MAYO CLINIC | School of Continuous Professional Development

DISEASE-MODIFYING THERAPIES FOR AD

REAL-WORLD EXPERIENCE

CANADIAN CONFERENCE ON DEMENTIA
HOT TOPICS (STREAM 1)
OCTOBER 2026

Vijay K Ramanan, MD PhD
Consultant and Associate Professor
Director, Alzheimer's Disease Treatment Clinic
Department of Neurology
Mayo Clinic – Rochester, MN



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LEARNING OBJECTIVES

- Identify potentially appropriate candidates for anti-amyloid therapies in early AD
- Characterize benefits and risks of anti-amyloid therapies
- Recognize potential near-term evolutions in individualized application of disease-modifying therapies for Alzheimer's disease and related dementias (i.e., ADRD precision medicine)

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BROAD-BASED AD MANAGEMENT

- Goal: optimize brain health, mental functioning, and quality of life
  - Maintaining regular physical, mental, and social engagement
  - Healthy and balanced diet
  - Consistent high-quality sleep, including treatment of sleep disorders
  - Treatment of neuropsychiatric symptoms (medication + non-medication)
  - Supportive therapies (e.g., speech/occupational therapy)
  - Safety/Supervision (e.g., driving) and caregiver resources
  - Management of medical comorbidities and coexistent medications
- These largely non-pharmacologic tenets are critical aspects of management

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AD: ORAL PHARMACOLOGIC MANAGEMENT

- Cholinesterase inhibitor therapy: first-line symptomatic approach
  - There is a deficit of cholinergic neurotransmission in AD
  - Drug mechanism: increase available Ach for neurotransmission
  - Goal: support cognitive functioning to prolong independence
    - Most patients will not observe an overt improvement
  - Options: donepezil, rivastigmine, galantamine
  - Major side effects: GI (nausea/vomiting, diarrhea, bloating), cardiac (obtain EKG prior to starting treatment to rule out contraindications)
- Memantine: second-line symptomatic approach (“moderate AD dementia”)
  - Mechanism: NMDA (glutamate) receptor antagonist (limit overactivation)
  - Favorable side effect profile
- Big picture: optimize symptom management to delay cognitive/functional consequences

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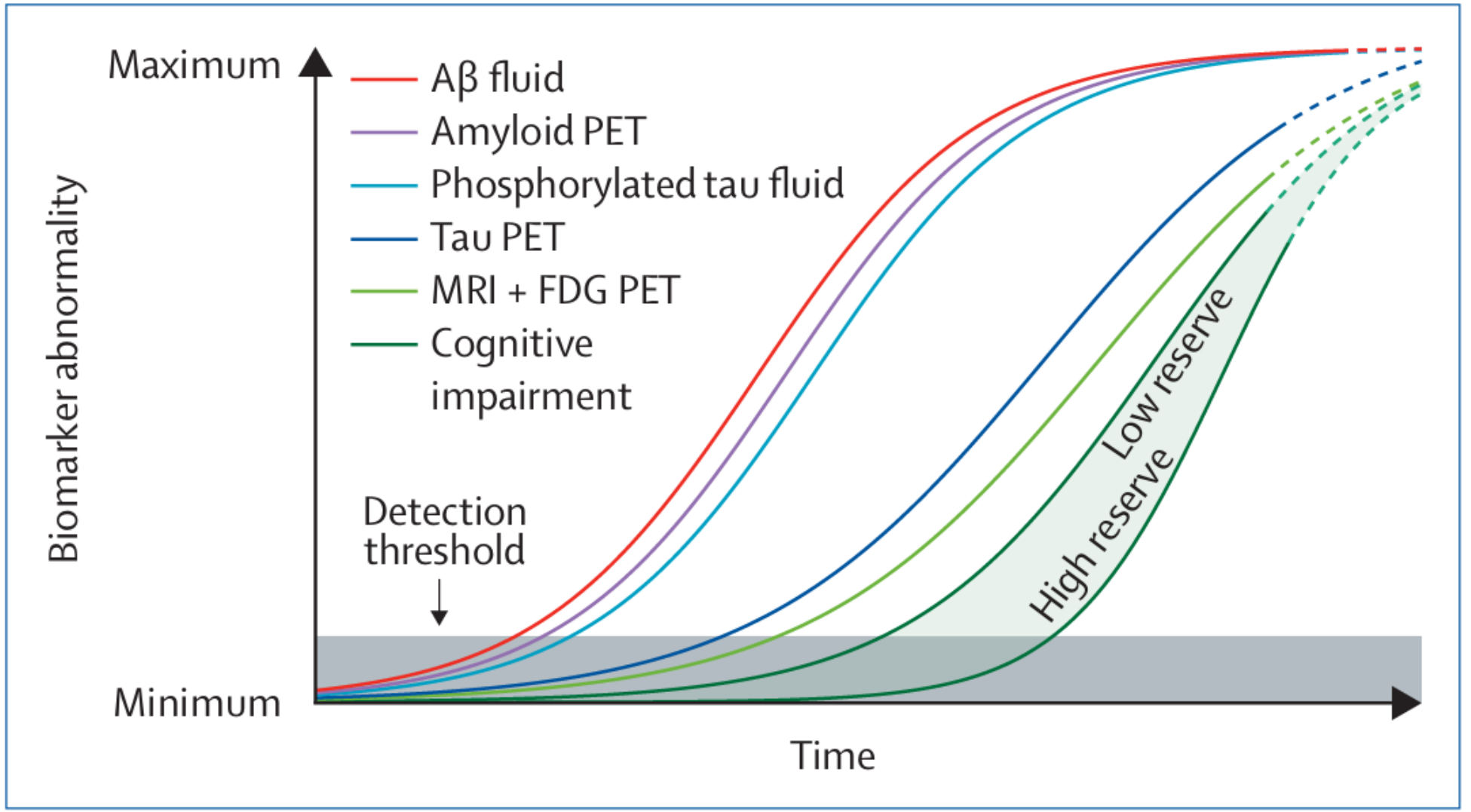
AD: PATHOPHYSIOLOGIC CASCADE MODEL



Jack CR, Lancet Neurology 2022

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EARLIER AMYLOID-TARGETING ATTEMPTS

