THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Alzheimer's Disease in the Disease-modifying Treatment Era

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UAB Neurology

Alabama Academy of Neurology
August 19, 2023

Disclosures

- Research support (paid to UAB):
  - Biogen, Cognition Therapeutics, Eisai, Genentech/Roche, Lilly, Janssen, Vaccinex
- Consulting fees:
  - Eisai, Genentech/Roche, HMP/CME, Lilly, Medscape, MedLearning Group, NFL Concussion Settlement Program, Premier Applied Science
- Stock holdings
  - Doximity

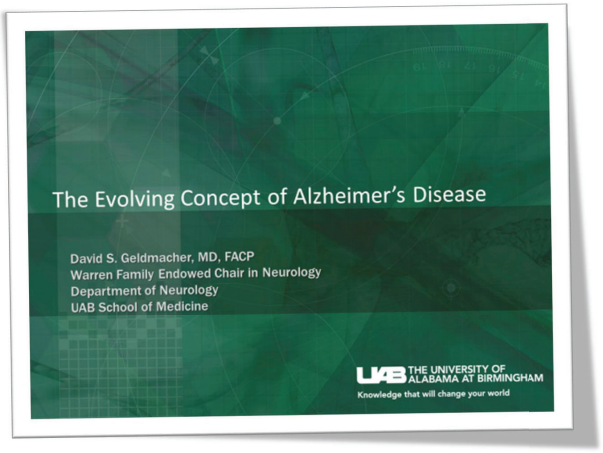
Off-label use

- No planned discussion of off-label uses of marketed products
- Research use of nonmarketed investigational products will be discussed

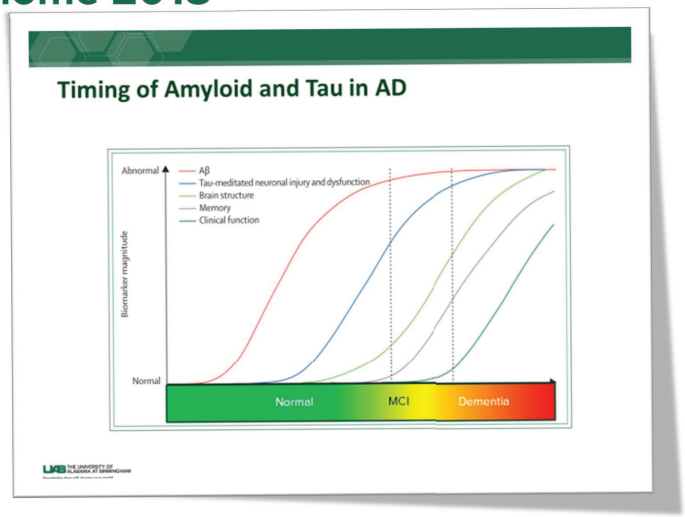
Learning objectives

- By the end of the presentation the learner should be able to:
  - Describe the mechanism of action of potential disease modifying therapies for Alzheimer's disease
  - Discuss patient-level factors that might influence risks and benefits of anti-amyloid therapies in persons with Alzheimer's disease
  - Employ appropriate steps to determine individual patient eligibility for anti-amyloid therapies
  - Implement safety and effectiveness monitoring plans for patients on anti-amyloid therapies as described in product labeling, "Appropriate Use Recommendations" publications, and CMS program requirements
  - Describe systems-level challenges to timely and equitable access to disease modifying therapies for Alzheimer's disease

