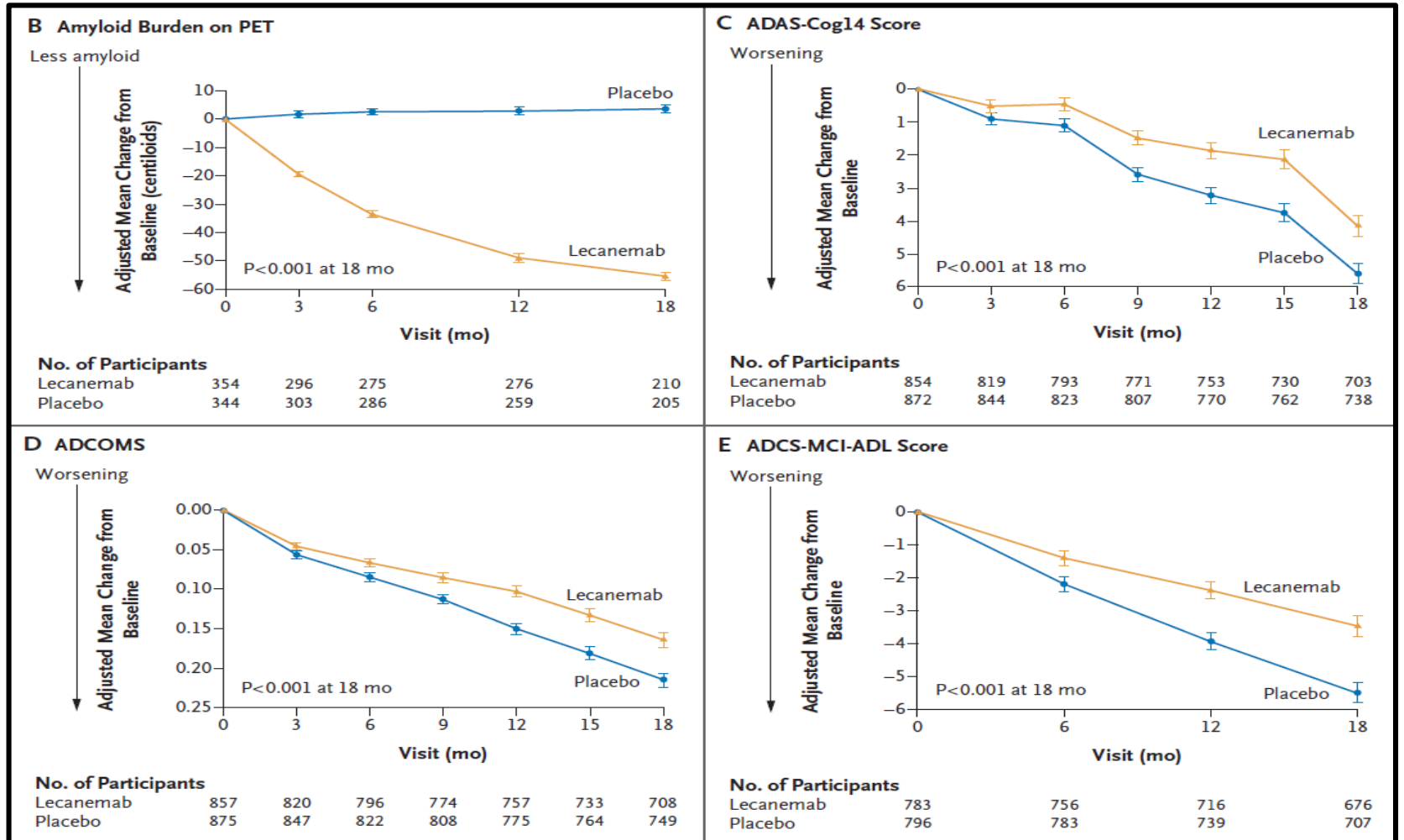
Alzheimer's disease: Eisai and Biogen release milestone data





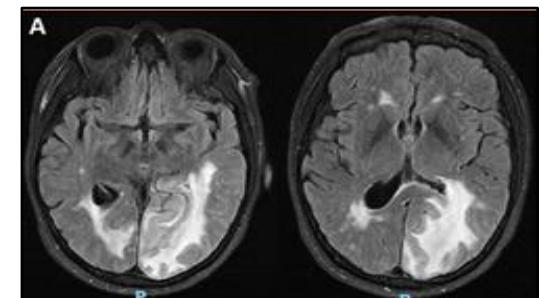
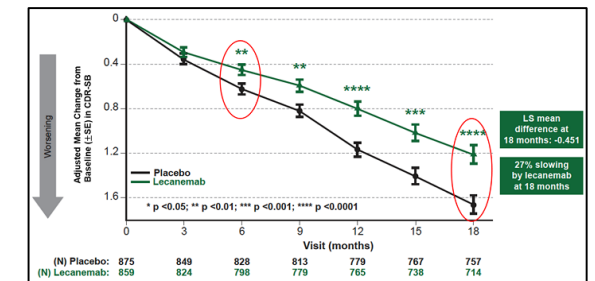
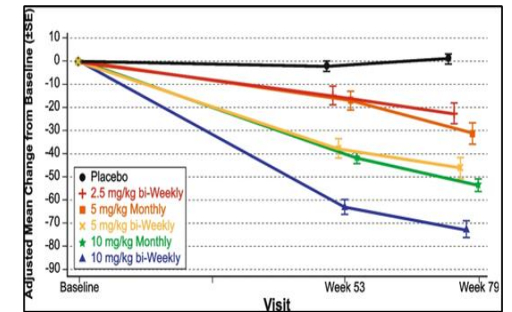
Lecanemab secondary endpoints?