- Some trials included a significant number of non-AD cases
  - AN1792, Solanezumab, Bapineuzumab
- Some trials targeted amyloid late in the disease
  - AN1792, Solanezumab, Bapineuzumab
- Some drugs did not sufficiently engage target (remove amyloid)
  - Crenezumab, Bapineuzumab, Solanezumab
- Amyloid biology is complex and drugs differentially impact this

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NEWER ANTI-AMYLOID THERAPIES IN EARLY AD

- Goal: clear brain amyloid-β → slow disease progression
- Phase 3 trials for lecanemab (CLARITY-AD) and donanemab (TRAILBLAZER-ALZ 2) resulted in FDA approvals in 2023/2024
  - Biomarker-positive MCI due to AD or mild AD dementia
  - Treatment → ~30% slowing of cognitive/functional decline
    - Primary outcomes: CDR-SB and iADRS (respectively)
  - All key secondary outcomes met as well
- ARIA = amyloid-related imaging abnormalities (E/H)
  - Usually asymptomatic/manageable
    - CLARITY-AD: ARIA-E 12.5% (symptomatic: 2.8%); ARIA-H 17.0% (symptomatic: 0.7%)
    - TRAILBLAZER-ALZ 2: ARIA-E 24%, ARIA-H 31.4%
  - Rarely (~2%) can be severe/serious → necessitates thorough counseling and appropriate patient selection and monitoring



The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

Authors: Christopher H. van Dyck, M.D., Chad J. Swanson, Ph.D., Paul Aisen, M.D., Randall J. Bateman, M.D., Christopher Chen, B.M., B.Ch., Michelle Gee, Ph.D., Michio Kanekiyo, M.S., +11, and Takeshi Iwatsubo, M.D. Author Info & Affiliations

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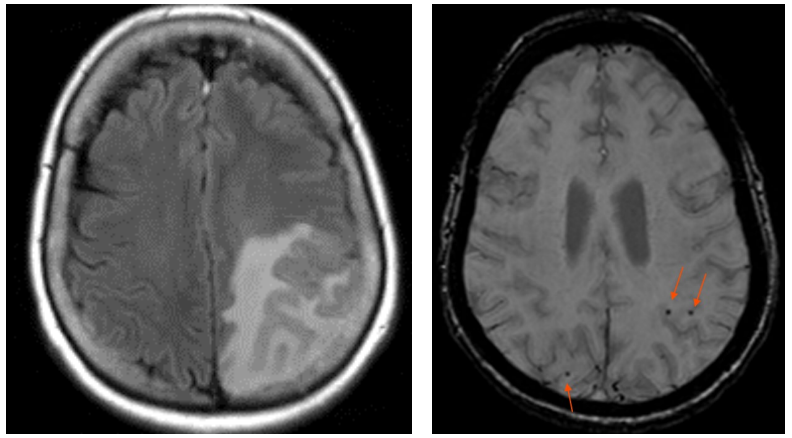
Home | JAMA | Vol. 330, No. 6

Original Investigation FREE

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD[1]; Jennifer A. Zimmer, MD[1]; Cynthia D. Evans, PhD[1]; Ming Lu, MD, MS, MPH[1]; Paul Ardayfio, PhD[1]; JonDavid Sparks, PhD[1]; Alette M. Wessels, PhD[1]; Sergey Shcherbinin, PhD[1]; Hong Wang, PhD[1]; Emel Serap Monkul Nery, MD[1]; Emily C. Collins, PhD[1]; Paul Solomon, PhD[2]; Stephen Salloway, MD[3,4]; Liana G. Apostolova, MD[5]; Oskar Hansson, MD, PhD[6]; Craig Ritchie, MD, PhD[7]; Dawn A. Brooks, PhD[1]; Mark Mintun, MD[1]; Daniel M. Skovronsky, MD, PhD[1]; for the TRAILBLAZER-ALZ 2 Investigators



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ARIA RISK MITIGATION AND ARIA MANAGEMENT

- Risk:
  - Consistent drivers include *APOE* ε4 status, number of baseline microhemorrhages, presence of superficial siderosis at baseline
  - Possible contributors to risk include baseline brain amyloid burden, mean arterial pressure, occipital amyloid load
- Management:
  - Identify higher risk patients prior to treatment
  - Adhere to MRI monitoring schedule
  - Dose titration, interruption, or discontinuation where appropriate
  - Use of corticosteroids for severe or symptomatic ARIA

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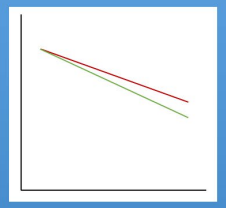
SHARED DECISION-MAKING IN CLINIC

Treatment Aims

Intervene at early symptomatic stages
Remove brain amyloid-β plaques
Slow disease-related cognitive decline



Treatment Caveats

The disease is more than just amyloid
Treatment does not cure the disease
Genetic factors influence side effects



Are monoclonal anti-amyloid therapies for Alzheimer disease an option for me?



Treatment Risks

High test and visit burden
Potentially high financial costs
Infusion reactions
Brain swelling or bleeding (ARIA)



Alternatives

Existing oral medications
Lifestyle modifications
Future approved drugs
Clinical trials

Ramanan et al., Neurology 2023 (with permission)

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EARLY REAL-WORLD EXPERIENCE

JAMA Neurology | Original Investigation

Lecanemab Treatment in a Specialty Memory Clinic

Madeline Paczynski, PA, MCMSc; Anna Hofmann, MD; Zachary Posey, MA; Maren Gregersen, MD; Michelle Rudman, MD, PhD; Dawn Ellington, RN; Melissa Aldinger, BS; Erik S. Musiek, MD, PhD; David M. Holtzman, MD; Randall J. Bateman, MD; Justin M. Long, MD, PhD; Nupur Ghoshal, MD, PhD; David B. Carr, MD; Alan Dow, MSHA, MBA; Sheyda Namazie-Kummer, MD, MBA; Nayid Jana, BA; Chengjie Xiong, PhD; John C. Morris, MD; Tammie L. S. Benzinger, MD, PhD; Suzanne E. Schindler, MD, PhD; B. Joy Snider, MD, PhD

IMPORTANCE Two monoclonal antibodies targeting amyloid plaques, lecanemab and donanemab, have received traditional US Food and Drug Administration (FDA) approval for the treatment of early symptomatic Alzheimer disease (AD). The most significant adverse events associated with these therapies are infusion-related reactions and amyloid-related imaging abnormalities (ARIA) with edema/effusion (ARIA-E) and/or hemorrhage/hemosiderin deposition (ARIA-H). The feasibility and safety of providing these treatments in clinical practice is unclear.