Flashback: 2018

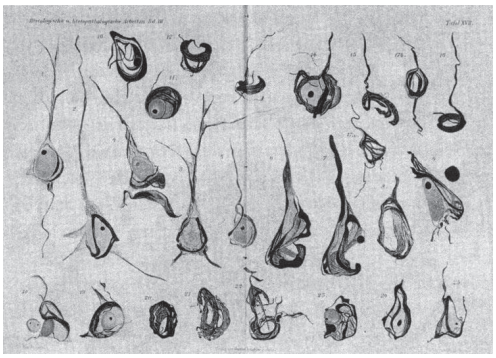


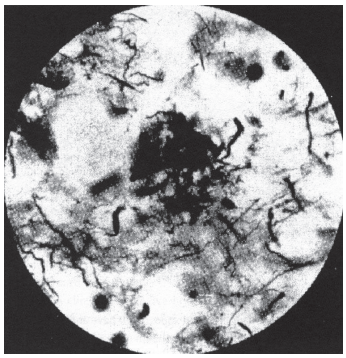
Key take-home 2018



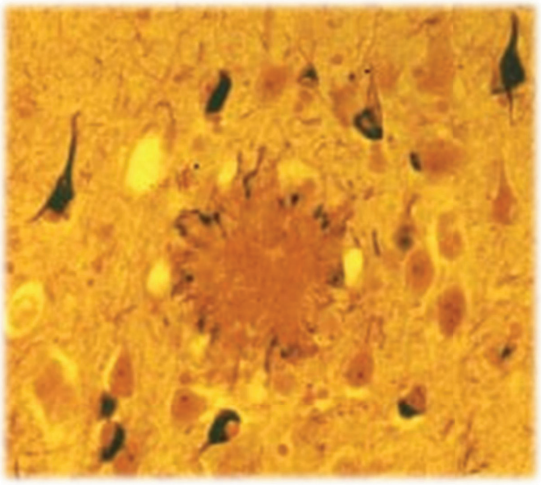
Historical Perspective: Alzheimer (the pathologist's) legacy

Dr. Alzheimer's original findings



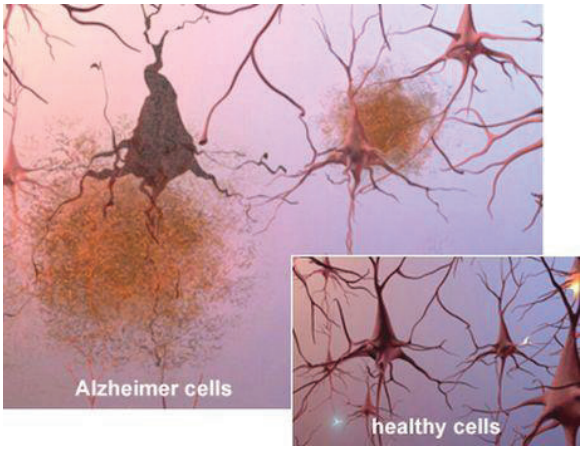


Plaque and tangles



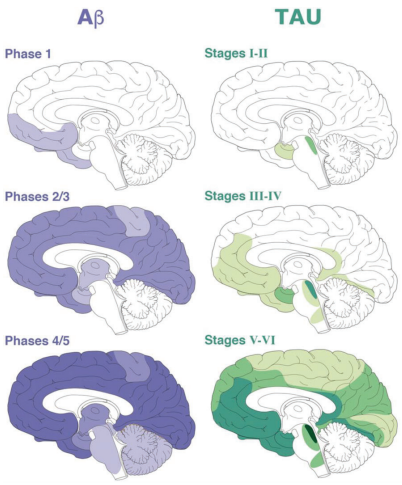
Traditional view

Amyloid plaque damages brain cells



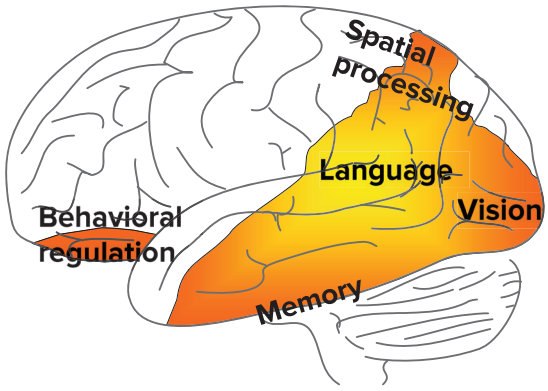
http://flippies.com/adflipoff/wp-content/plugins/RSSPoster_PRO/cache/5ccdd_cells.jpg