- Full FDA approval expected in 3 mos
- VA has already chosen to cover this medicine
- It will be here at UK in the next 6 months
- Let's get ready...



Lecanemab Lessons Learned 2022

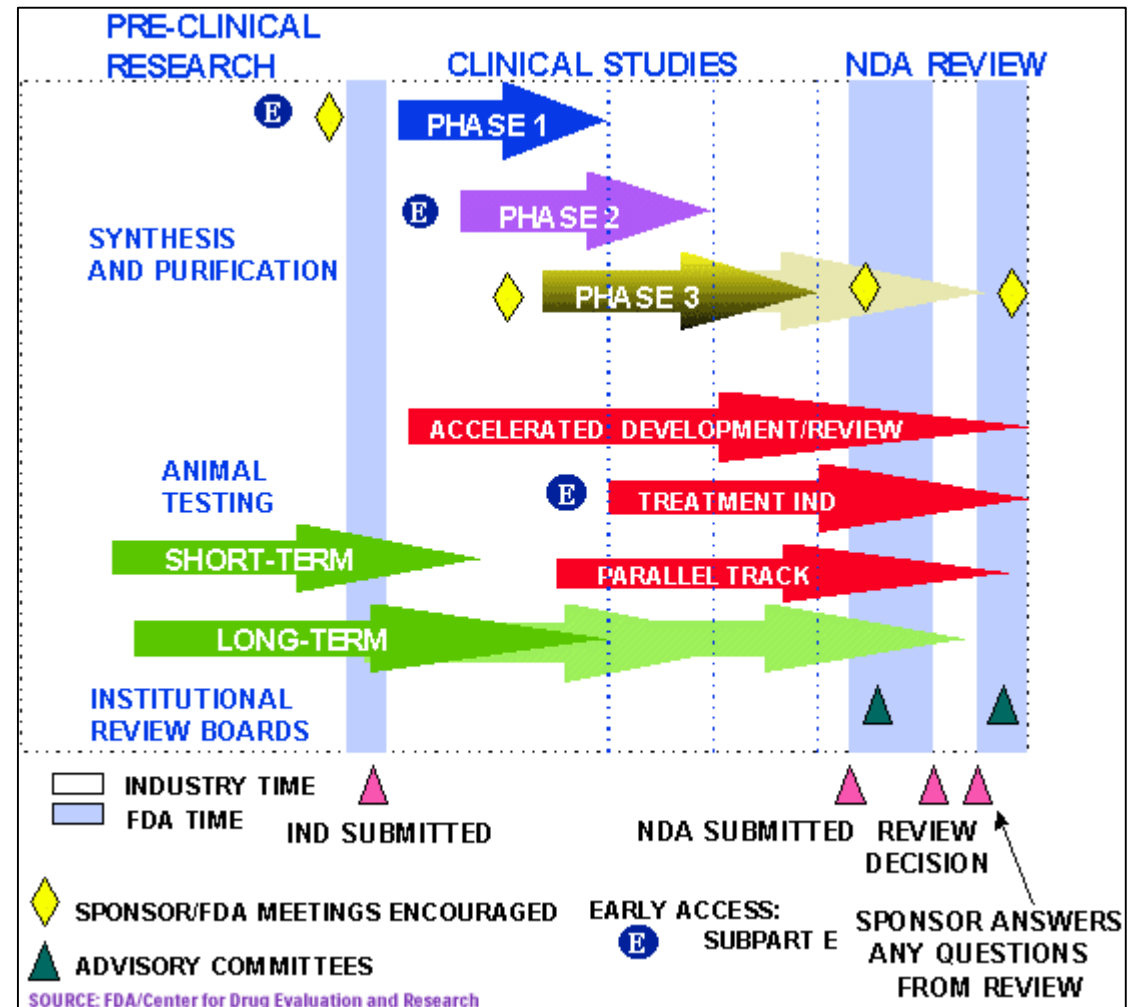
- The Phase 3 CLARITY data is considered by most in the field to be definitive evidence of clinical benefit in addition to the previously accepted demonstration of A β removal
 - The Phase 2b/3 data led to FDA accelerated approval on January 6, 2023 based solely on A β removal
- Clinical benefit ranges 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
- ARIA rates appear low despite full clearance of A β but risks do still exist



