Practice Transformation at the UAB Memory Clinic: Preparing for the DMT era

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ANA 2024 | 149TH ANNUAL MEETING of the American Neurological Association | ORLANDO • FLORIDA
September 14-17 • Opening Symposium September 14
AMERICAN NEUROLOGICAL ASSOCIATION
INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

DISCLOSURES

Research Funding (paid to UAB)

- Biogen, Eisai, Janssen, Vaccinex, NIH

Consulting fees (paid to speaker)

- Biogen, Eisai, Lilly, NFL Concussion Settlement, Roche/Genentech, Premier, Inc.

Stock (held personally)

- Doximity

Goals of the UAB Memory Clinic

- Offer comprehensive and progressive diagnostic, medical care, and education services for Alzheimer's Disease and related disorders
- Provide ongoing support to patients and their families in their journey to tackle cognitive decline
- Address disparities that serve as barriers to access to services
- Ensure access to cutting edge research and therapies
  - Anticipating availability of monoclonal antibody disease modifying therapies

UAB Memory Clinic

Starting points

- **Workforce vs. Population**
  - 90,000 prevalent AD cases in Alabama in 2016
    - Projected 23% increase to 110,000 cases in 2025
    - AD case load will double from 2020-2040
  - Training pipeline produces only about 30 cognitive neurology specialists per year
    - 7% growth in ALL neurologists, geriatricians, and geriatric psychiatrists

UAB Memory Clinic

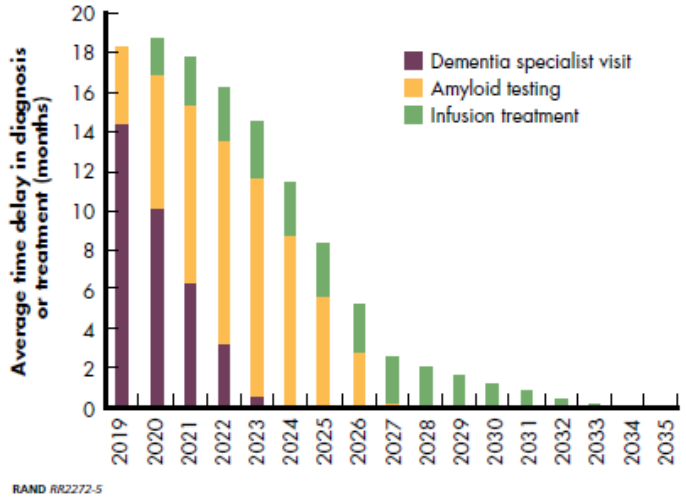
Starting points

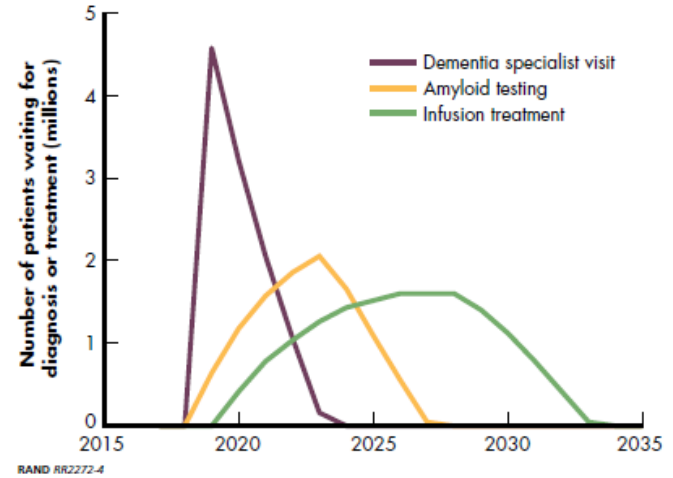
- Only dementia-specialty clinic in AL and FL Panhandle
  - 3 Neurologists, total 0.6 clinical FTE
- 2017-2019 growth plan prioritized the role of CRNPs
  - 22% increase in arrived visits
  - 35% increase in wRVUs
  - 3rd available appointment wait *increased* from 233 to 327 days

Developing an AD Care Path

Simulations Predict of a daunting future – 2017

- AD patients would wait >18 months to receive DMTs
- ~2.1 million patients would develop AD dementia between 2020 and 2040 *while on waiting lists.*





"Addressing capacity constraints requires solving a complex puzzle consisting of payment policy, regulatory requirements, workforce considerations, and capacity planning at the national and local levels, combined with awareness campaigns."

RAND corporation report (2017)

Developing an AD Care Path

Clinical Transformation Priority Areas

- Practice Transformation
- Access
- Space/Facilities
- Visit Types and Locations
- Strategic Partnerships
- Support for Non-Neurology Services
- Finance
- Marketing
- Research
- Training

Our Roadmap:

"Five Imperatives for a Financially Sustainable Dementia Care"

1. Define program scope
2. Prioritize prevention and early diagnosis
3. Build a collaborative care model
4. Elevate Nurse Practitioners
5. Participate in research

https://www.advisory.com/topics/classic/2015/05/building-a-financially-sustainable-alzheimers-disease-memory-disorders-program (2015)

Our Starting Point

1. Define program scope
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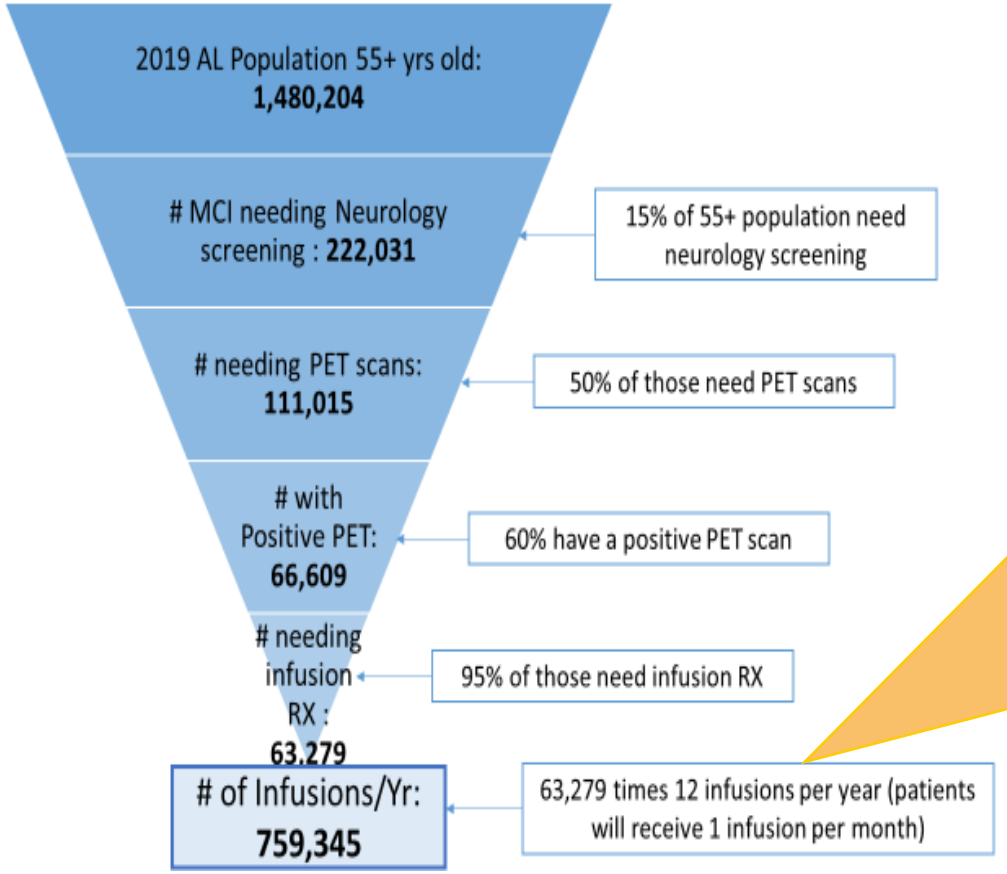
https://www.advisory.com/topics/classic/2015/05/building-a-financially-sustainable-alzheimers-disease-memory-disorders-program (2015)