Amyloid and tau are temporally and spatially dissociated



Goedert et al. Brain. 2017;140(2):266-278

Tau distribution explains symptomatic expression of AD



= Regions of Highest Density Neurofibrillary Tangle Accumulation

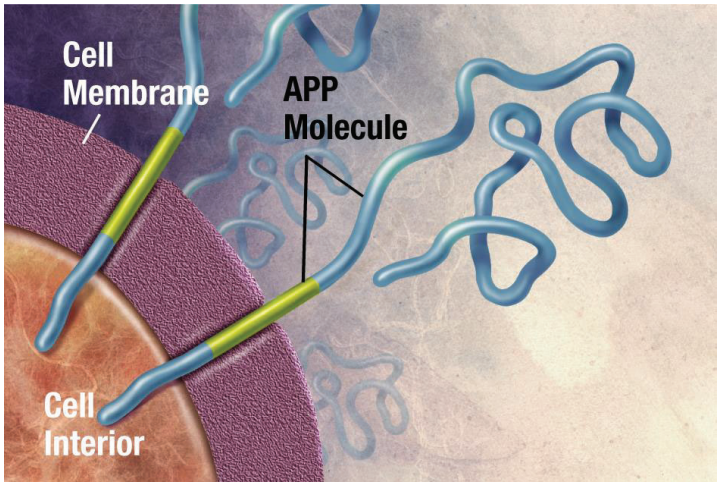
Adapted from Braak, H.; Braak, E. Acta Neuropathologica. 1991;82: 239–59.

The path toward anti-amyloid therapies for AD

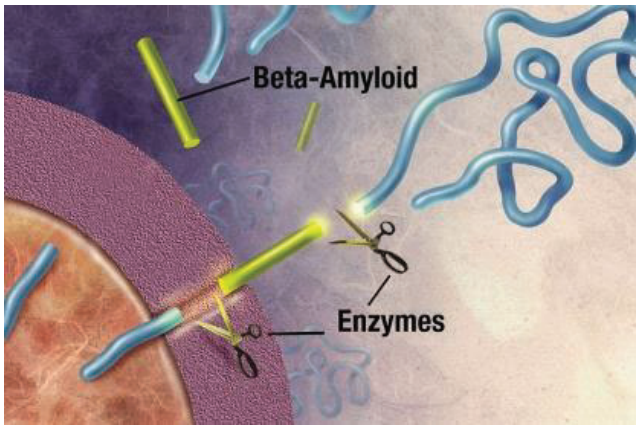
Preliminary steps

- 1984, Glenner and Wong: identified two species of amyloid from blood vessels in AD autopsy tissue (α and β)
  - Antibodies to the β-form cross reacted with senile plaques
  - Identical peptides in Down Syndrome and Alzheimer plaques
- 1985, Masters et al: sequenced Aβ
- 1987, Goldgaber et al: localized Amyloid Precursor Protein (APP) gene to Chromosome 21

Amyloid Precursor Protein



APP processed by β and γ secretase complexes



- β-amyloid production is normal
- Large-scale accumulation into plaque isn't

Preliminary steps

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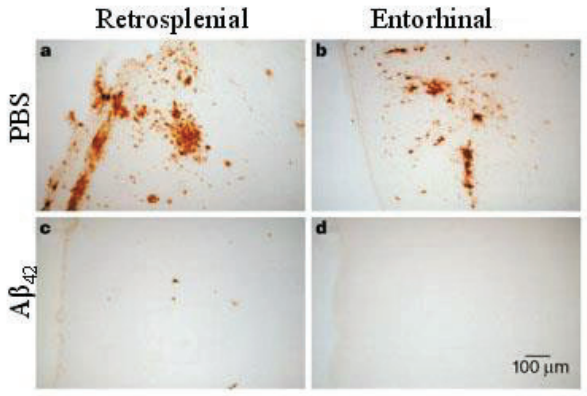
- 1985, Masters et al: sequenced Aβ
- 1987, Goldgaber et al: localized Amyloid Precursor Protein (APP) gene to Chromosome 21
- 1991-95: Causative mutations associated with APP processing were characterized
- 1995: First transgenic mouse model (PDAPP)
- 1999: Shenk et al inject Aβ into PDAPP mice with hopes to drive pathology
  - But, they had a problem…

Vaccinating PDAPP mice with amyloid *removed* plaques



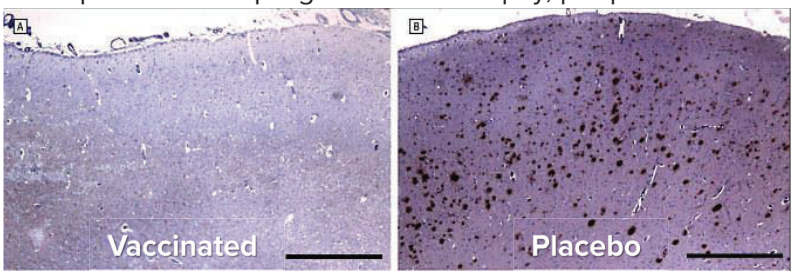
Schenk D et al. Nature 1999;400:173-177

Problem solved, right?