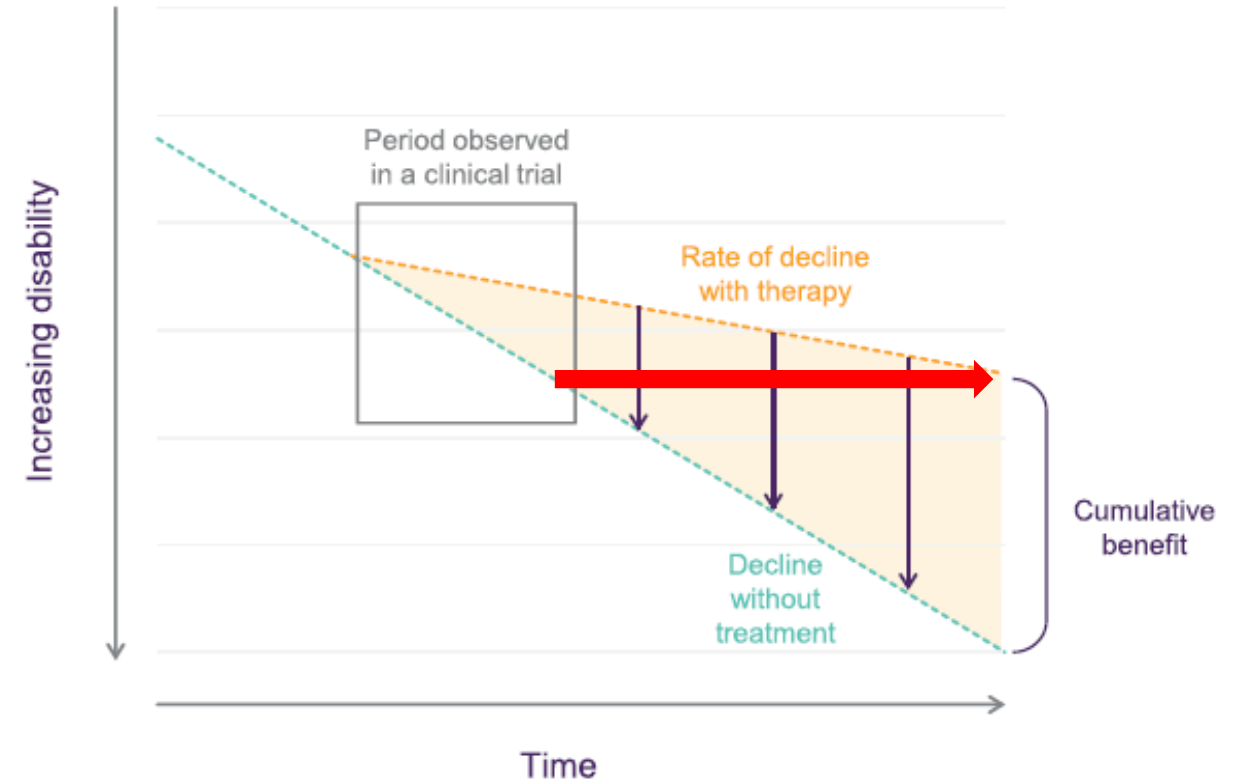
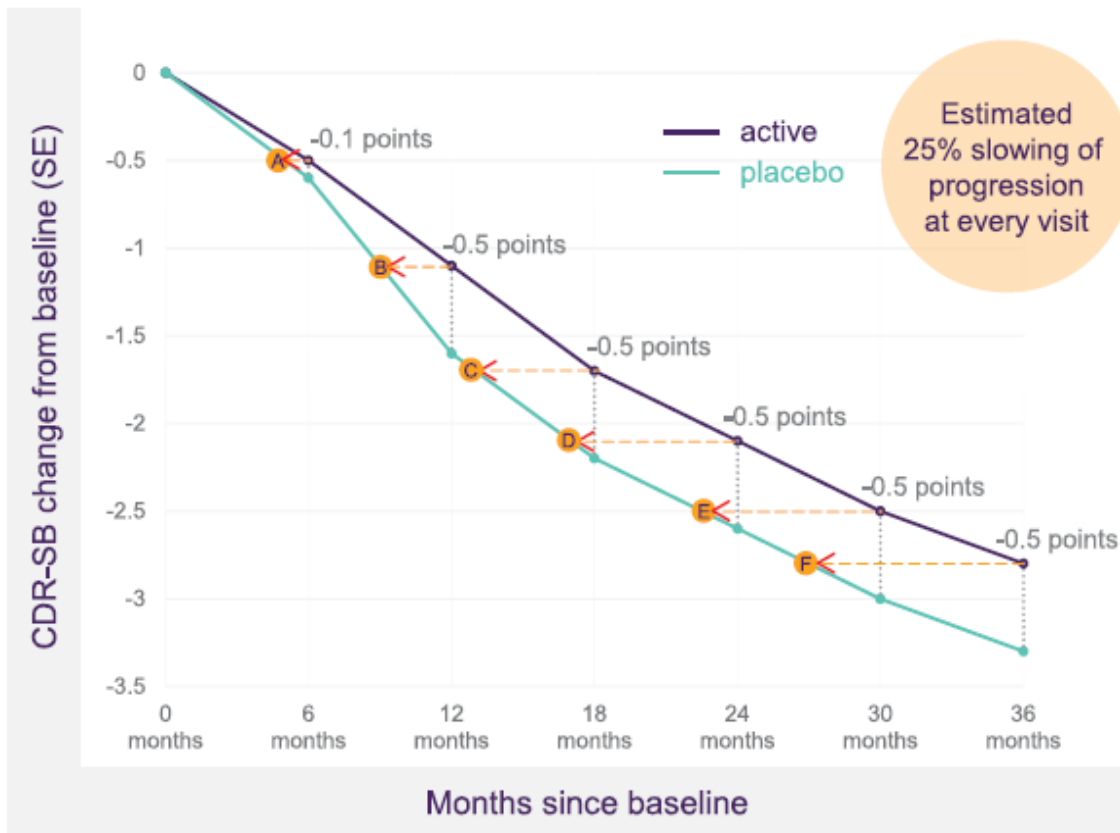
FDA Full Approval?



- **Drug approval is based on the ultimate Phase 3 data**
 - Typically, 2 independent studies are needed
 - Surrogate outcomes can be used in some instances (i.e. BP lowering for antihypertensives)
- **A β -PET lowering was a move to surrogate endpoints for AD**
 - Warranted “accelerated”, but not full approval as of yet
- **Full FDA approval of Lecanemab is expected in June 2023**
 - Medicare coverage will likely follow
 - The VA has already made the decision to cover the costs of Lecanemab (Leqembi®)