OBJECTIVE To examine the feasibility and safety of treating patients in specialty memory clinics with lecanemab.

DESIGN, SETTING, AND PARTICIPANTS This retrospective analysis of consecutive patients in whom lecanemab was initiated between August 1, 2023, and October 1, 2024, at Washington University Memory Diagnostic Center, an outpatient specialty memory clinic. Lecanemab was initiated in 234 patients with early symptomatic AD. Eligibility was based on the FDA label and appropriate use recommendations with occasional exceptions.

Journal of Neurology (2025) 272:394
https://doi.org/10.1007/s00415-025-13142-9

ORIGINAL COMMUNICATION

Monoclonal antibody administration in an academic institution and private neurological practice: a tale of two clinics

Michael Rosenbloom[1,2,3] · Andrea Schnee[1] · Saanvi Nimma[4] · Helen Lutz[4] · Dan Gzesh[4] · David Weisman[4]

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Abstract
The emergence of monoclonal antibody (MABs) drugs since the FDA approval of lecanemab has resulted in dramatic changes in the clinical approach and management of early-stage Alzheimer's disease (AD). Challenges with MAB adoption into clinical practice may vary depending on whether the institution is an academic/integrated healthcare organization versus a private neurological practice. We have combined demographic and clinical data from a high-volume East coast private neurology practice and a West coast academic memory clinic at post-MAB adoption. Combined data of $N = 165$ patient showed the following demographics: mean age 72, 67% female, 92% Caucasian, average MOCA 18/30 with amyloid status confirmed by CSF in 72% of patients. Overall, ARIA rates were 8% for ARIA-E and 7% for ARIA-H, and there were no mortalities over the observation period. Three patients required immediate medical attention due to ARIA radiographic findings associated with clinical symptoms. The private practice enrolled patients with lower average cognitive screening scores than the academic practice, but was more efficient at initiation therapy (mean # of weeks between diagnosis and treatment 97 versus 149 days). The average patient out-of-pocket cost was ($654.38) significantly less than the 20% of the annual drug cost as previously estimated. The findings from two separate clinical environments support the notion that ARIA risk associated with lecanemab is no greater than what was found in the CLARITY-AD trial and that the costs to the patient were less than predicted. This study was limited by the lack of 12 month efficacy data. Additional real-world data relating to the clinical effectiveness of MAB use in clinical practice will be necessary to best determine the risk/benefit ratio of these drugs in community populations.

MAYO CLINIC PROCEEDINGS

ORIGINAL ARTICLE

Establishing an Alzheimer Disease Therapeutics Clinic: Experience From a Year of Evaluations

Bryan J. Neth, MD, PhD; Jonathan Graff-Radford, MD; Petrice M. Cogswell, MD, PhD; Derek R. Johnson, MD; Hugo Botha, MD; Stuart J. McCarter, MD; David T. Jones, MD; Megan M. Conkins, MS; Dale B. Hardin, MPH, MBA; Jodi J. Spence, BA; Carolyn L. Rhegness, BS; Laura A. Allen, APRN, CNP, MS; Ryan P. Coburn, MD; Johnson D. Pounders, MD; Brian J. Burkett, MD; Jay J. Pillai, MD; Gregory S. Day, MD; Neill R. Graff-Radford, MD; Christian Lachner, MD; Steven A. Messina, MD; Manoj K. Jain, MD; Nikki H. Stricker, PhD, LP; Mary M. Machulda, PhD, LP; Julie A. Fields, PhD, LP; Elizabeth A. Boots, PhD, LP; Paula A. Aduen, PhD, LP; Leland R. Barnard, PhD; Michelle A. Remold, MSW, LICSW; Amanda M. Anderlik, RN; Kayla M. Asleson, RN; Lori L. Martin, RN; Janice A. Klaassen, MA, RN; Jennifer J. Larsen, MSN, RN, CRNI; Alicia Algeciras-Schimnich, PhD; Joshua A. Bornhorst, PhD; Ande M. Rumilla, MD; Clifford R. Jack Jr, MD; Bradley F. Boeve, MD; David S. Knopman, MD; Ronald C. Petersen, MD, PhD; and Vijay K. Ramanan, MD, PhD

Abstract

Objective: To describe the establishment and initial experience of a multidisciplinary Alzheimer disease treatment clinic (ADTC), focusing on the evaluation of eligibility for novel disease-modifying therapies, as well as the treatment and monitoring of qualifying patients.

Patients and Methods: We completed a retrospective review of cases seen through the Mayo Clinic ADTC between October 2, 2023, and December 31, 2024. Typical evaluations occurred over 4 to 5 days and included multimodal testing, office visits, and a weekly case conference modeled on tumor board meetings.

Results: Patients evaluated in the ADTC (N=232) ranged from 52 to 85 years of age (mean age, 71.2 years). Most patients had mild cognitive impairment (128 of 232 [55%]) or mild dementia (72 of 232 [31%]) syndromes. Overall, 121 patients (52%) were judged eligible for antiamyloid therapy. Eligibility rates were higher among internal (from our institution) referrals compared with external referrals (63% [146 of 232] vs 37% [86 of 232]). Reasons for treatment ineligibility were typically multiple but commonly included magnetic resonance imaging features, too severe cognitive/functional impairment, and general health conditions believed likely to increase therapeutic risks. In some