The Alzheimer vaccine story

The bad news

- Human Aβ vaccination (with adjuvant)
  - People with mild-moderate AD
  - Cerebral edema and inflammation in 6% of the subjects
- Dementia progression was unaltered
- Among treated patients who progressed to autopsy, plaques were cleared



Bombois et al. *Arch Neurol* 2007;64(4):583-7

Tales of the times: 2007

Passive Aβ immunotherapy enters human trials

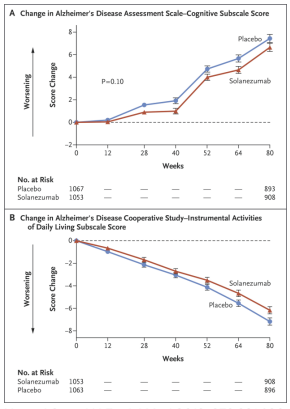
"Within three years, it's all but certain we'll have disease-modifying drugs that fundamentally change the nature of Alzheimer's"

-Sam Gandy, M.D., Chair, Alzheimer's Association National Medical and Scientific Advisory Council, June 2007

https://www.mountsinai.org/files/ISMMS/Assets/Media/Profiles/Sam%20Gandy%20Statement%20to%20Congress%203_20_07.pdf

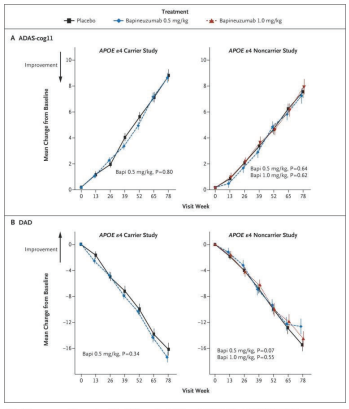
Passive Immunotherapy – A disappointing Wave 1

- Solanezumab – targets Aβ monomers



Honig LS et al N Engl J Med 2018; 378:321-330

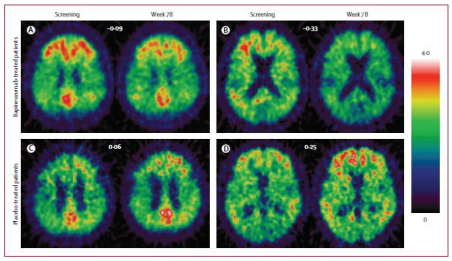
- Bapineuzumab – targets fibrillar Aβ, plaque-clearing



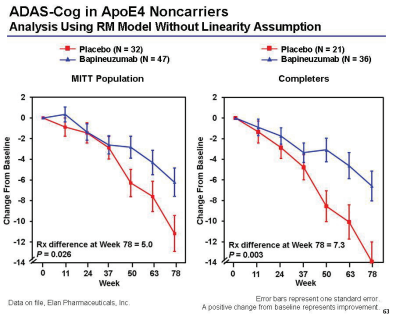
Salloway S, et al N Engl J Med 2014; 370:322-333

Passive Immunotherapy – Some hints from Bapi
The good

Plaque clearance:



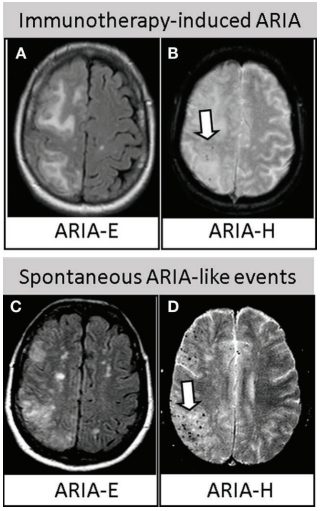
APOE ε4 effects:



Rinne et al, *Lancet Neurology* 2010;9:363-72
Elan presentation, ICAD, 2008

Passive Immunotherapy – Some hints from Bapi
The bad

- "Amyloid-related imaging abnormalities" (ARIA) are discovered and characterized
  - Edema/Effusion (ARIA-E); Hemorrhage (ARIA-H)
  - 35% frequency on retrospective review
    - Only 17% prospective recognition
  - ARIA-H at about half the frequency of ARIA-E
    - Most often co-localized
- Gene dose effects in APOE ε4 carriers
    - ε4/ε4 10-fold more risk than ε4 heterozygotes
- Drug dose related
    - Led to discontinuation of high-dose bapineuzumab in trials
    - Dose reduction likely led to negative results
- Probable mechanistic relationship to vascular amyloid (i.e., CAA-related inflammation)



Sperling RA, et AL. Alzheimers Dement. 2011 Jul;7(4):367-85. doi: 10.1016/j.jalz.2011.05.2351.