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



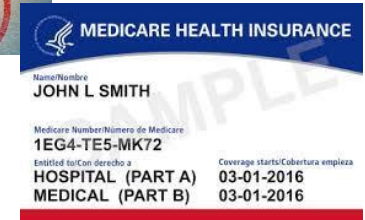
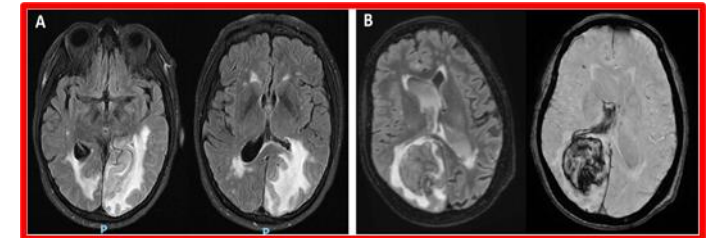
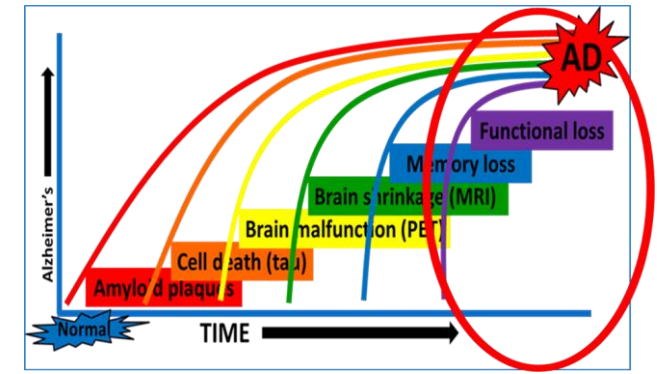
	A	B	C	D	E	F
points	-0.1	-0.5	-0.5	-0.5	-0.5	-0.5
months difference vs. placebo	-1.5	-3	-4.5	-6	-7.5	-9

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...

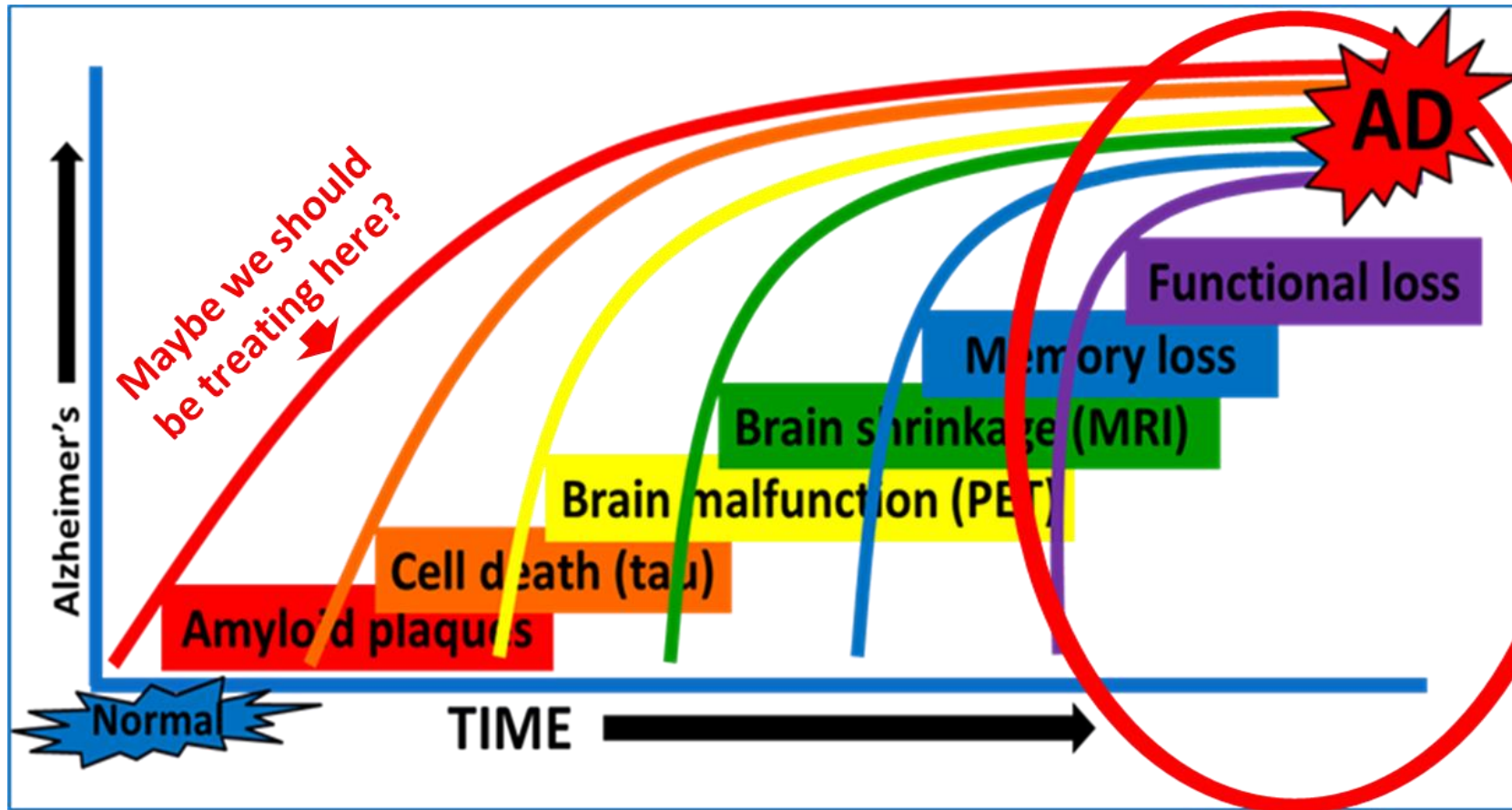
Lecanemab is unfortunately not for everyone...