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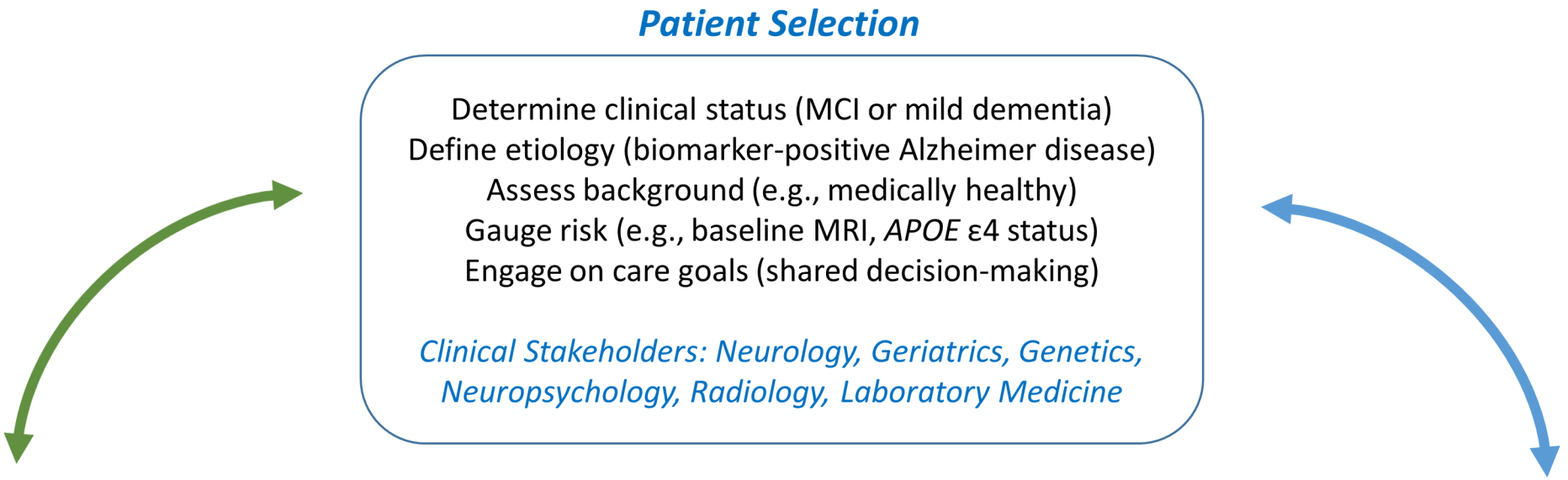
STAKEHOLDER IMPLICATIONS



Ramanan et al., Neurology 2023

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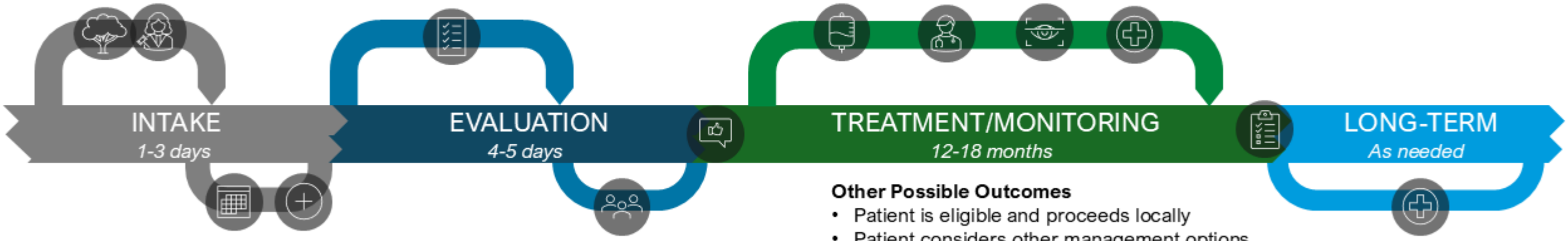
PATIENT JOURNEY THROUGH THE MAYO ADTC

Referral Sources
- External
- Mayo Internal

Monday-Wednesday
- Neuropsychological assessment
- Brain MRI; blood tests and *APOE*
- Behavioral Neurology
- Amyloid PET or lumbar puncture

Eligible Patients Treated at the ADTC
- Treatment + monitoring MRIs and visits
- Repeat biomarker and cognitive testing



Pre-Visit
- Appointment scheduling
- Virtual Social Work touchpoint

Thursday-Friday
- Multidisciplinary conference
- Shared decision-making
- Nursing/Coordinator visits

Other Possible Outcomes
- Patient is eligible and proceeds locally
- Patient considers other management options

Follow-Up
- Clinical care
- Registry tracking

October 2023-August 2026
- Evaluated ~800 patients → 52% have been treatment-eligible
  - 34% of external referrals, 64% of internal referrals
- ~150 patients have started/will start treatment in Rochester
  - 68% of eligible local patients have proceeded with therapy here
  - 60+ patients at 12+ months of therapy; ~35 at 18+ months
- ARIA-E rates same or lower than the trials (~10%), no cases serious

Neth et al., Mayo Clinic Proceedings 2026

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CASE 1: CLINICAL UNCERTAINTIES

- Early 60s, high school graduate, strong family history of dementia
- 3-5 years of subjective concerns (needing lists, repeating questions, slower at work); family was less convinced of a change (thought worry was a factor)
- STMS 27/38 (equivalent to MMSE 23/30)
- CSF biomarkers were obtained: p-tau181/abeta42 = 0.031 (↑)
- Recommendations: (1) use hearing aids, (2) discontinue amitriptyline, (3) treat depressive/anxiety symptoms → STMS 35/38 (MMSE 28/30)
- Initial neuropsychological assessment with some soft scores, but felt generally within expectations given educational and occupational background