Moving on
Lessons learned

- Second wave of anti-amyloid monoclonals
  - Aducanumab
  - Crenezumab
  - Donanemab
  - Gantenerumab
  - Lecanemab
- Fibrillar amyloid target for mAB is desirable
- Under-dosing is a problem
  - ARIA might need to be accepted
- Disease stage is important
  - There may be a "ca-*tau*-strophe" event associated with plaque load

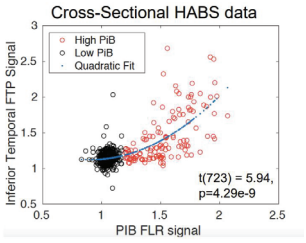
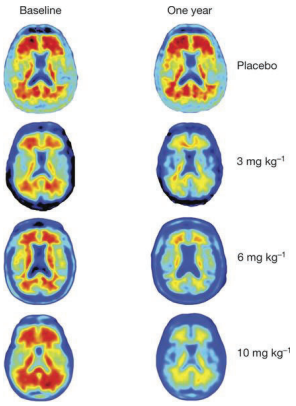
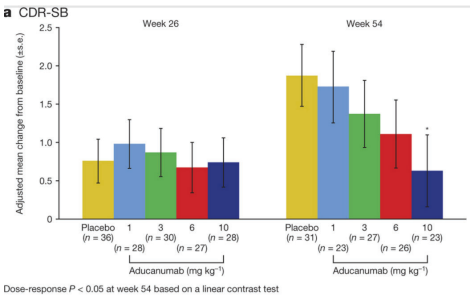


Image via RA Sperling RA,
Harvard Aging Brain Study

van Dyck CH. Biol Psychiatry. 2018 Feb 15;83(4):311-319.

Aducanumab Phase II data
Dose-response over time





Dose-related response in early AD

September 1, 2016

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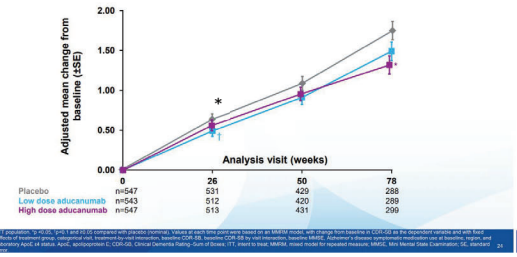
Knowledge that will change your world

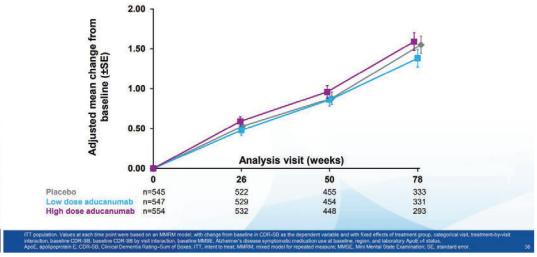
Aducanumab Phase III – primary data*

Overall Results (Global Function)

EMERGE: Longitudinal change from baseline in CDR-SB



ENGAGE: Longitudinal change from baseline in CDR-SB



https://www.evaluate.com/vantage/articles/news/trial-results/biogen-stacks-deck-path-forward-no-clearer-alzheimers

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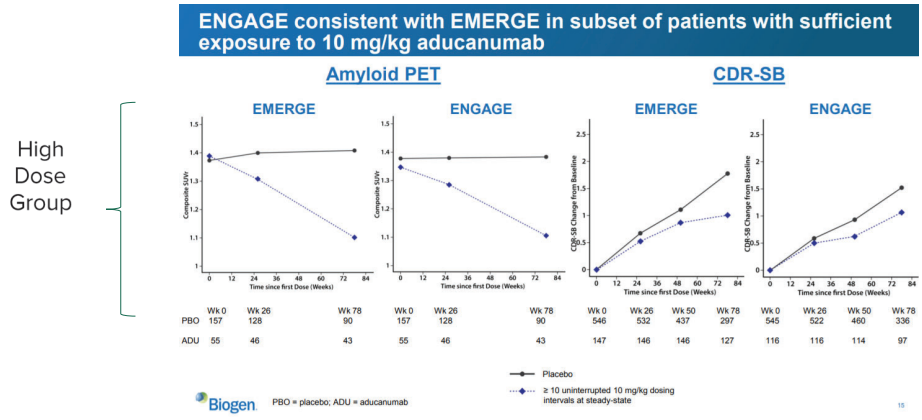
Aducanumab Phase III post hoc analysis*
Efficacy suggested by high-dose exposure