Financial opportunity
Preliminary market analysis



Take Home Points:

- Even with a 10-fold overestimate, the potential market far exceeds capacity
- Even a small per-patient contribution margin could provide substantial revenue

System-based practice transformation

Envisioning both demand and new treatments

- Simply adding more neurologists at UAB would not meet demand
  - We needed to enact change – system wide – how we approach dementia care
- Priorities
  - Emphasize interprofessional practice at top of licensure
    - Social work/Case management
    - Caregiver counseling
    - Pharmacy
    - Nursing
  - Ensure access to non-neurology services
    - Mental health services, Sleep medicine, Pain management
  - Equip primary care providers to make more appropriate referrals

Progress

- EMR order set for internal Primary Care referrals to Memory Clinic
  - Cognitive tests, Depression and sleep screening, Blood work, MRI
- CRNP “Rapid Access Clinic”
  - For self-referrals and outside referrals with no prior work-up
- Blood based biomarker protocols
  - APOE for risk counseling
  - Amyloid status for PET triage
- Radiology protocols for MRI reporting (diagnostics and ARIA)
- RN Case Managers oversee treatment implementation
  - Prior Auth, infusion scheduling, registry entries, safety protocols

Idealized UAB Care Path

- Patient with Memory Concerns
  - In system:
    - Primary Care evaluates for severity and treatable causes, guided by order set
    - If objective decline, order MRI brain, refer to memory clinic
  - Out of system:
    - APP triage “Rapid Access Clinic” – often telemedicine
- Memory Clinic MD visit for cognitive testing, specialty differential diagnosis
  - When AD is suspected: APOE testing, Blood-based Biomarkers
- If BBM are positive
  - Amyloid PET or CSF confirmation of pathology
- If positive, APP review of treatment expectations and risks
  - Refer to UAB Neuropsychology Rapid Access Program for insurance qualification as needed
  - Engage to Memory Clinic Case Management RN for ongoing coordination of Rx

Lessons learned
(Still learning…)

- Case management is much more demanding than predicted
  - ARIA responses, MRI (re)scheduling, etc.
- A treatment consensus panel is important
- Quality control for outside MRI safety monitoring is limited*
- Managing patient/family expectations is continuous

*'*Limited*' is a generous attribution

Anti-Amyloid Antibody Therapy

Gwenn Garden, MD, PhD
Distinguished Professor and Chair
Department of Neurology, UNC
Co-Director, Duke-UNC Alzheimer Disease Research Center

Disclosures

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- Paid Advisor
  - Lilly
  - Eisai

Topics for this talk:

1) AD diagnosis using biomarkers

2) Evidence for current AD treatment options

3) Treatment monitoring

Dementia results from overlapping pathology

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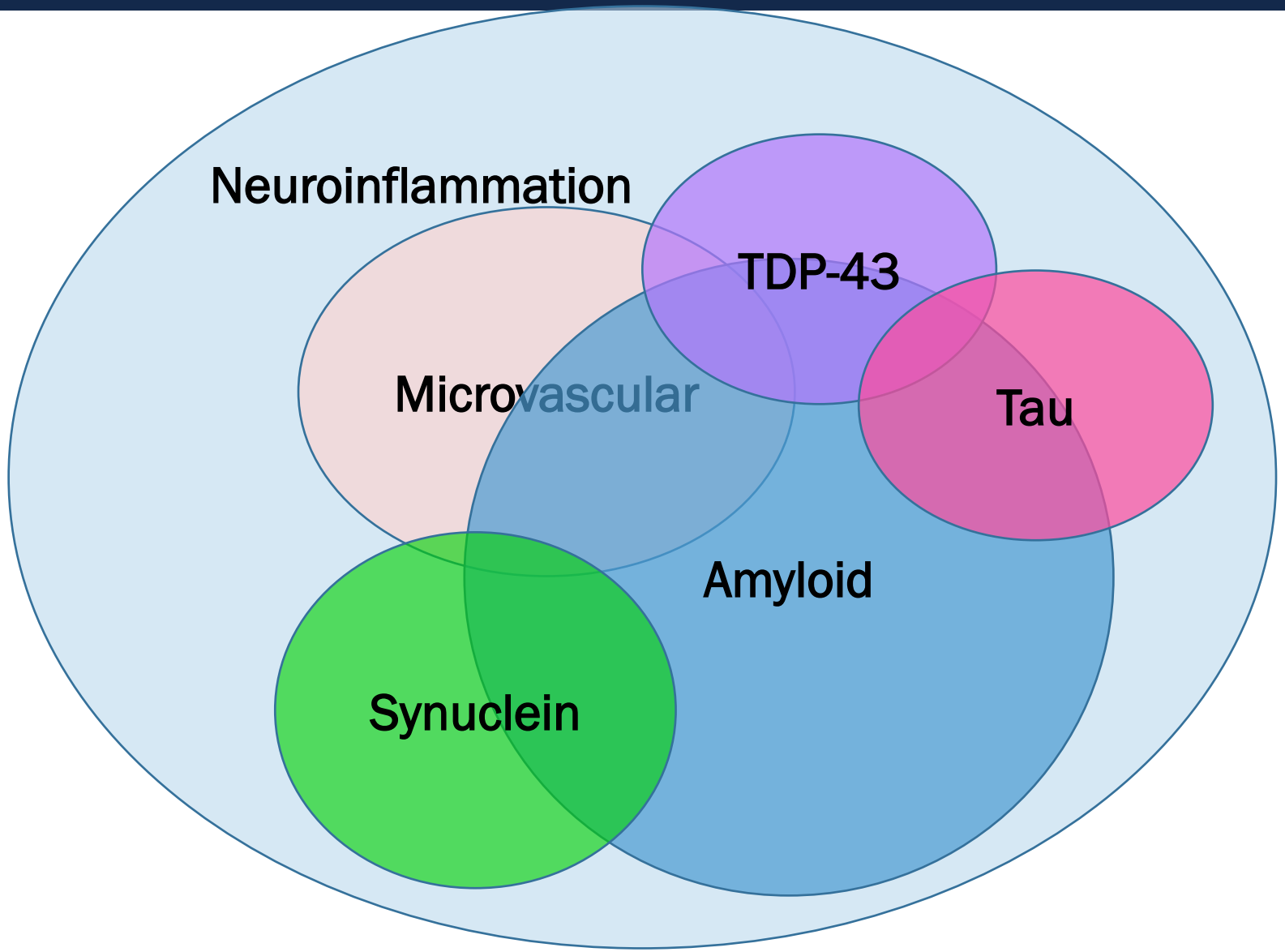
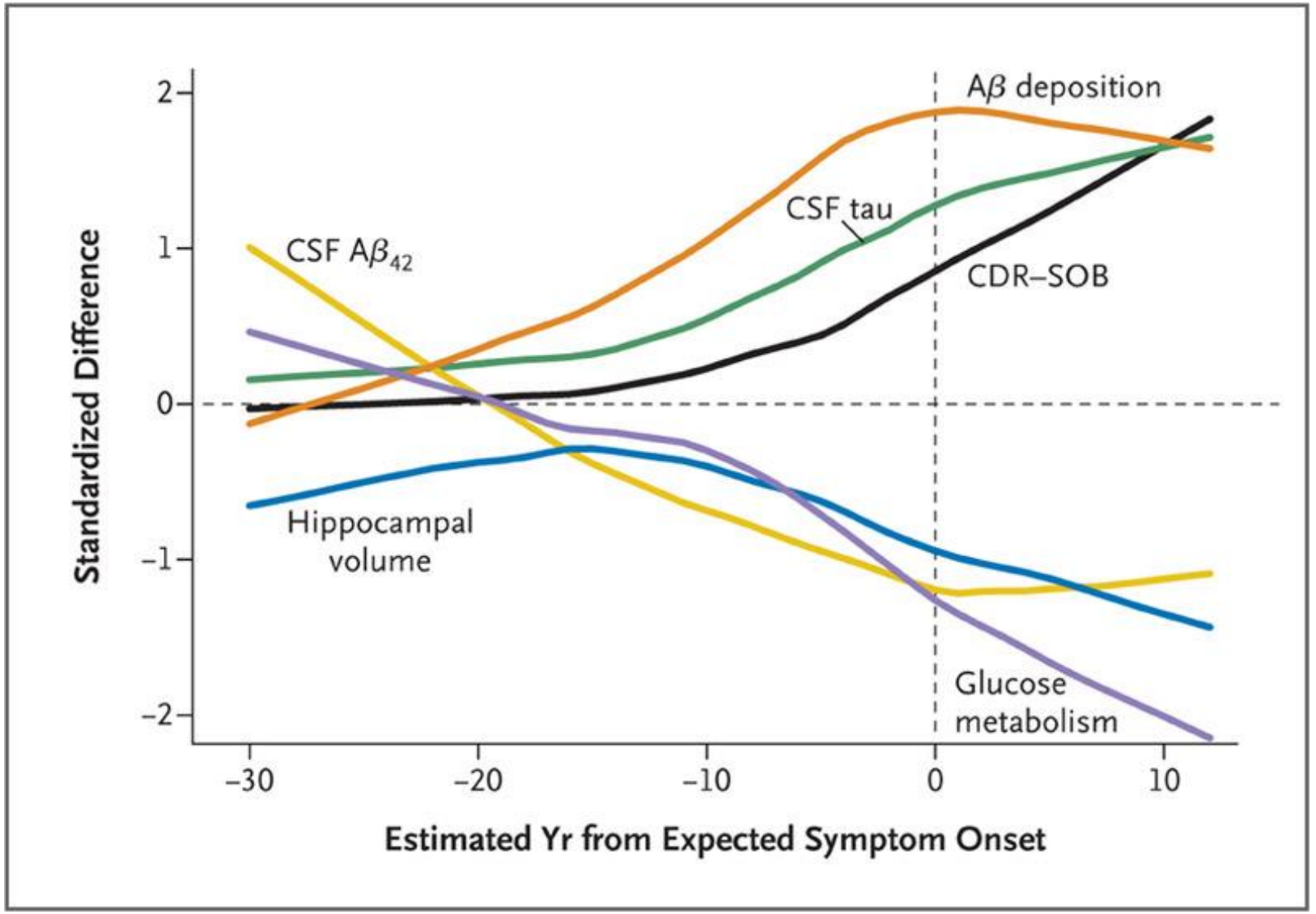