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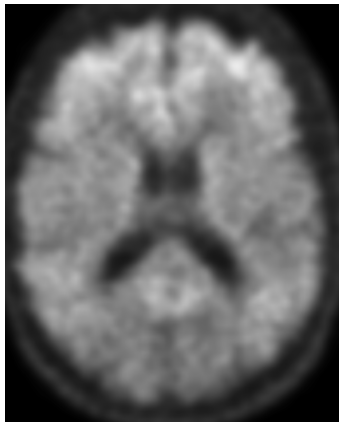
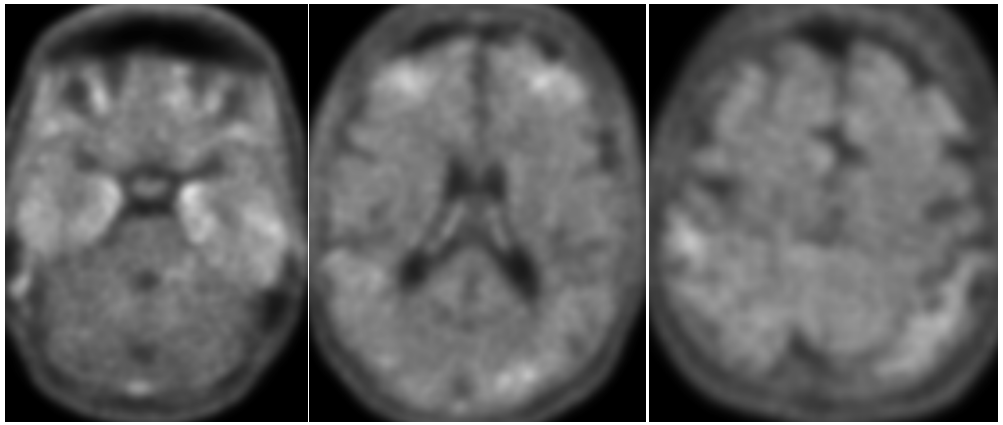
CASE 1: *EARLY* MCI IN DECLARATION

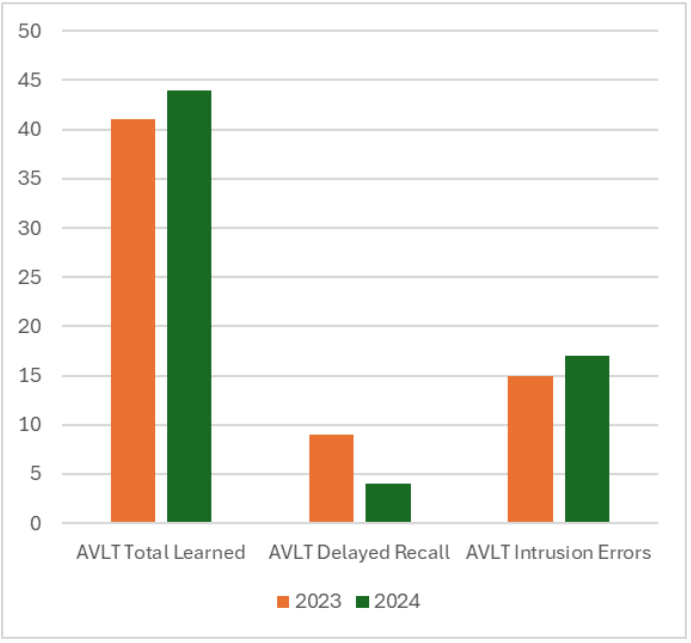
Amyloid PET



Tau PET



Serial Neuropsychological Testing



Outcomes of Evaluation/Follow-Up

- Patient/Spouse felt there had been a slight decline
- Ultimately felt to have early MCI due to AD
- Medically healthy; *APOE* ε3/ε3; MRI unremarkable
- Patient was offered anti-amyloid therapy and is proceeding
- Scenario highlights a value of neuropsychological testing at borderzones (e.g., SCD vs. MCI, mild vs. moderate dementia)
  - Data still needs to be interpreted in clinical context
  - May not be practical or necessary to obtain in all cases

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CASE 2: AD VS. (AND/OR) LATE

- Initially seen in mid-70s for a year of memory symptoms
  - Forgetting recent conversations/events, repeating stories
  - STMS 34/38 (equivalent to MMSE 28/30)
  - Neuropsychological testing and neuroimaging essentially normal
  - Slight declines in verbal and nonverbal memory on repeat testing at 1 yr
- Subsequent years:
  - Very gradual (subtle, but noticeable to family) symptomatic declines
  - More independent than not in daily activities
  - Concurrent B12 deficiency was treated
  - After 5 years: STMS 30/38 (equivalent to MMSE 25/30)