ENGAGE consistent with EMERGE in subset of patients with sufficient exposure to 10 mg/kg aducanumab



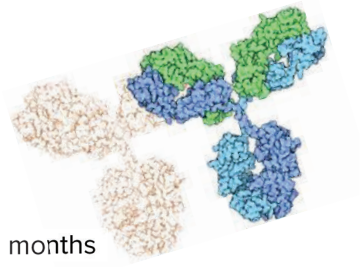
* Biogen proprietary data obtained from public sources; reproduced under Fair Use doctrine

https://www.baybridgebio.com/Images/biogen_slide15.png

Treatment landscape
Aducanumab *(Aduhelm)*

- Controversial “accelerated approval” June 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”
- Appropriate Use Recommendations paper published by Cummings JL et al, 2021
- Limited uptake
  - Uncertain clinical data
  - No meaningful 3rd party coverage

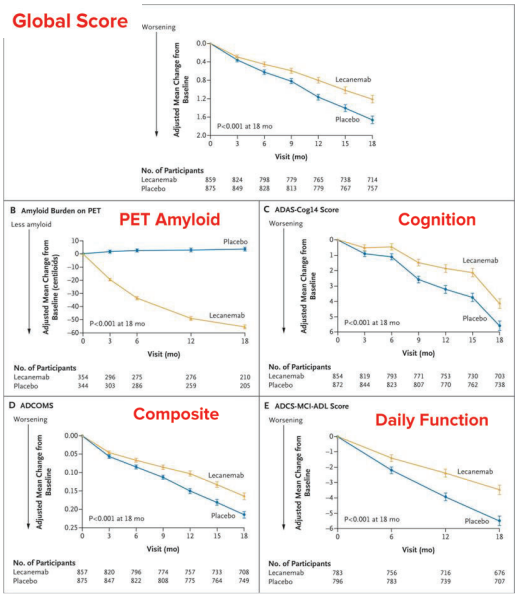
Lecanemab
Leqembi, Eisai



- Monoclonal antibody directed at Aβ peptide
  - Targets amyloid proto-fibrils
  - Plaque-removing properires
- Phase II reported in 2021 (UAB was a site); 854 subjects over 18 months
  - Established dosing at 10mg/kg IV q2weeks
  - Biomarker efficacy
- Phase III reported November 2022; 1795 subjects over 18 months
  - Statistically significant results on all primary and secondary clinical outcomes
  - No major methodological or statistical critiques
- FDA Approval
  - Accelerated approval (based on Phase II) , January 2023
  - Full approval (based on Phase III), July 2023
  - CMS coverage determination: approved, subject to
    - Local MAC authority and
    - Coverage with Evidence Development (CED

Lecanemab Phase III
Clinical Outcomes

- Studied in amyloid-positive MCI and mild dementia
- Efficacy
  - ~25-35% slowing of clinical decline over 18 months
- Adverse events
  - 26% infusion reactions
  - 12% rate of ARIA-E (focal edema/effusion)
  - 17% rate of ARIA-H (hemorrhage):
    - < 1/10 of these are symptomatic
  - APOE ε4 influences ARIA risk
    - Heterozygotes 3x risk increase
    - Homozygotes 10x risk increase



Lecanemab
ARIA rates by APOE status in Phase III

	APOE ε4 noncarrier		APOE ε4 heterozygote		APOE ε4 homozygote	
	Placebo	lecanemab	Placebo	lecanemab	Placebo	lecanemab
ARIA-E total	0.3	5.4	1.9	10.9	3.8	32.6
ARIA-E symptomatic	0	1.4	0	1.7	0	9.2
ARIA-E serious	0	0.7	0	0.4	0	2.1
ARIA-H	4.2	11.9	8.6	14.0	22.1	39.0
ARIA-H symptomatic	0	0.4	0.2	1.0	0.8	0
ARIA-H serious	0.3	0.7	0	0.2	0	1.4

Indication

Lecanemab (Leqembi®), an anti-amyloid monoclonal antibody, is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of Alzheimer's disease (AD) initiated in early AD (mild cognitive impairment (MCI) or mild dementia due to AD).