- *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)*
- *Providing this medication may still be dependent on the uncertainty of FDA full approval & a decision by Medicare and other 3rd party payors to cover costs*





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

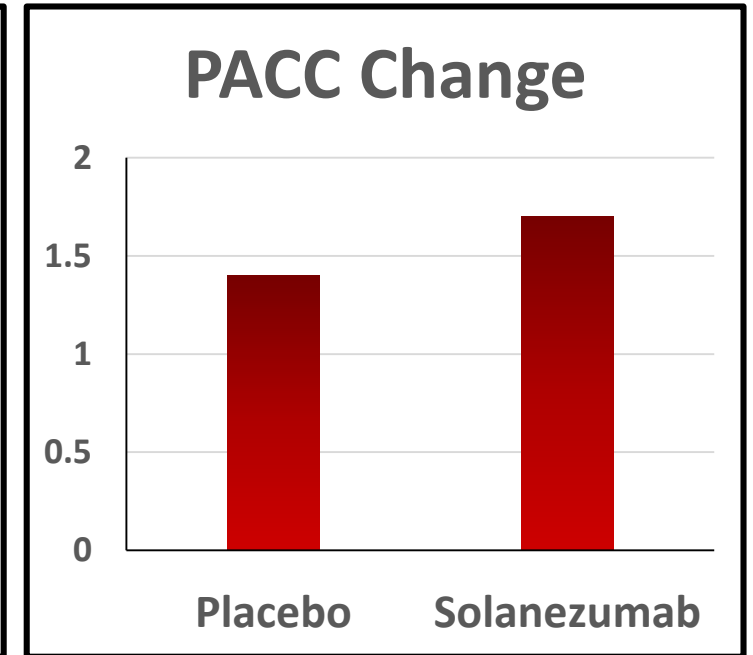
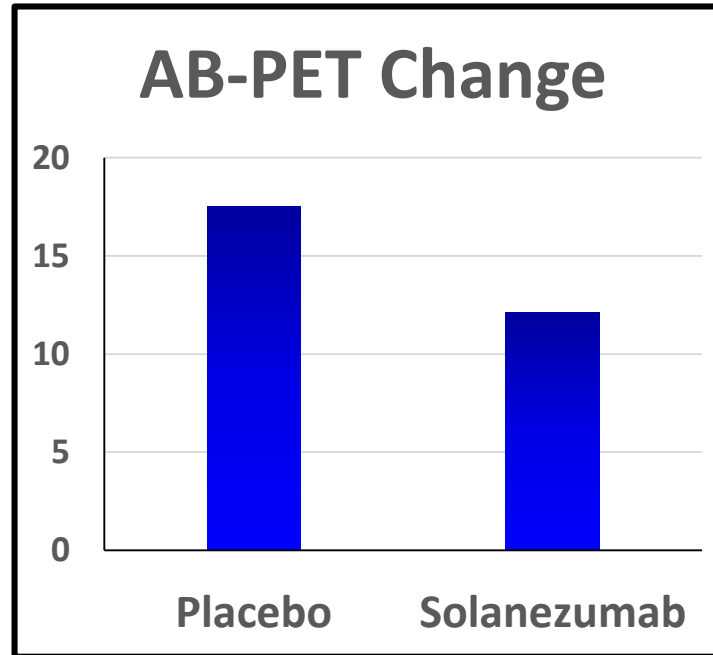
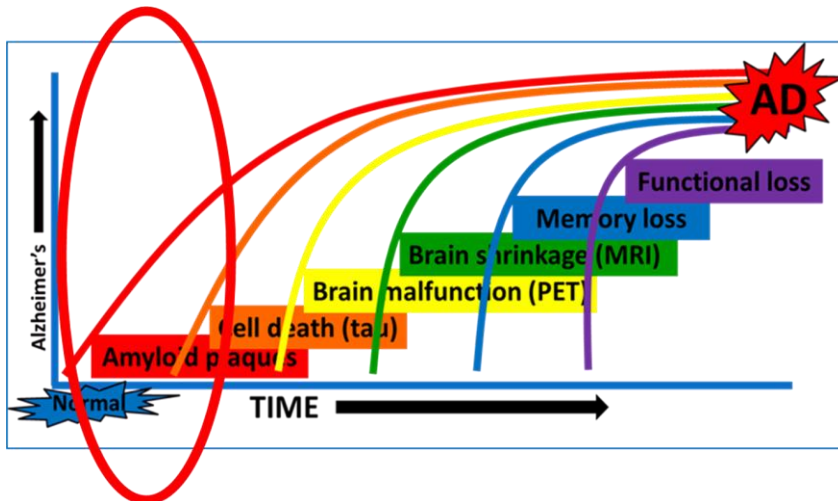


Maybe we are treating way too late, and we can slow but not stop AD completely once irreversible damage to the brain occurs...

Let's continue the journey with Solanezumab in pAD 2012...

A The A4 Study NOW IS THE TIME

- In 2011, the NIH funded the A4 (*anti-amyloid in asymptomatic AD*) study
- 1,150 participants were treated for 3-9 years



- $A\beta$ was not removed as was expected from prior Sola data
- $A\beta$ accumulation was slowed by about 2 years