Biomarker studies demonstrate an AD prodrome



Bateman et al., N Engl J Med; 367:795-804

Biomarkers Change the Paradigm of AD diagnosis

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- A/T/N Biomarker based diagnostic scheme
  - A=Amyloid
  - T=Tau
  - N=Neurodegeneration

	Cognitively unimpaired	MCI	Dementia
A- / T- /(N)-	Normal AD Biomarkers	Normal AD biomarkers with (non-AD) MCI	Normal AD biomarkers with (non-AD) dementia
A+ / T- /(N)-	Preclinic AD pathology	Early AD pathology with MCI	Early AD pathology with dementia
A+/ T- /(N)+	Preclinical AD with additional pathology	AD and non-AD pathology with MCI	AD and non-AD pathology with dementia
A+ / T+ /(N)-	Preclinical AD	AD with MCI (prodromal AD)	AD with dementia
A+ / T+/(N)+	Preclinical AD	AD with MCI (prodromal AD)	AD with dementia

Adapted from Jack et al., Alzheimer's and Dement; 14(4):536-562

New Research Diagnostic/Staging Scheme

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- Combination of clinical and biomarker stage
  - Clinical stage 0-6
  - Biomarker stage A-D
  - Stage 0 = Asymptomatic with deterministic gene

	1=Normal cognition	2=mild change, no functional impact	3=MCI, early functional change	4=Dementia, mild functional impairment	5=Dementia, mod. functional impairment	6=Dementia, severe functional impairment
Amyloid + Tau PET -	1A	2A	3A	4A	5A	6A
Tau PET, Med. Temp. Lobe uptake	1B	2B	3B	4B	5B	6B
Tau PET Moderate neocortical	1C	2C	3C	4C	5C	6C
Tau PET high neocortical	1D	2D	3D	4D	5D	6D

Adapted from Jack et al., *Alzheimer's and Dement*, (2024)20:5143–5169

PET Alternatives

(A) Amyloid

CSF: Aβ42/40, pTau-181/Aβ42, t-Tau/Aβ42

serum: pTau-217

(B) pTau-205

(C) MTBR-tau-243

(D) Non-phospho Tau fragments

Adapted from Jack et al., *Alzheimer's and Dement*, (2024)20:5143–5169

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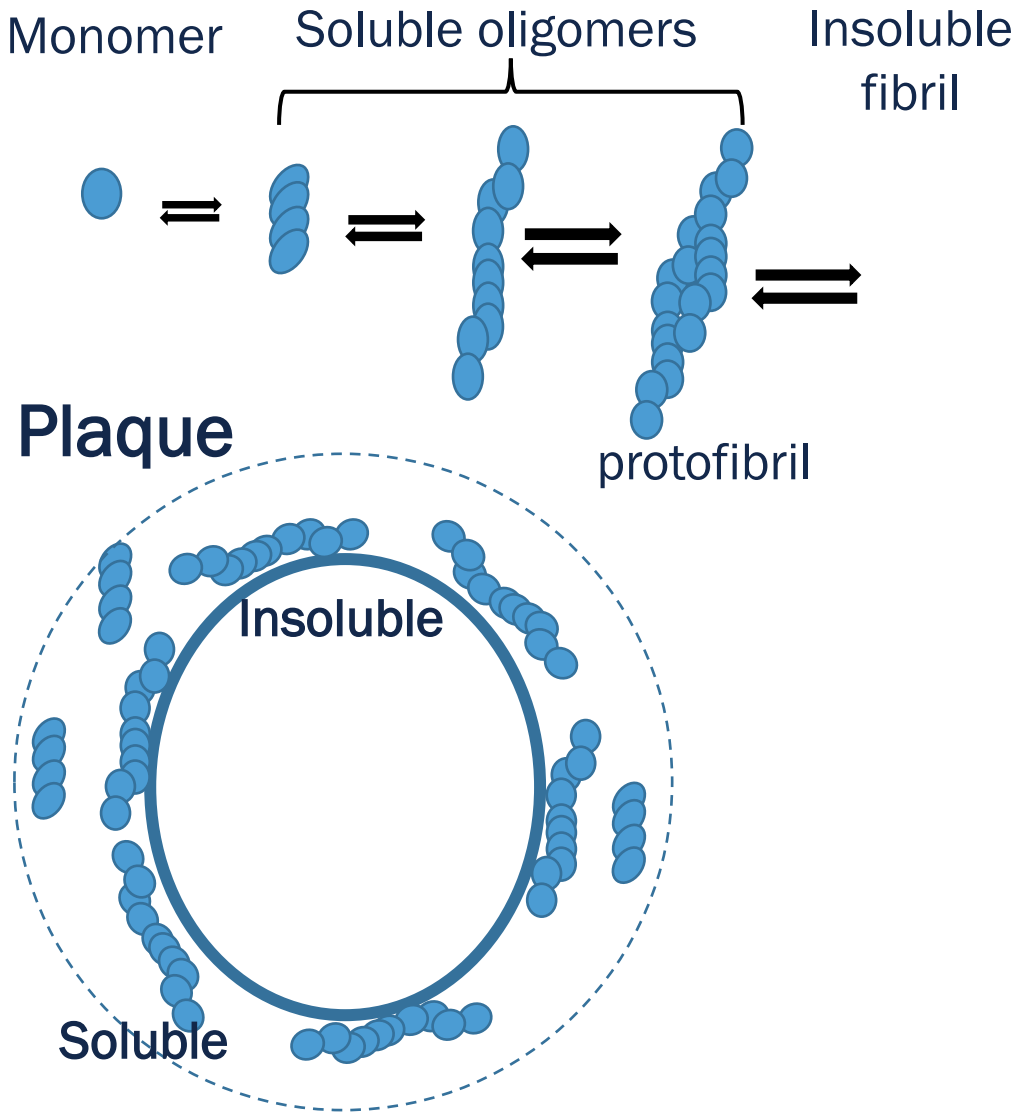
Why use biomarker based diagnosis in the clinic today?