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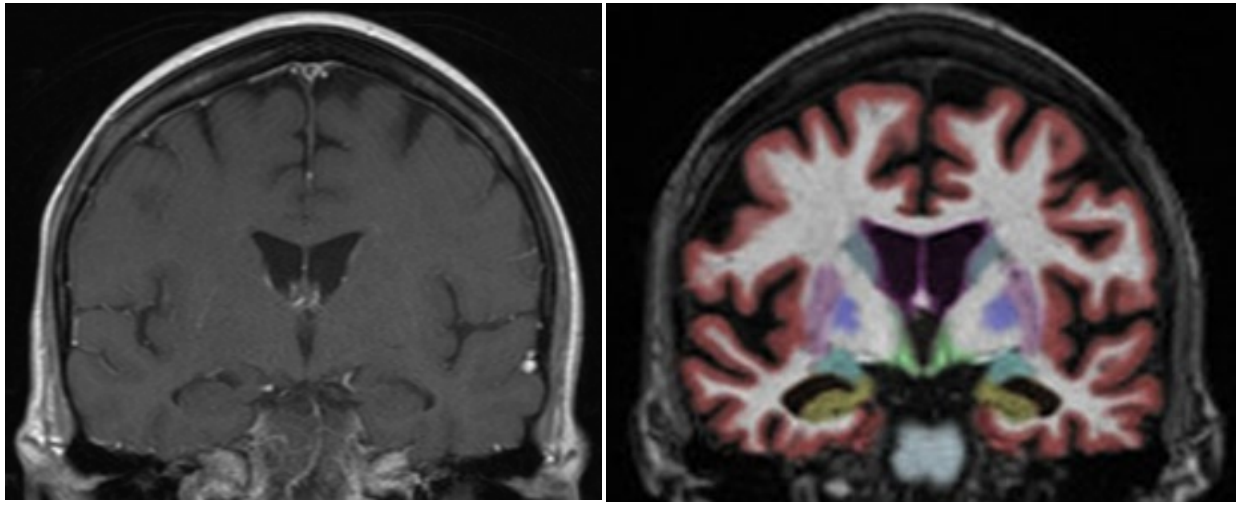
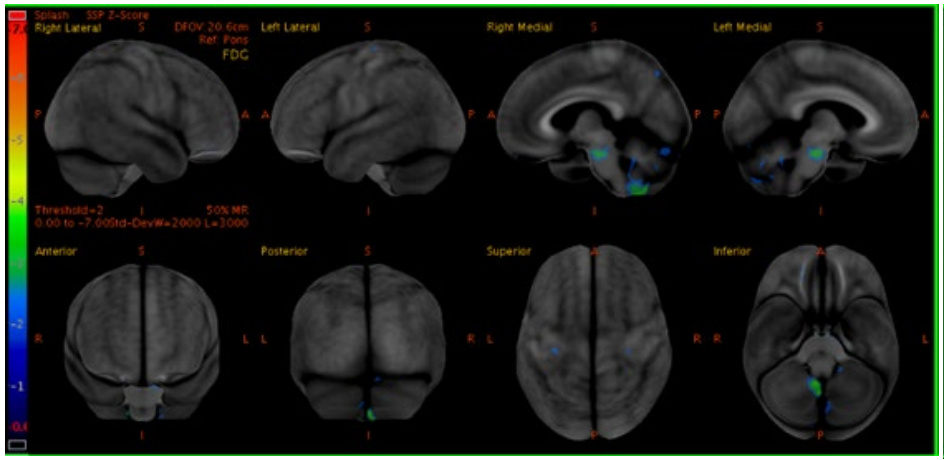
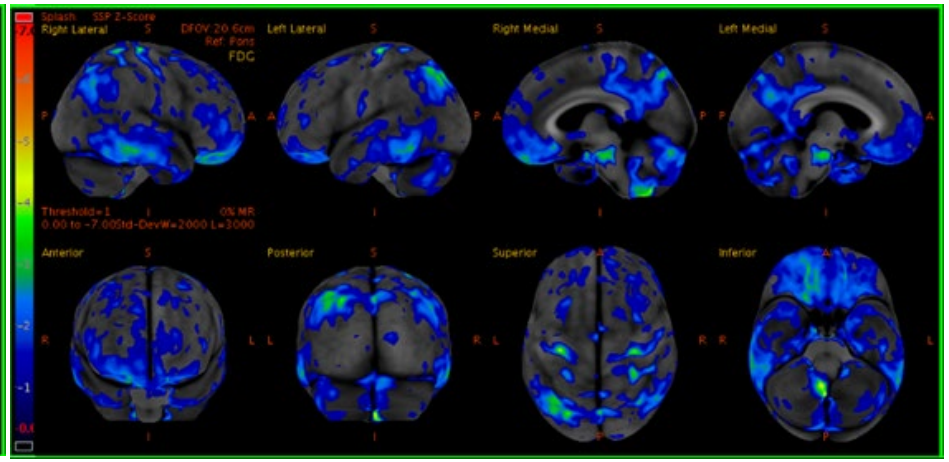
CASE 2: NEUROIMAGING OVER 5 YEARS



Outcomes of Evaluation/Follow-Up

- Amyloid PET positive
- Patient was offered anti-amyloid therapy, with counseling on possibility of co-pathology
- Has now completed 18 months of lecanemab





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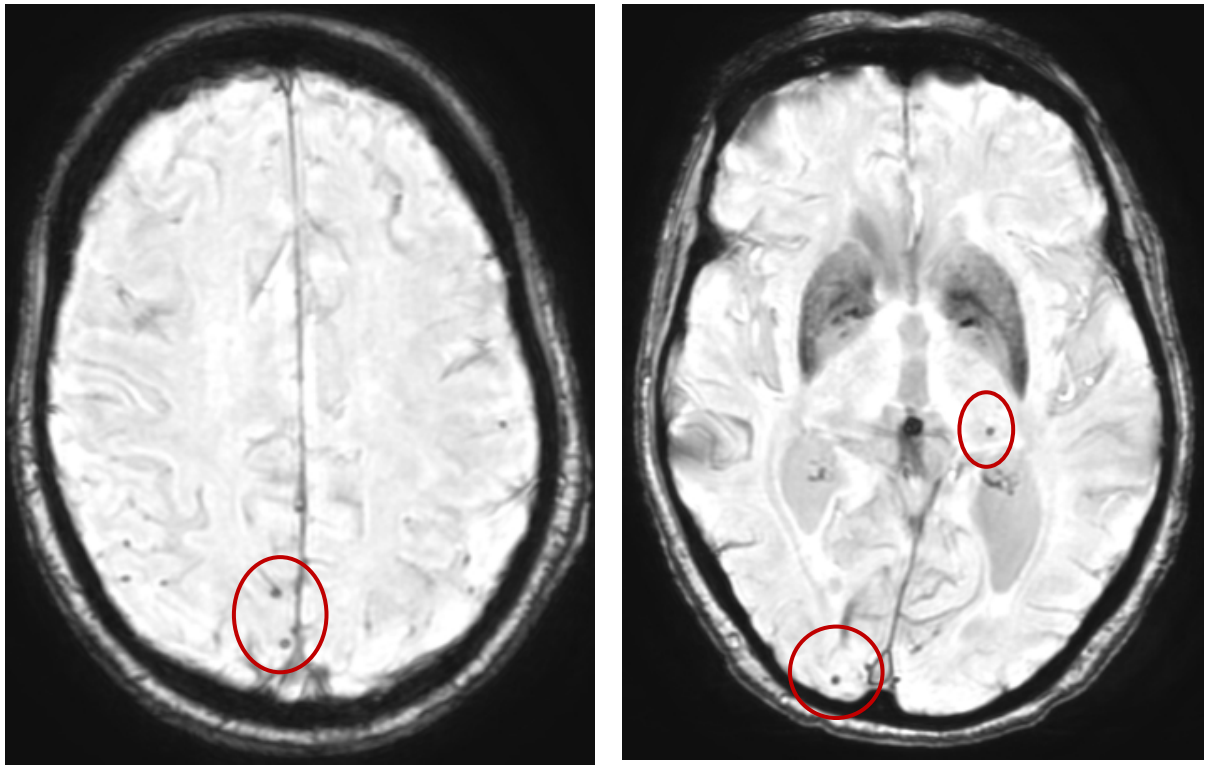
CASE 3: TIMING OF PRETREATMENT MRI

