BEACON 2026

Emerging Therapies

What is real now, what is promising, and how to think about it clearly

A PRESENTATION BY
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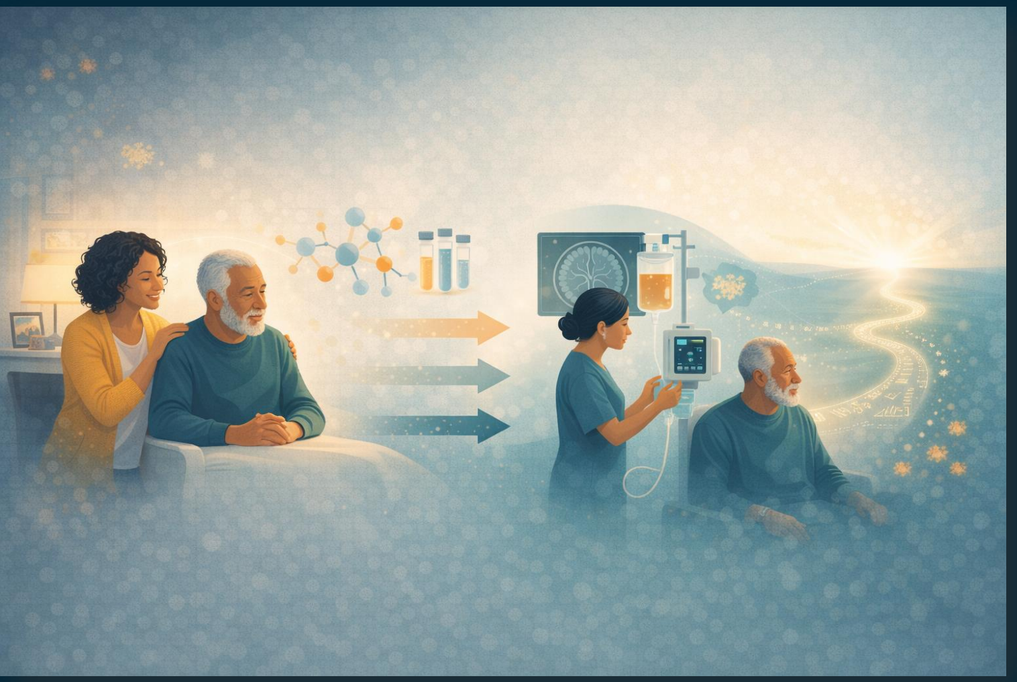


Brain health care is becoming more biologic, more precise, and more personal

Why this matters now

- **Neurocognitive care has entered a new era**
  - For years, treatment was largely symptomatic
  - We now have therapies that can slow early Alzheimer disease
  - Biomarkers now help guide real treatment decisions

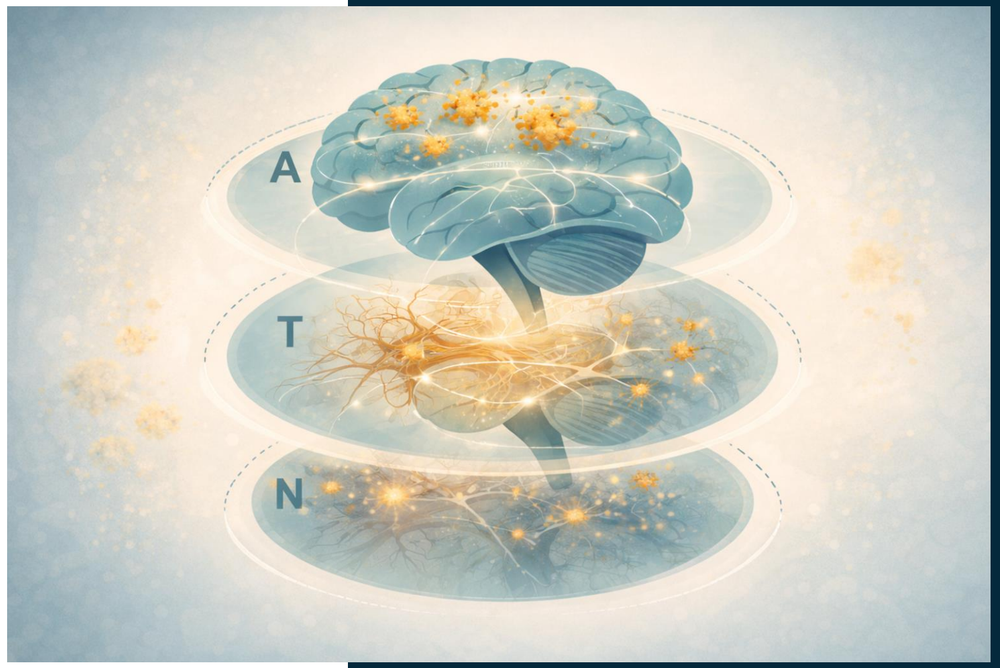
- **That progress comes with new complexity**
  - Earlier diagnosis matters more than ever
  - Treatment is not cure, reversal, or the right fit for everyone
  - Success depends on matching the right patient, right stage, and right goals

Alzheimer Disease:
Biology Behind the Symptoms

- Alzheimer disease is defined by abnormal protein accumulation.
  - **A = amyloid pathology**
  - **T = tau pathology**
  - **N = neurodegeneration / neuronal injury**

- Amyloid often begins **years before symptoms**, while tau and neuronal loss track more closely with clinical decline.