Treatment is available

Early treatment will be more effective

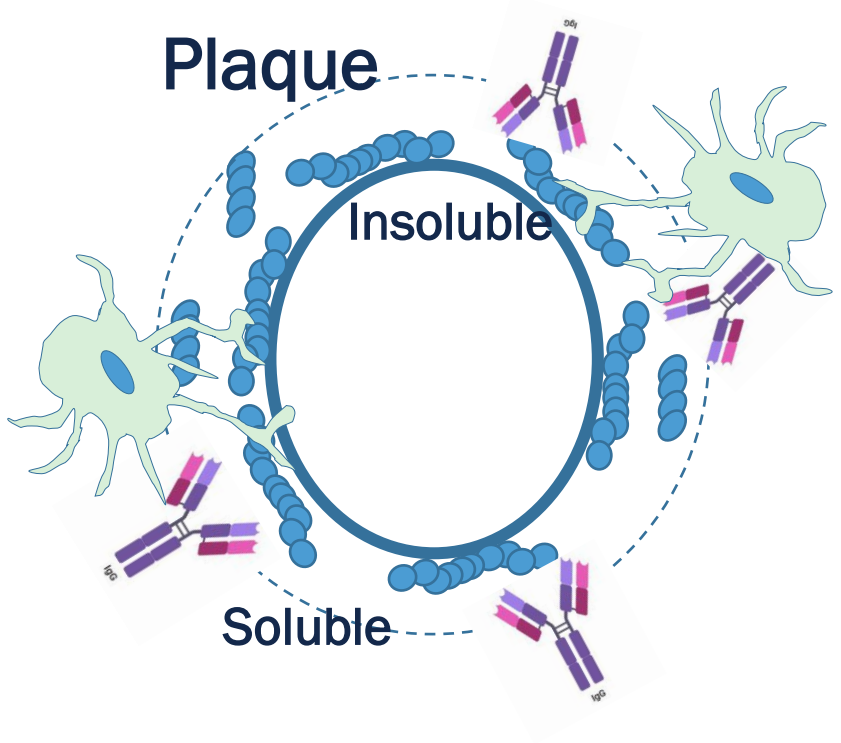
Amyloid-β Oligomers are a Therapeutic Target

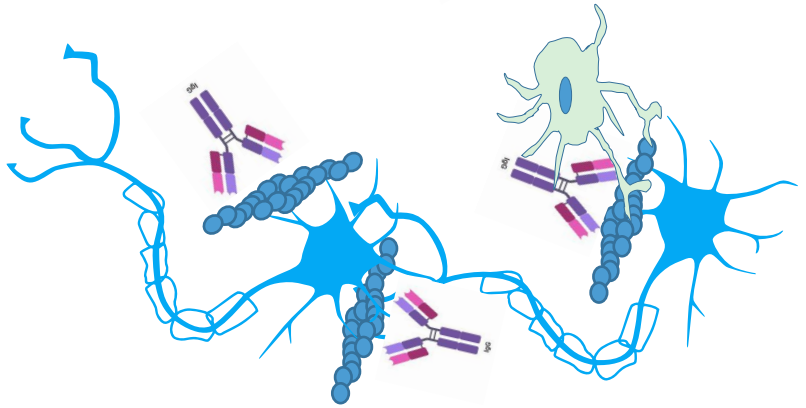
- Alzheimer's Disease (AD) pathology includes Amyloid-β (Aβ) plaques.
- Genetic and biomarker studies support the hypothesis that Aβ contributes to AD pathogenesis
- Variants in the amyloid precursor protein gene (*APP*) cause early onset familial AD.
- Two *APP* variants (Dutch and Nordic) produce Aβ that fails to transition from protofibril to fibril.



What is Lecanemab?

- Humanized IgG_1 monoclonal antibody raised against oligomers and protofibrils
- Selectively binds to soluble Aβ (monomer, oligomer, protofibrils)
  - > 1000-fold selectivity for protofibrils over monomers
  - > 10X affinity for protofibrils over fibrils





Phase III trial – Clarity AD (Lecanemab)

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- 1795 individuals randomized
- Age 50-90 (mean age 71)
- Amyloid positive (PET or CSF)
- MCI or early AD
- Objective memory deficit
- MMSE mean 25.5
- CDR-SB was primary endpoint

- What is CDR-SB?
  - 3 cognitive domains
    - Memory, orientation, judgment
  - 3 functional domains
    - Personal Care, community affairs, home and hobbies
  - Scored from 0 (normal) to 18 (maximally impaired in 6 domains)