Treatment landscape
Lecanemab *(Leqembi)*

- FDA Approval
  - Accelerated approval (based on Phase II) , January 2023
  - Full approval (based on Phase III), July 2023
- CMS payments approved, subject to
  - Local MAC authority and,
  - Coverage with Evidence Development (CED)
- UAB Infusion Formulary initially approved in July (self-pay)
  - Formulary revision to accept standard Medicare processes expected by September
- Registry Status
  - IRB review for UAB use of the CMS-run Registry is underway
    - "Waiver of Consent" is projected
    - Any CMS Provider can participate
    - Quantified measures of cognition and daily function required every 6 months
  - Outside infusion center push-back on Registry management

Appropriate Use Recommendations

J Prev Alz Dis 2023;
Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Review

Lecanemab: Appropriate Use Recommendations

J. Cummings[1], L. Apostolova[2], G.D. Rabinovici[3], A. Atri[4], P. Aisen[5], S. Greenberg[6], S. Hendrix[7], D. Selkoe[8], M. Weiner[9], R.C. Petersen[10], S. Salloway[11], For the Alzheimer's Disease and Related Disorders Therapeutics Work Group

- AUR generally follows the Phase III clinical trial enrollment rules:
  - Early AD = MMSE > 22
  - No anticoagulants
  - Test APOE for risk counseling

Qualification: what an

Appropriate Use Recommendations paper, Table 9:

- MRI scanners readily available for unscheduled scanning of symptomatic patients

Step	What	Why
1.	Review for exclusions	**Exclusions** include anticoagulants (not antiplatelets agents), limitations on MRI access (including pacemakers, shunts, etc.), age over 90

Qualification: what and why

Step	What	Why
1.	Review for exclusions	**Exclusions** include anticoagulants (not antiplatelets agents), limitations on MRI access (including pacemakers, shunts, etc.), age over 90
2.	MRI within one year with GRE/FFE/SWI	**Contraindications** include >4 microhemorrhages and significant superficial siderosis
3.	APOE	**Risk Counseling**

Qualification: what and why

Step	What	Why
1.	Review for exclusions	**Exclusions** include anticoagulants (not antiplatelets agents), limitations on MRI access (including pacemakers, shunts, etc.), age over 90
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3.	APOE determination	**Risk Counseling**
4.	Amyloid Probability	**Reduce risks and costs associated with uninformative PET scans and LPs**

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3.	APOE determination	**Risk Counseling**
4.	Amyloid Probability by blood testing	**Reduce risks and costs associated with uninformative PET scans and LPs**
5.	Amyloid PET or	**Establish therapeutic target and pre-treatment baseline**

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Qualification: what and why

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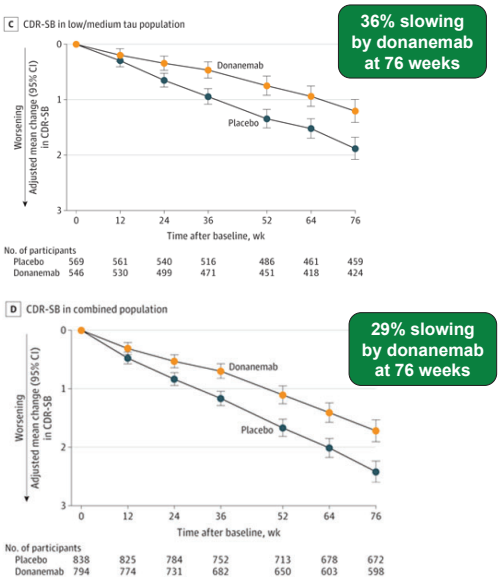
3.	APOE determination	**Risk Counseling**
4.	Amyloid Probability by blood testing	**Reduce risks and costs associated with uninformative PET scans and LPs**
5.	Amyloid PET or CSF Aβp/Tau profile	**Establish therapeutic target and pre-treatment baseline**