- Anti-amyloid therapies target the **A in ATN.**

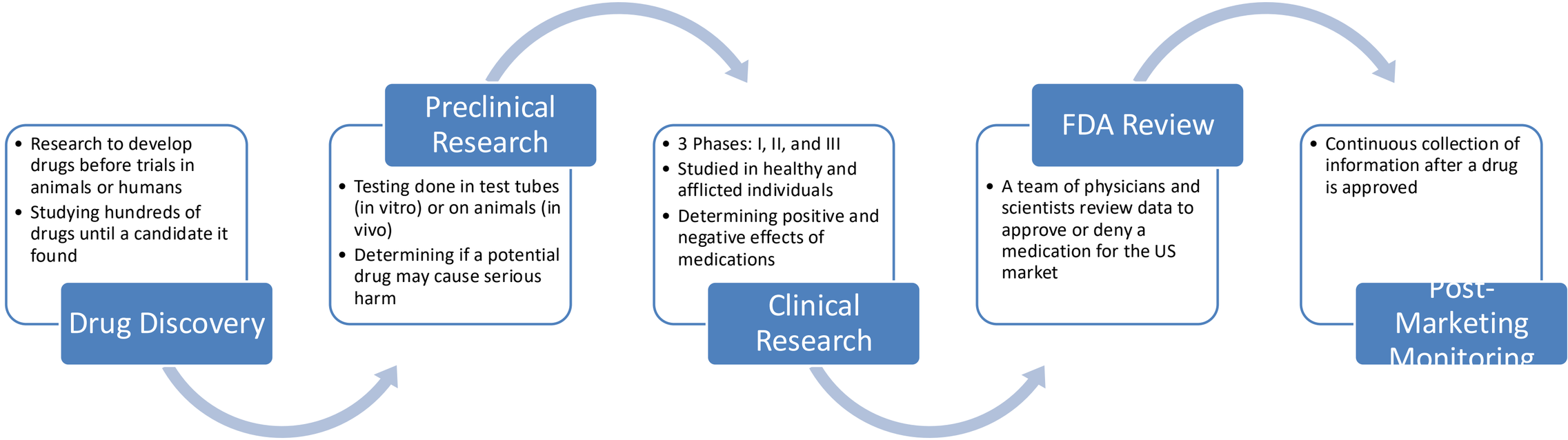


This is why anti-amyloid therapy is important — but also why it is not the whole story.

Bakker et al., 2012;
Vossel et al., 2021;
Mohs et al., 2024;
Mohamadi et al., 2025