Adapted from van Dyck et al. *N Engl J Med* (2023);388:9-21

Lecanemab slows AD progression

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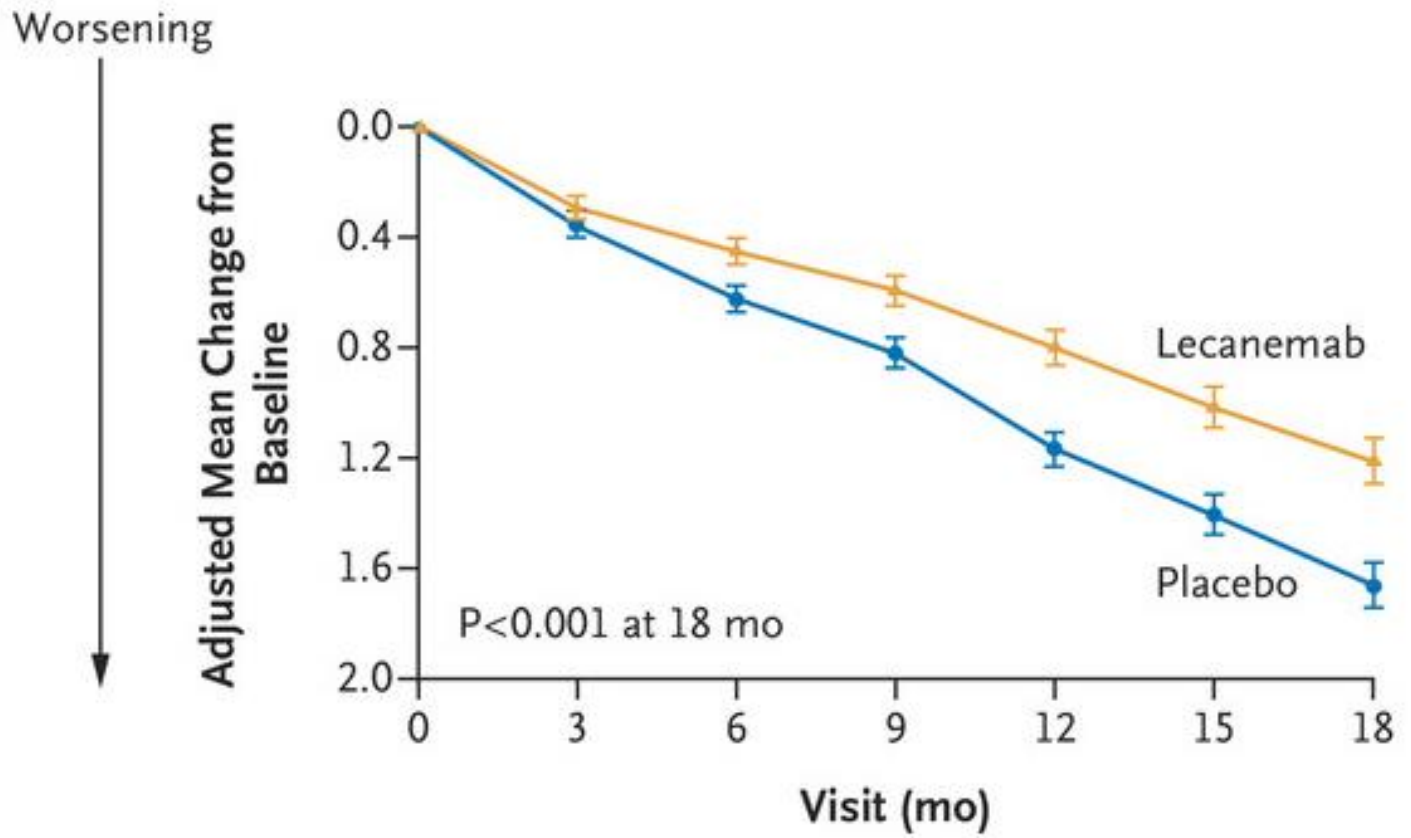
Primary Endpoint



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Adapted from van Dyck et al. *N Engl J Med* (2023);388:9-21

TRAILBLAZER-ALZ2 (Donanemab)

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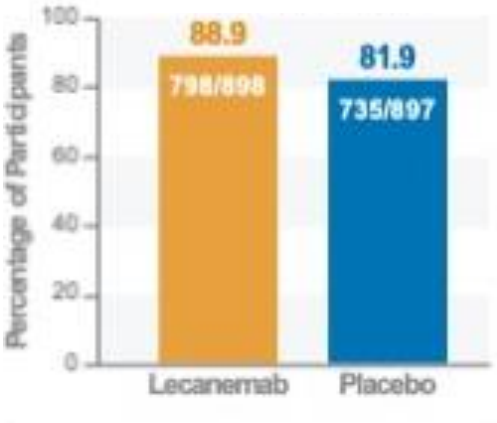
- Monoclonal antibody against insoluble plaque associated Aβ
- Primary and secondary endpoints met.
- Achieved amyloid clearance by PET
- Segregated participants by age, Tau PET and pTau-217
  - Participants <75 years old had greater slowing of decline
  - Participants <lower Tau PET had greater slowing of decline
  - Participants < lower pTau-217 had greater treatment effect

Adapted from Sims et al., *JAMA* (2023) 330(6):512-527

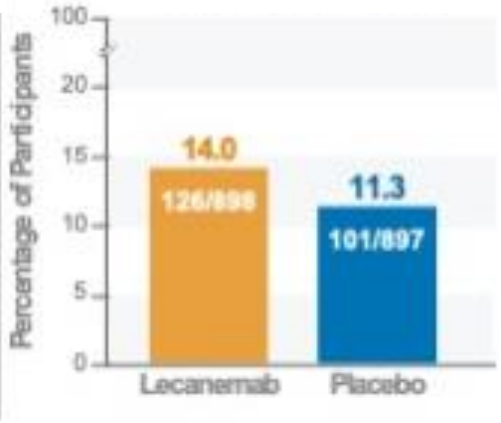
Safety Outcomes

Clarity AD

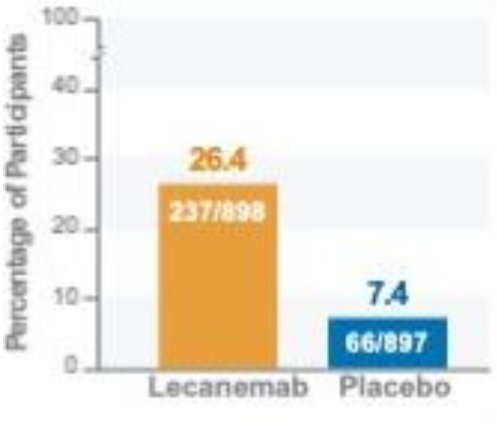
Any Adverse Event



Serious Adverse Event



Infusion Reactions



Amyloid-Related Imaging Abnormalities

Adapted from van Dyck et al. *N Engl J Med* (2023);388:9-21

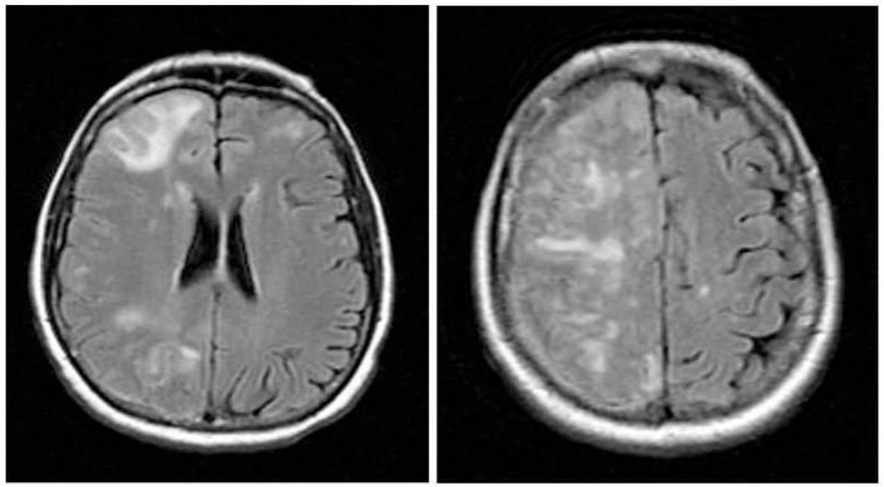
Trailblazer 2

Event	Donanemab	Placebo
Death	3 (0.4)	1(0.1)
SAE	148 (17.4)	138 (15.8)
Infusion Reaction	74 (8.7)	4 (0.5)
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	65 (7.4)
Symptomatic ARIA	52 (6.1)	1 (0.1)
% ARIA (no E4)	15.7	0.8
% ARIA (E4 Het)	22.8	1.9
% ARIA (E4 Homo)	40.6	3.4