- Patient with mild dementia due to AD
  - STMS 28/38 (MMSE 24/30)
  - MRI from 9 months ago: 1-2 CMBs
  - Amyloid PET positive
  - *APOE* ε3/ε4
- Updated MRI was obtained per site workflows
  - 8 total CMBs (including 5 cortical)
  - Area of superficial siderosis
- Anti-amyloid therapy was not initiated
- Illuminates potential challenges in identifying "treatment-emergent" change
- Consider a more proximal scan than < 1 year in select scenarios (e.g., baseline microbleeds)



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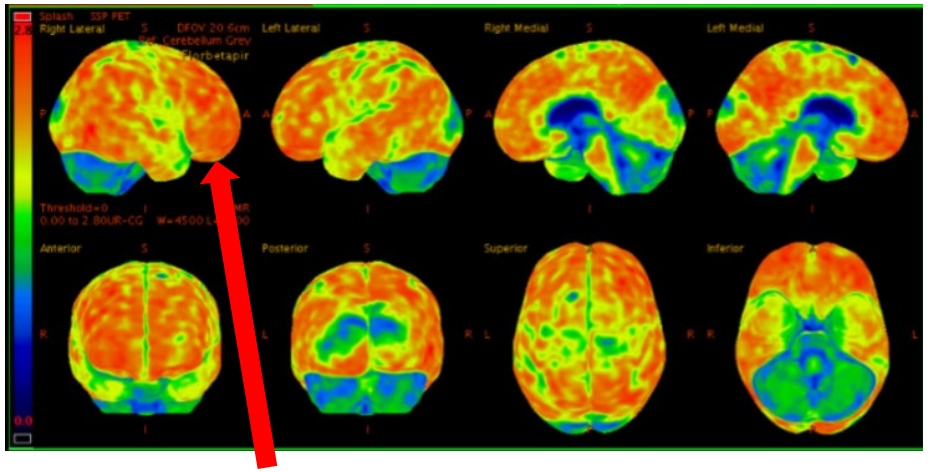
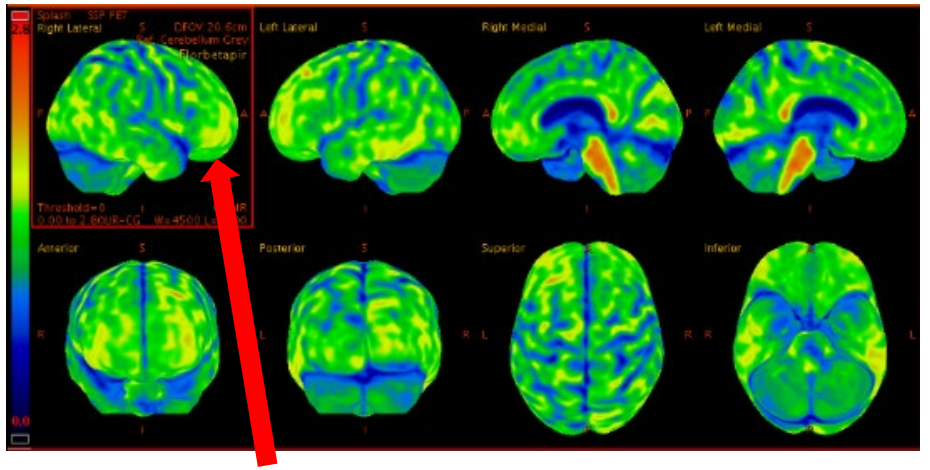
CASE 4: TREATMENT RESPONSE (1 YEAR)

Pre-Treatment: Positive Amyloid PET (CL=143)



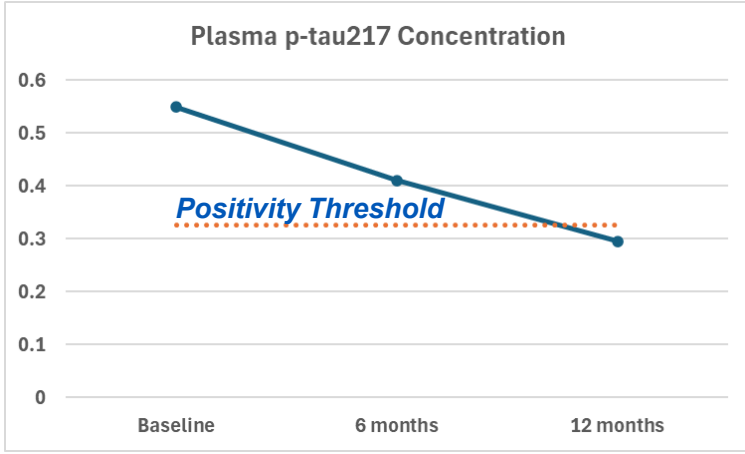
Amyloid plaque deposits

Post-Treatment: Negative Amyloid PET (CL=26)



Plaque clearance with therapy

- **Plasma p-tau217 also trended down over time with therapy**
  - **Potential for noninvasive and infrastructure-efficient treatment monitoring**
- **Cognitive and functional status stable after 12 months**
  - **Short Test of Mental Status = pre-treatment 32/38 → post-treatment 35/38**



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DRUG ADAPTATION AND DEVELOPMENT

- Donanemab: modified dose titration associated with less ARIA
- Lecanemab: weekly subcutaneous formulation
  - Maintains biomarker engagement similarly to IV infusions
- Next generation anti-amyloid therapies (e.g., trontinemab, remternetug)
  - Aim is for fast/potent amyloid clearance and fewer side effects
- Trials of anti-amyloid therapies in cognitively normal older adults
- Drug trials and development targeting other mechanisms
- Combination therapy is widely seen as part of the future