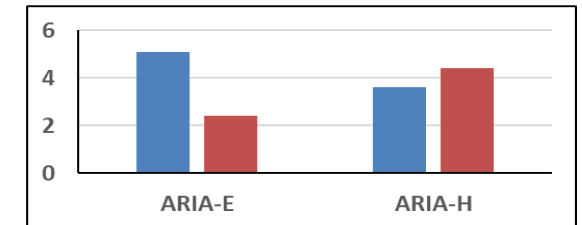
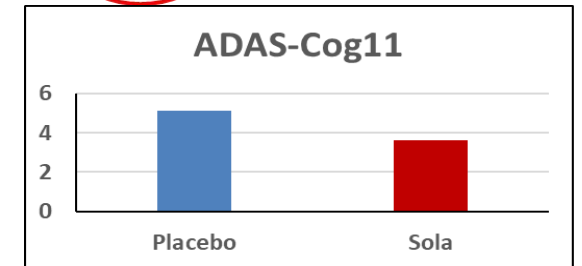
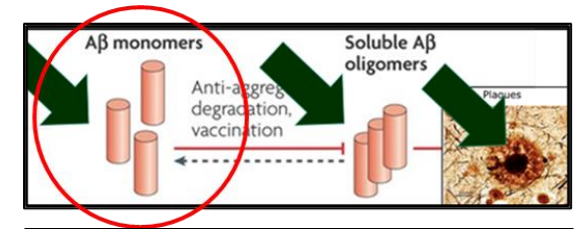
- No improvement in cognition was seen
- No difference in 36% transition rate to MCI was seen

<https://investor.lilly.com/news-releases/news-release-details/lilly-provides-update-a4-study-solanezumab-preclinical>



pAD Lessons Learned 2023

- **Slowing A β accumulation in those with AD levels of A β will not change disease progression**
 - Reinforces that A β removal is what matters
 - These medicines work the same way regardless of disease stage (safety and efficacy the same as in AD)
- **Rather than giving up, the field is pushing ahead with new pAD studies using Lecanemab**
 - A45 studies the same stage of pAD
 - A3 moves even earlier



AHEAD 
STUDY

*Enrolling
now at UK
and across
the globe!*



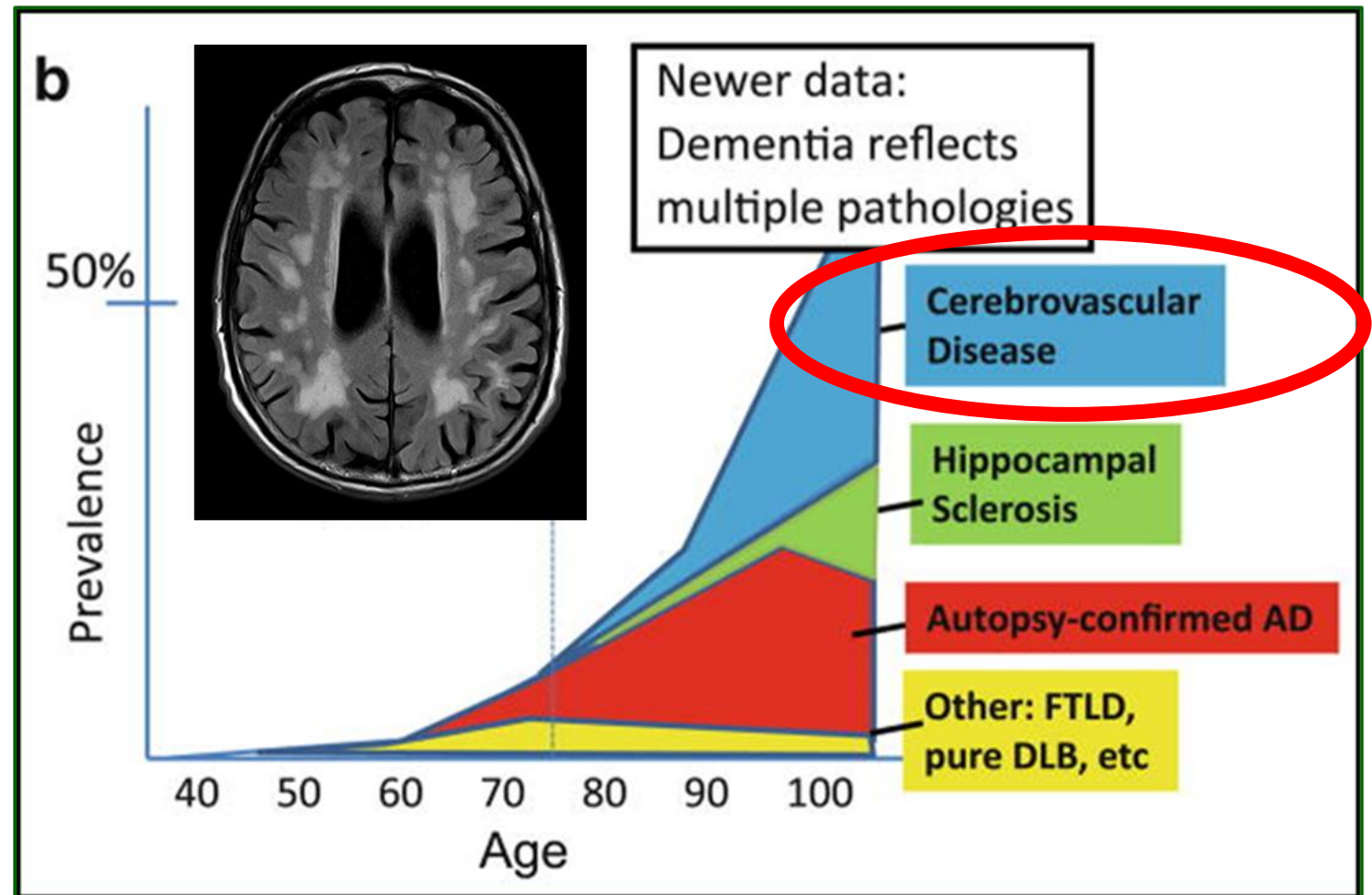
Alzheimer's
Disease Center
at the Sanders-Brown Center on Aging