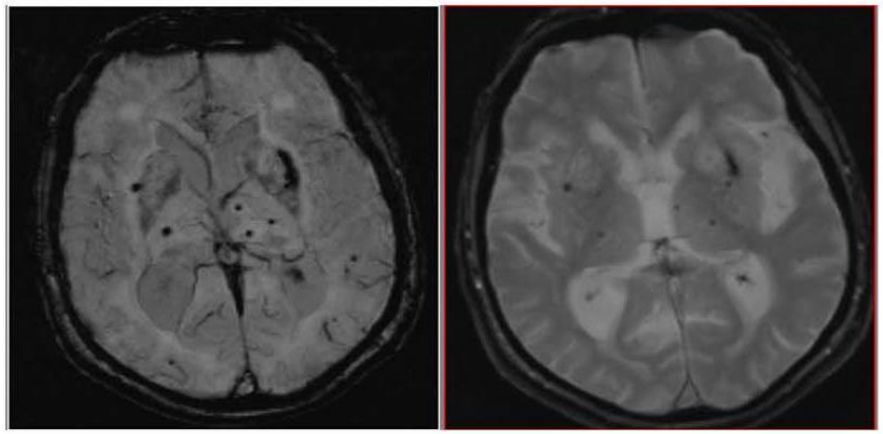
Adapted from Sims et al., *JAMA* (2023) 330(6):512-527

What is ARIA?

ARIA-E



ARIA-H



Sperling et al. *Alzheimers Dement*. (2011) 7(4):367-385.

ARIA: clinical presentation and monitoring

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- Non-localizing symptoms
  - HA, confusion
- Seizures
- Stroke like symptoms
- Most are asymptomatic at time of identification by imaging
  - 1, 3, 6, 12, and 18 months
  - Need to image on same scanner used for baseline.

ARIA intervention

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- Consensus still in gestation
- Asymptomatic ARIA – Stop/slow infusions
- Symptomatic ARIA – Steroids + stop/slow infusions
- Stroke like episodes/ER visits
  - EHR cues
  - Wallet Cards
  - Avoid TPA

Acute Cerebral Amyloid Angiopathy

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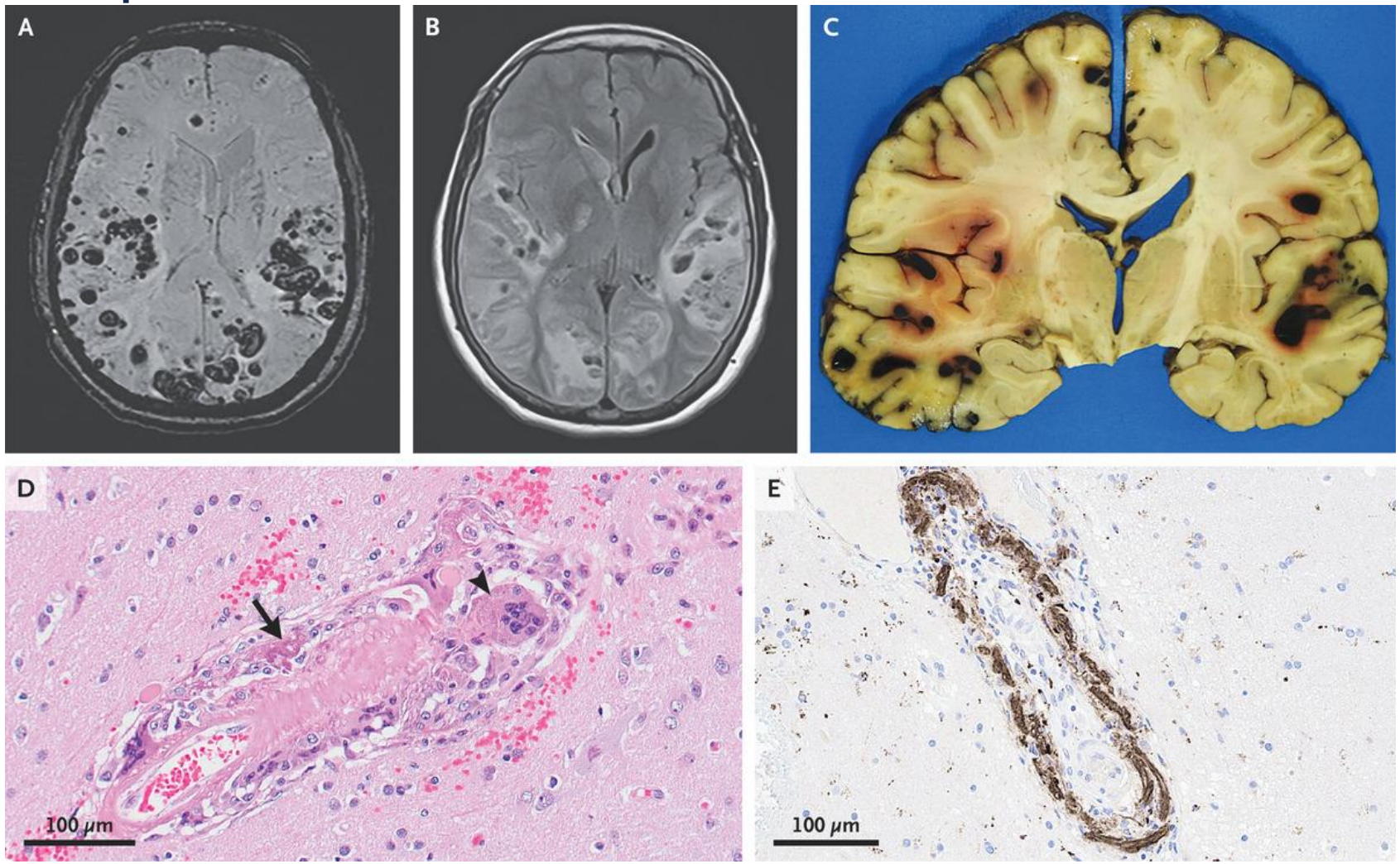
Fatal ICH in open label extension



NJ Reish et al. N Engl J Med 2023;388:478-479.

Summary

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- AD pathology can be confirmed in early-stage patients using biomarkers.
- Treatment with anti-amyloid antibody therapy slows symptom progression in MCI and early AD.
- Benefits are greatest for those identified at earliest disease stage.
- On target toxicity (ARIA) requires close monitoring of patients undergoing anti-amyloid antibody therapy.

Implementation of anti-amyloid therapy treatment model in a health system

Highlights from Duke University implementation of lecanemab

Kim G. Johnson, MD
Division Chief, Memory Disorders
Department of Neurology
Duke University