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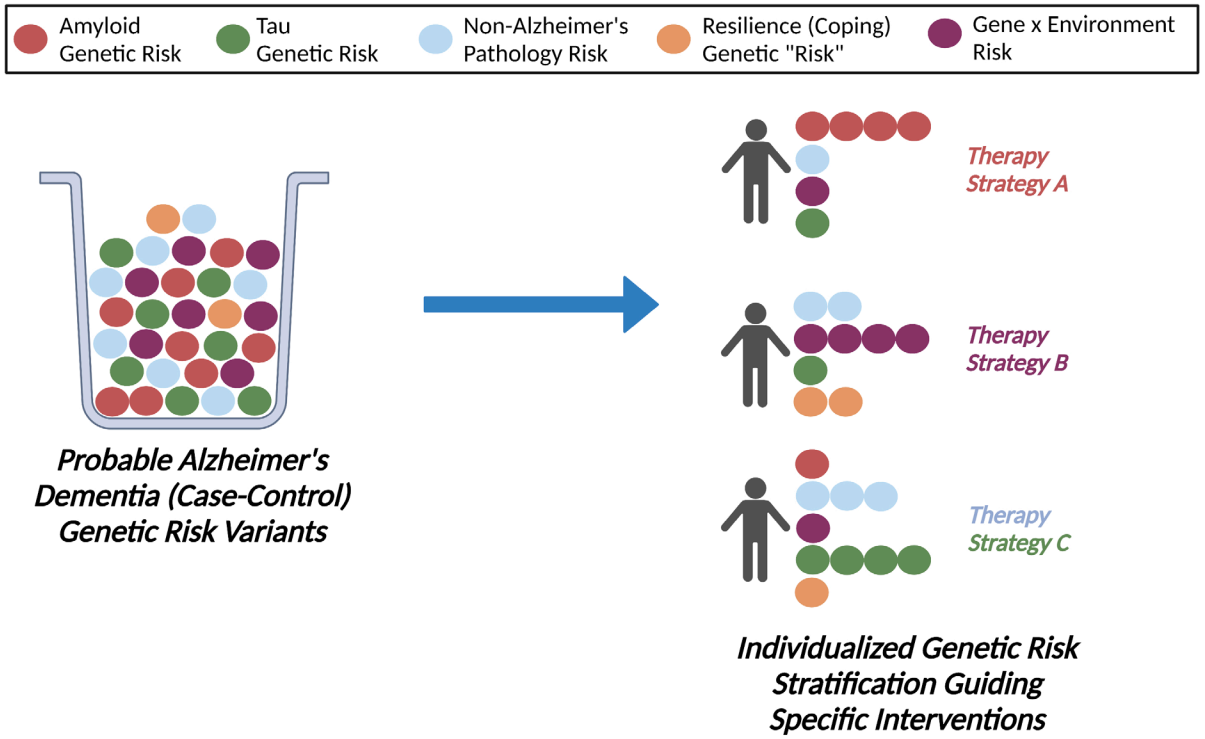
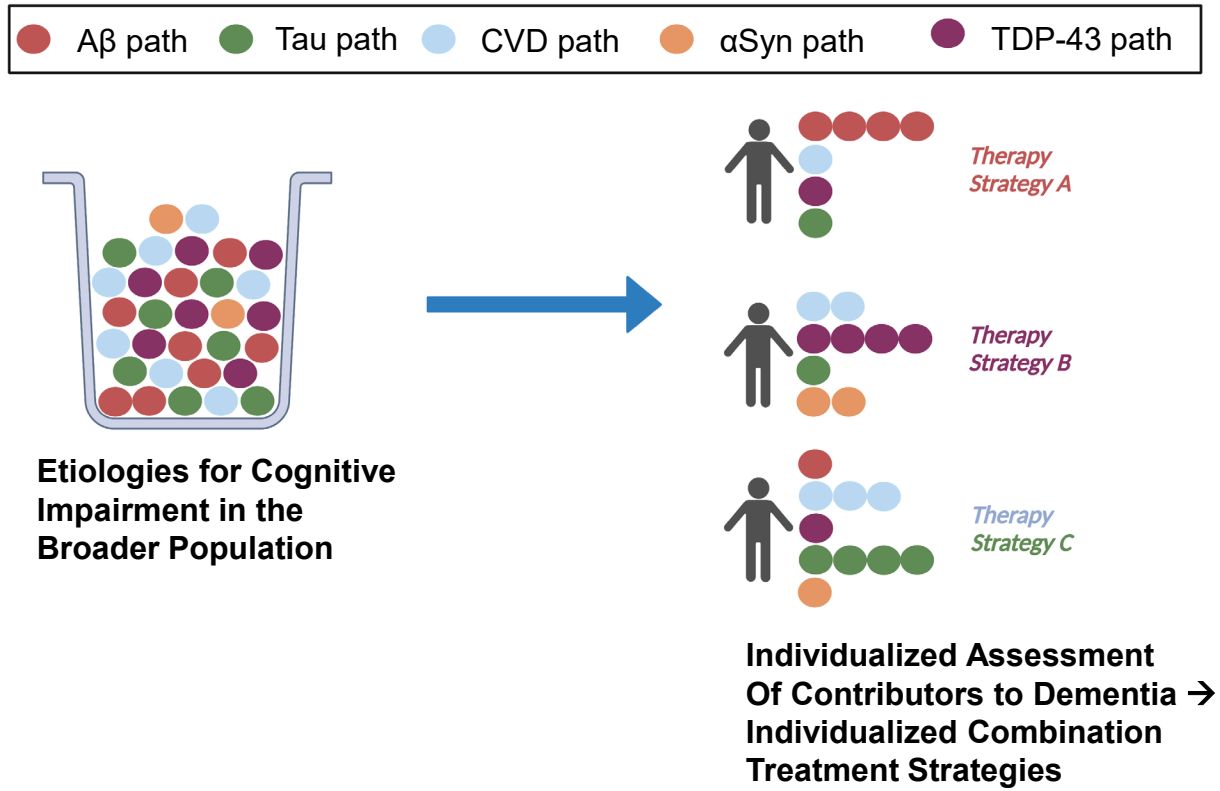
FUTURE VISION OF INDIVIDUALIZED THERAPY





Adapted from Ramanan et al., JAD 2022

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TAKE-HOME POINTS

- Emerging management tools for AD = good news for patients and the field
- Anti-amyloid therapies have a well-founded role in clinical practice
- Important to embrace the new era of ADRD therapeutics (+more to come!)
- Current state has historical analogs to other areas of neurology/medicine
- Anticipated future state: individualized combination therapy approaches

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