**Sign up to see if you are at risk and
if the AHEAD study is right for you**

AHEAD STUDY

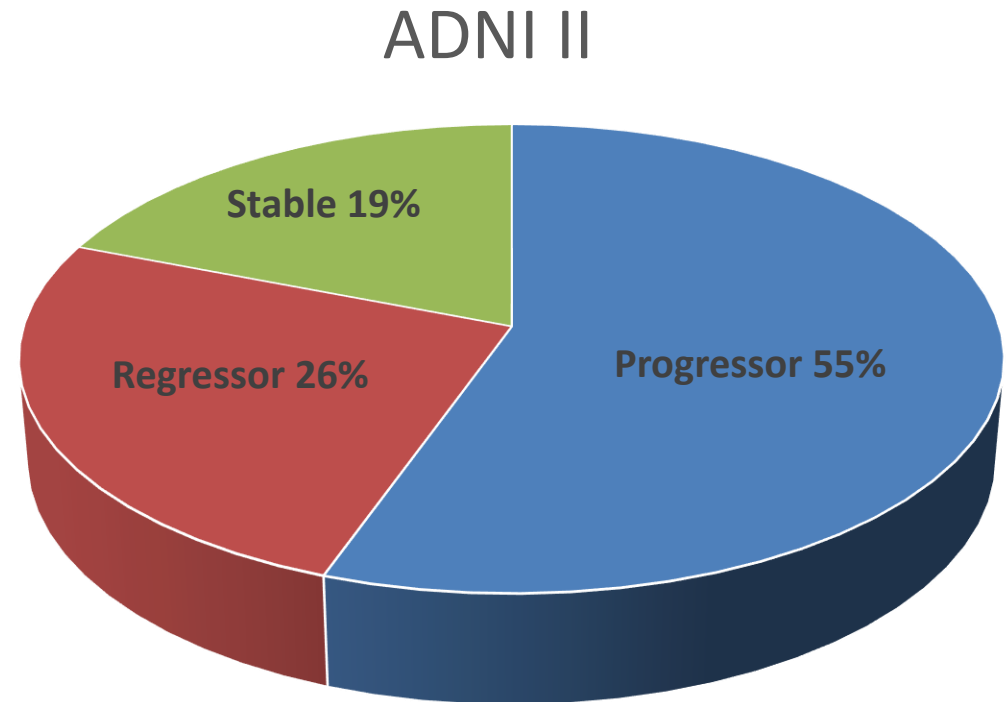
Vascular Cognitive Impairment & Dementia: “Hardening of the arteries”

- We have been studying VCID for over 12 years
- We know that:
 - Hypertension is the #1 risk for this hardening of the arteries
 - It is just as devastating as Alzheimer's disease
- Much active work is being done to gear up for clinical trials in this area
- Let's take a look...

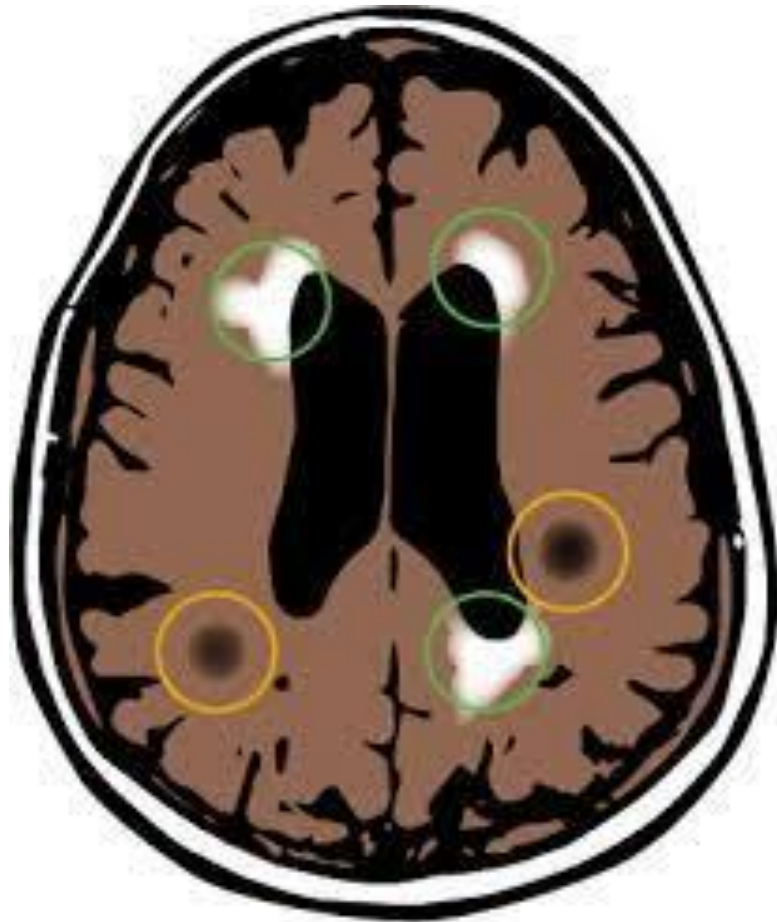


WMH are highly dynamic

- Participants were 72 ± 7.2 years old, 48.3% female, had 16.5 ± 2.6 of education with 55.7% having MCI, 37.4% being cognitively normal, and 6.9% having AD.
- There were no significant differences between regression, stable, and progression groups in age, education, sex, marital status, diagnosis, or Δ EF.