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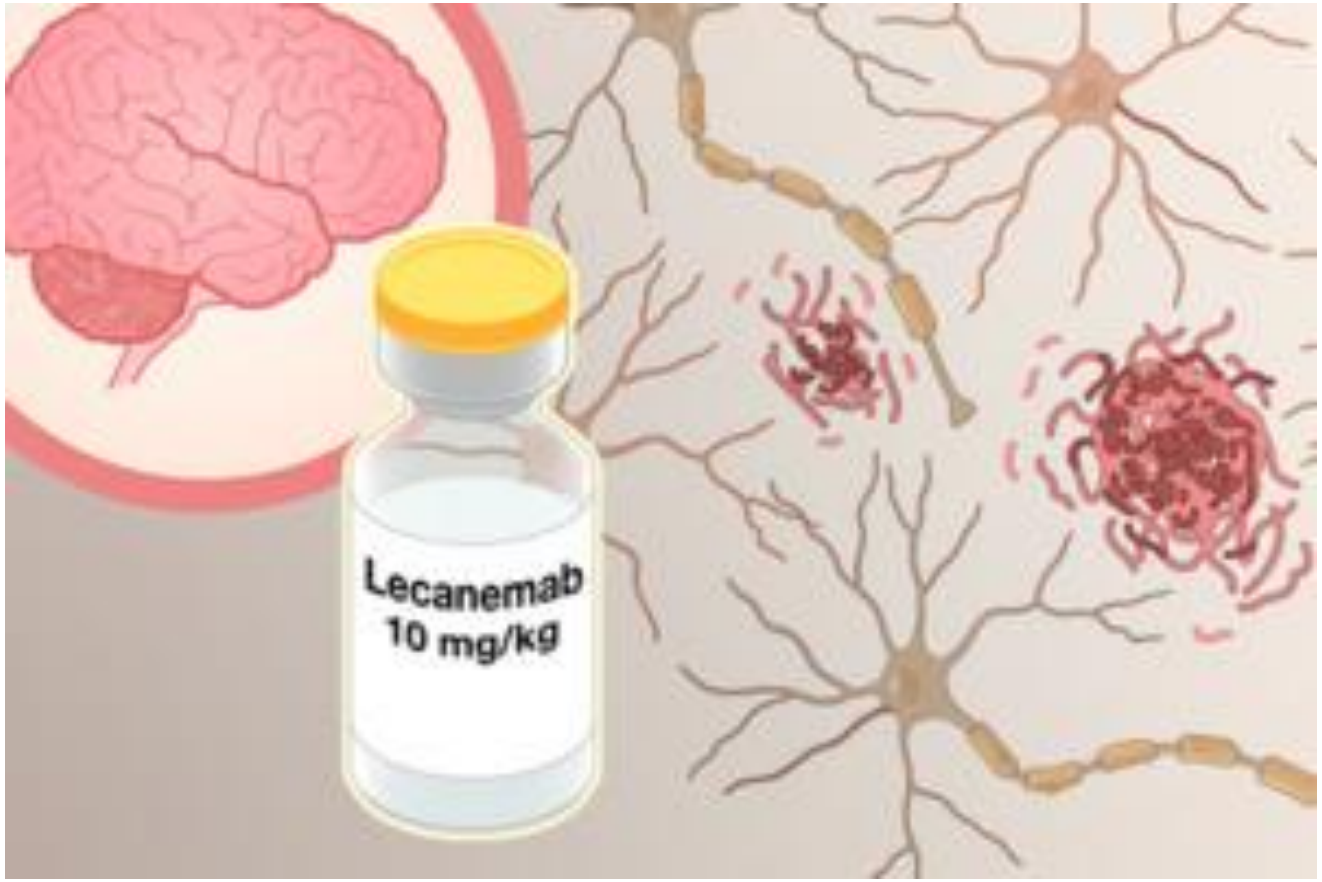
DISCLOSURES

Kim G. Johnson, MD

Department of Neurology
Duke University School of Medicine
North Carolina

- Principal investigator on the AHEAD 3-45, LIFT-AD, and LX1001 clinical trials
- Principal investigator on ALZ-NET registry
- Research Consultant, University of Southern California
- Speaker, Eisai Inc.
- Facilitator, PeerView Institute for Medical Education

New drugs, new delivery, new treatment models . . . .



The Duke University Health System initiative

Weekly meetings with key stakeholders

- Health system administration
- Memory clinic providers
- Clinic nursing staff
- Pharmacy
- Infusion center leadership and staff
- Radiology (MRI, LP)
- Medicare payment specialists
- Electronic health record specialists
- Financial counselors

Duke Memory Disorders Clinic multidisciplinary approach to AD care

Behavioral neurology - 2

Geriatric psychiatry - 1

Geriatric medicine - 2

APP's – 4

Nurses specialized in memory

Social work – 2

Dedicated clinical and research coordinator - 1

- Hired 1.5 FTE APP positions and 1.0 FTE clinical and research coordinator to assist with lecanemab
- Offered website scheduling with held clinic slots
- Worked with Geriatric Medicine Clinic to create a "Memory Referral Pathway" based on age and severity of symptoms – MCI/early AD routed to Memory Clinic

Current status in the Duke University Health System

- May 2023: First infusion with cash payers
- July 2023: Medicare beneficiaries received their first infusions
- There are currently infusion plans ordered for approximately 150 patients
- Patients get all infusions and MRI’s at Duke
- Patients must register in CMS registry (Medicare patients) and/or ALZ-NET

Duke Memory Disorders Clinic prescribing guidelines: Clinical Inclusion Criteria

The following are treatment eligibility criteria:

- MCI or mild AD diagnosis
- MMSE ≥22 or MoCA ≥17
- Amyloid positive by CSF (Aβ42/40, p-tau/Aβ42) or amyloid PET
- Care partner for treatment duration
- Patient understands treatment requirements and benefit/harm
- Must undergo MRI scans (no claustrophobia, pacemaker, defibrillator, metal implant contraindications)

Duke treatment facilities require patients to undergo *APOE-ε4* genotyping prior to infusion