Qualification process: pragmatics

- APOE genotype/proteotype for risk determination
  - We have used C2N diagnostics Precivity-AD blood test. (self pay; $1250)
  - Also provides an "Amyloid Probability" score
    - predictive of amyloid PET results
- Precivity-2 launches this month
  - Adds pTau217 to enhance prediction
  - Will require "reflex" APOE testing
- Amyloid confirmation: CSF aβ/tau (self-pay) or amyloid PET (now CMS approved)
  - Local CMS payment decision on amyoid PET is pending
- We plan 18 months of treatment

Coming soon?
Donanemab (Lilly)

- Plaque clearing mAb
- Denied FDA accelerated approval in early 2023
- Phase III results reported July 2023
  - Efficacy and Adverse Events generally commensurate with lecanemab
    - Possibly more ARIA
    - Fewer infusion reactions
- Full approval anticipated by early 2024

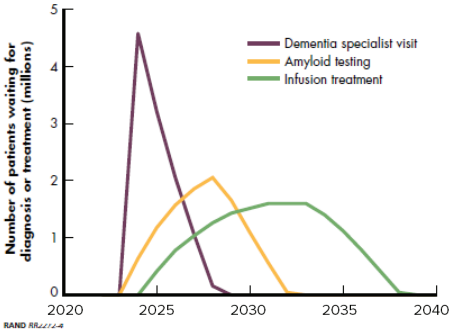


Sims JR, et al. JAMA. 2023;330:512–527.

Wait..., More problems?

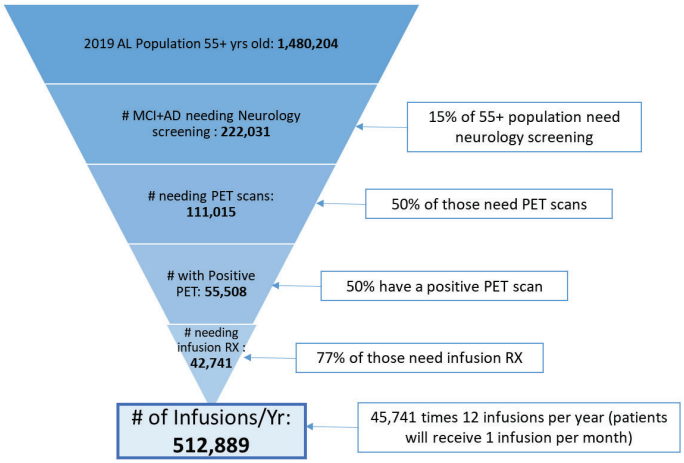
Projected impact of a disease modifying therapy

- By including MCI, the potential "early AD" treatment pool increases to >15 million people in the US
  - >200,000 potential cases in Alabama
- Simulations predict patients will have to wait an average of 18.6 months to begin immunotherapy for Aβ
- Nationwide, ~2.1 million patients would develop Alzheimer's dementia between 2025 and 2040 while on waiting lists to see a "dementia specialist"
  - NB: "Dementia specialists" in this model include ***all neurologists***



RAND corporation report (2017)

Projected impact of a monthly IV DMT in Alabama



Source: 2019 AL population based on Advisory Board Demographic Profiler, Percentages from Alzheimer's Facts & Figures and Dr. David Geldmacher

Further critiques
Unanswered questions

In this model-based economic evaluation, we found that neither aducanumab nor donanemab is likely to be cost-effective by US standards at their expected prices of more than $25 000/y. To become cost-effective, aducanumab's price would need to decrease to less than $3000/y; donanemab, in contrast, could be cost-effective at a price of $20 000/y.

Ross EL, et l JAMA Neurol. 2022;79:478-487

"It's well documented that marginalized communities and people don't get access to diagnostic services as do more privileged populations, because our medical care is two-tiered."

https://www.psychiatryadvisor.com/home/topics/[illegible]-disorders/alzheimers-disease-and-dementia/alzheimer-disease-drug-leqembi-black-patients/

Summary and conclusions

- The "disease modifying" era in for Alzheimer's disease has arrived
  - The pathology is (almost) unarguably altered
- Clinical meaningfulness of the outcomes is incompletely established
  - Are they individually discernable?
  - Do they provide a benefit to the public health?
- Patient selection is critical
  - Managing risk (APOE, anticoagulation, existing CAA)
  - Predicting benefit (AD pathology, disease stage, concomitant illness)
- Patient burden is significant
  - Frequency of infusions and adverse events
  - Risk for life-altering, drug-induced, complications
- Provider burden is substantial and uncompensated
  - Potential organizational benefits are highly attractive
- Access and equity concerns will continue challenge health systems