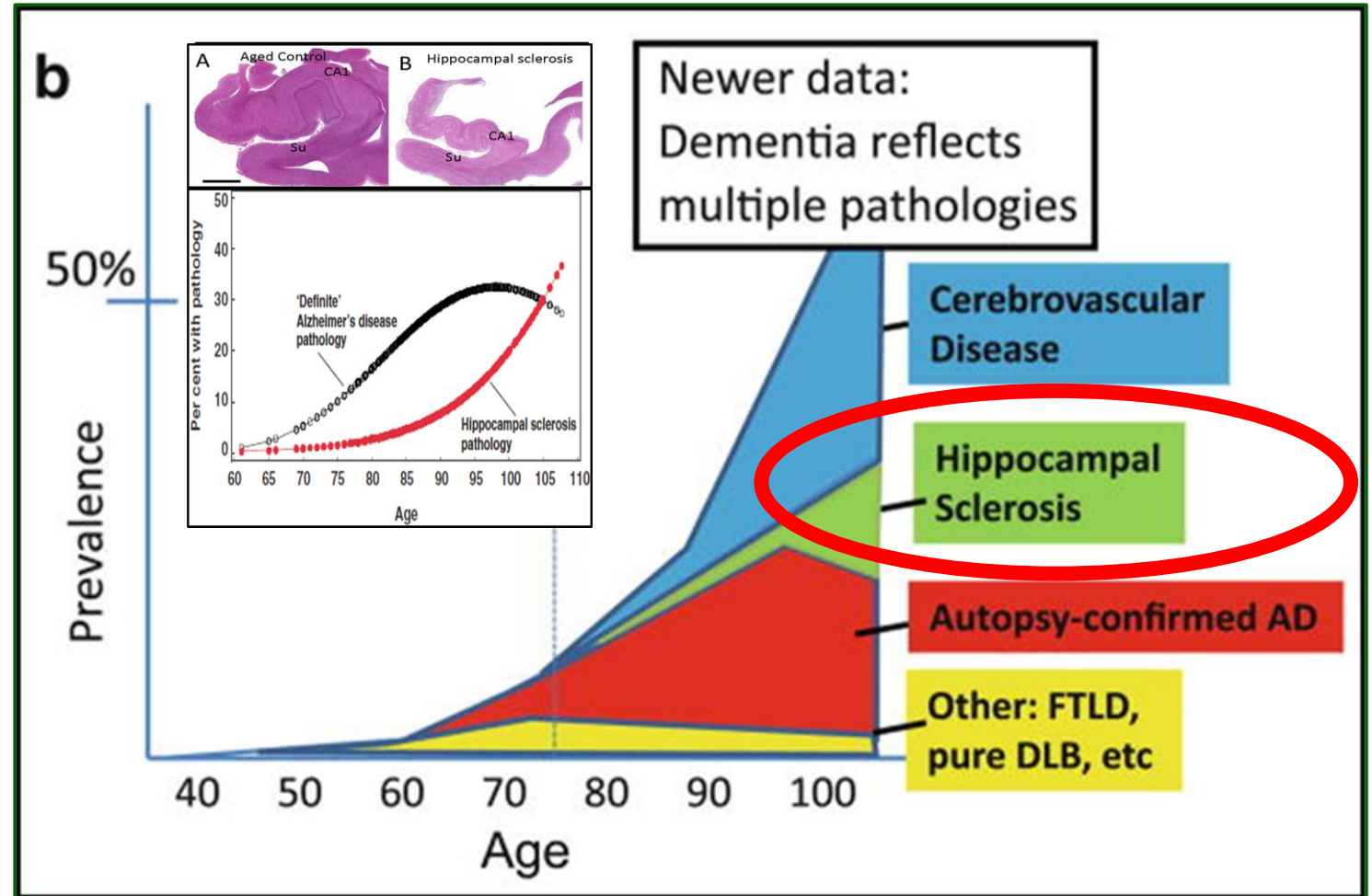


Hispanics and Blacks are hit heavy with VCID



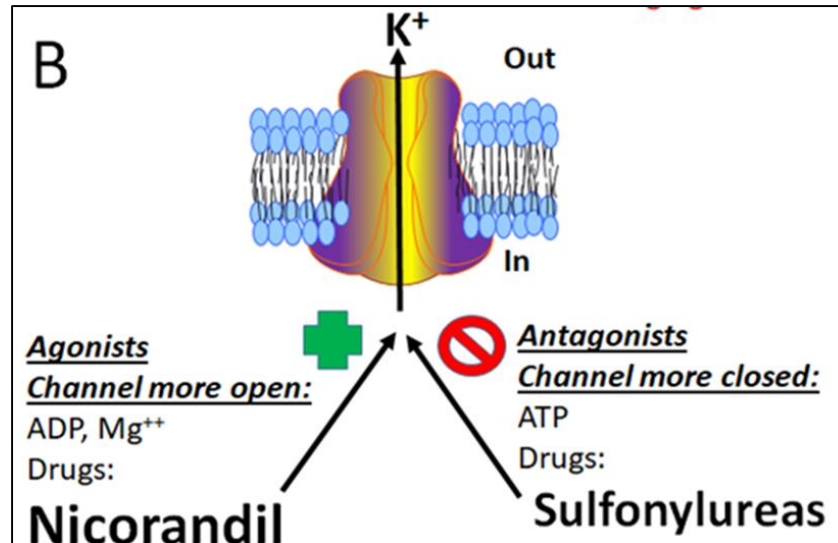
LATE: “hippocampal sclerosis of aging” looks just like AD...

- **We know that:**
 - If you are over the age of 75 your risk is increasing everyday
 - It is just as devastating as Alzheimer's disease
- **We have the only medicine in the world that may stop this disease, right here, right now...**
- **A simple blood test can tell if this study is right for you!**



The older you are, the greater risk you have, and the more you can help!

SMART-HS



Questions? Discussion?

- **We are entering a new world for the prevention of dementia**
- **It has been too long, and there has been too much suffering and death**
- **Change is finally here and I for one embrace this new world!**