Duke Memory Disorders Clinic prescribing guidelines: Clinical Exclusion Criteria

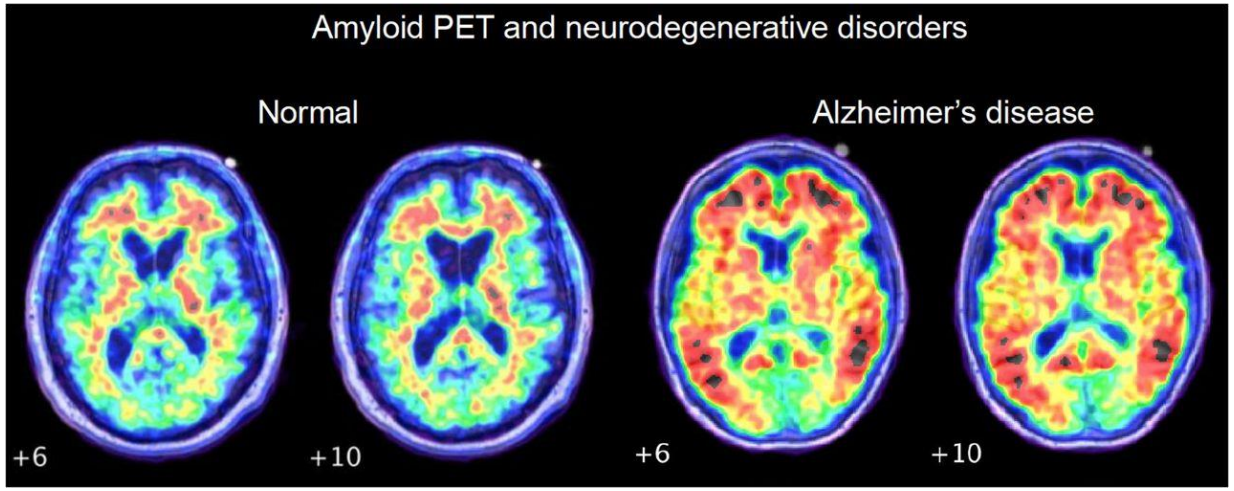
Medical conditions

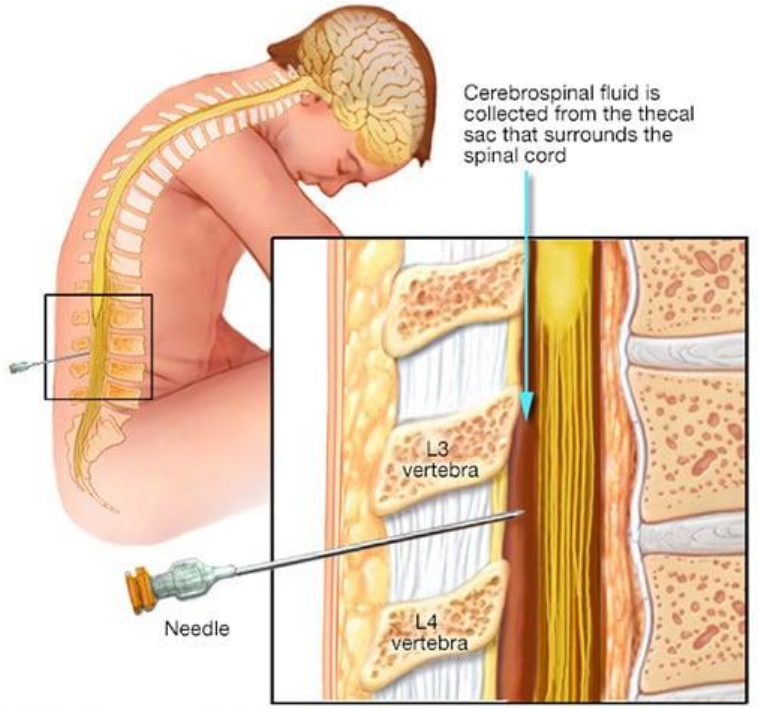
- History of immunologic conditions (e.g., SLE, RA, Crohn's disease)
- Systemic therapy with immunoglobulins, monoclonal antibodies, or immunosuppressants or plasmapheresis
- Any unstable medical conditions
- History of stroke (including cortical), TIA, bleeding disorders (including uncontrolled, platelet count <50,000 or INR >1.5), and/or seizures
- Mental illness (psychosis) or depression interfering with understanding requirements and benefit/harm
- Therapy with anticoagulants, thrombolytics, or vitamin K antagonists
- Clotting disorders

History of MRI findings

- ≥ 4 microhemorrhages (<10mm)
- Any macrohemorrhage (>10mm)
- Cortical stroke
- Superficial siderosis
- Evidence of vasogenic edema
- Severe subcortical white matter hyperintensities
- (Fazekas score of 3 or more)
- CAA-related inflammation and Aβ-related angiitis
- MRI abnormalities (e.g., cerebral contusion, encephalomalacia, brain aneurysm or other vascular malformations, CNS infection, brain tumors other than meningioma or arachnoid cysts)

Amyloid testing





Amyloid PET – unlimited now covered by Medicare

Cerebrospinal fluid testing – preferred (early indicator)

- Mayo Labs ADEVL: Alzheimer's Disease Evaluation (p-tau/abeta 42, abeta 42, t-tau, p-tau)
- Mayo Labs AMYR: Beta Amyloid Ratio (1-42/1-40)
- LP clinic and radiology with XR guidance

Informed consent

- Providers have discussions about benefits versus risks (harms) of lecanemab
- Risk discussion is informed by APOE genotype of the patient
- Patient must sign a consent form (general Duke
- consent for procedures)
- Process is documented in patient's chart with smartphrases

- Summary note (lecanemab checklist) placed in the chart outlining cognitive test scores; functional status score; CDR; baseline imaging results; amyloid study; CMS registry number and dates for all – assists with coverage

APOE risk stratification

APOE-E3/E3
Risk of brain swelling with lecanemab: 5.4%
Risk of brain swelling with associated symptoms (headache, confusion, vision changes, etc.): 1.4%
Risk of small areas of brain bleeding (microhemorrhages): 11.9%*
*In the CLARITY-AD study, 4.2% of people in the placebo group (group that did not get lecanemab) also developed small areas of bleeding in the brain as this can happen in Alzheimer's disease.

APOE-E3/E4
Risk of brain swelling with lecanemab: 10.9%
Risk of brain swelling with associated symptoms (headache, confusion, vision changes, etc.): 1.7%
Risk of small areas of brain bleeding (microhemorrhages): 14.0%*
*In the CLARITY-AD study, 8.6% of people in the placebo group (group that did not get lecanemab) also developed small areas of bleeding in the brain as this can happen in Alzheimer's disease.

APOE-E4/E4
Risk of brain swelling with lecanemab: 32.6%
Risk of brain swelling with associated symptoms (headache, confusion, vision changes, etc.): 9.2%
Risk of small areas of brain bleeding (microhemorrhages): 39.0%*
*In the CLARITY-AD study, 22.1% of people in the placebo group (group that did not get lecanemab) also developed small areas of bleeding in the brain as this can happen in Alzheimer's disease.

Infusion monitoring

10 mg/kg infusion every 2 weeks – completed over 1 hour	• Hypersensitivity protocol for acute reactions
Transfer to ED for severe acute reactions	• Diphenhydramine and acetaminophen pre-treatment for infusion reactions

Patients have to be accompanied for the first 5 visits

MRI monitoring

Collaboration with Neuroradiology

- Use 3T scanner - T2 flair and SWI sequences
- ARIA report with template
- Health system gives lecanemab scans preference
  - Same day as 4th, 6th, 13th treatment
  - 12 month scan in APOE4
  - Emergent MRI

INTERNATIONAL STROKE CONFERENCE POSTER ABSTRACTS
SESSION TITLE: ACUTE NEUROIMAGING POSTERS II

Abstract 3208: Sensitivity and Reliability of SWI Compared to T2* GRE MRI for Detection of Microbleeds in Cerebral Amyloid Angiopathy

Ah-Ling Cheng, Cheryl R McCreary, M. L Lauzon, Richard Frayne, Mayank Goyal and Eric E Smith

Originally published 7 May 2018 | https://doi.org/10.1161/str.43.suppl_1.A3208 | Stroke. 2012;43:A3208

MRI ARIA report template

COMPARISON: MRI brain exam dated 9/5/2023

TECHNIQUE/PROTOCOL: Noncontrast ARIA monitoring protocol brain MRI was performed. The presence of microhemorrhages was assessed using SWI imaging. Neuroquant analysis: Automated volumetric analysis was performed with NeuroQuant Software. Percentiles listed account for age and gender.

FINDINGS:
Amyloid related imaging abnormalities (ARIA):
- ARIA-E Edema: None
- ARIA-H microhemorrhage: None
- ARIA-H superficial siderosis: None
- Additional details/lesion localization: N/A

IMPRESSION:
1. ARIA grading as follows:
    - ARIA-E edema: None
    - ARIA-H microhemorrhage: None
    - ARIA-H superficial siderosis: None

Reimbursement

Traditional Medicare

- Pays 80% of cost of drug, 20% may be covered by supplemental coverage

Medicare Advantage

- Cover on plan-by-plan basis

Private Insurance

- Cover on plan-by-plan basis if patient is enrolled in a registry (ALZ-NET)

Weekly meetings to discuss reimbursement issues (denials) and quality improvement

Disparities in AD patient care

Access to diagnostic services such as lumbar punctures and PET imaging

Availability of specialists

Healthcare coverage for marginalized populations

Variability in patient mobility and care support to get to the clinic for regular treatment procedures

Access to support system (e.g., family, friends, or others)

Future considerations

- Consider repeat amyloid testing at 18 months for lecanemab patients
  - What is the cost to the health system?
  - Is proving amyloid clearance necessary?
- Can home health or outside centers provide infusions?
- How do we increase traffic to our website for online appointment requests?
- How do we provide more efficient care and how will the needs of our patients change?
- How will we continue our relationship with geriatric medicine?
- How will the delivery model change with injection methods?