The Long Road to Anti-Amyloid Therapy

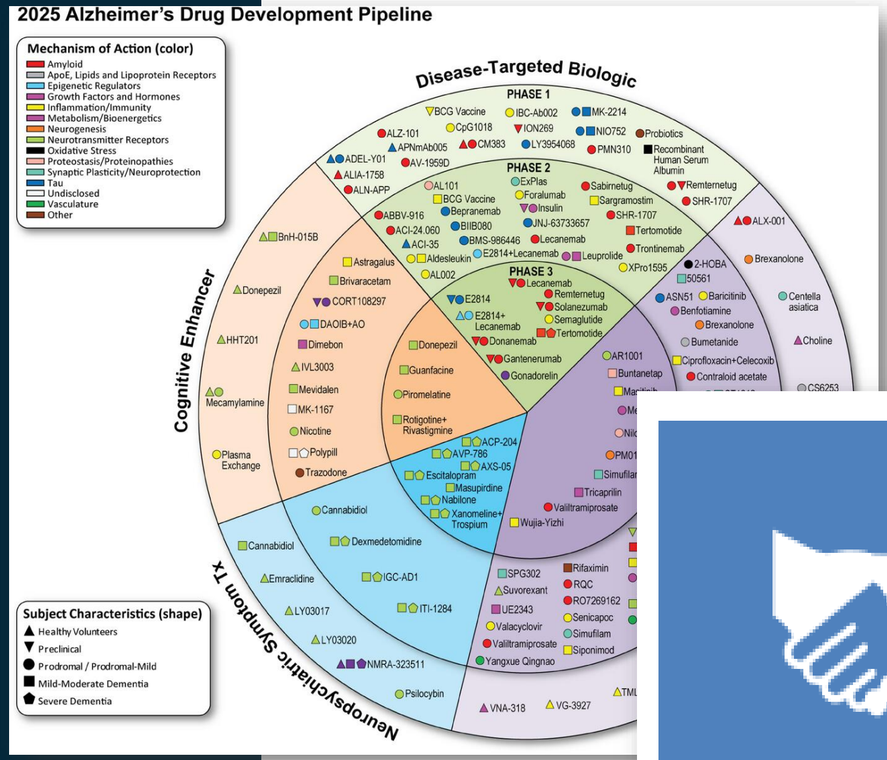
Emerging Therapies



- Early amyloid trials often failed to show meaningful benefit
- Many studies likely treated too late or without biomarker confirmation
- Better antibodies and better patient selection changed the field
- Modern approvals came after decades of refinement, not all at once

ThermoFisher Scientific Content Team. Oct 10, 2023.

Emerging Therapies



Cummings et al. 2025.

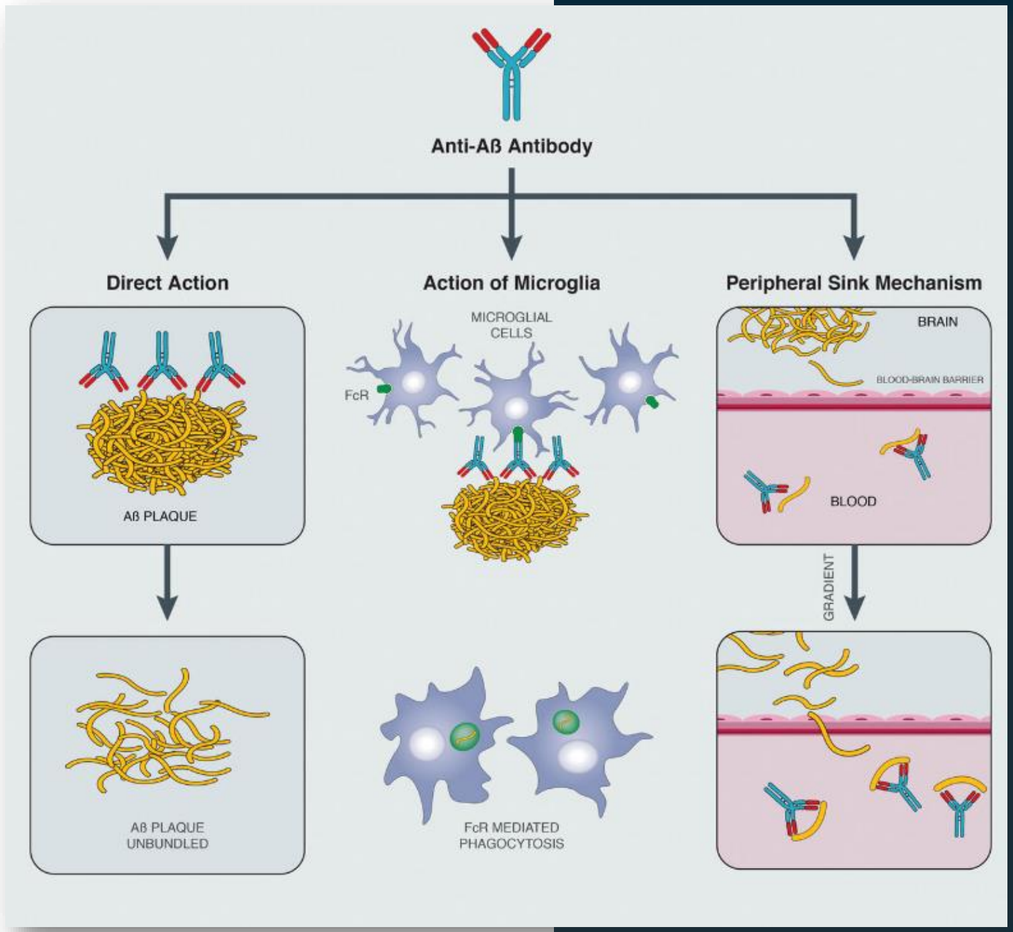
What Anti-Amyloid Therapy Actually Does

- Anti-amyloid therapies use antibodies to help the immune system clear amyloid from the brain.

- Targets include:
  - Soluble amyloid aggregates (protofibrils)
  - Insoluble amyloid plaques

- Effect of therapy:
  - ↓ Amyloid burden in the brain
  - ↓ Rate of cognitive decline

- Important reality:
  - They **slow disease progression**
    They **do not reverse existing damage**



Luna-Muñoz et al., 2013;
Olsson et al., 2016;
Hansson., 2021

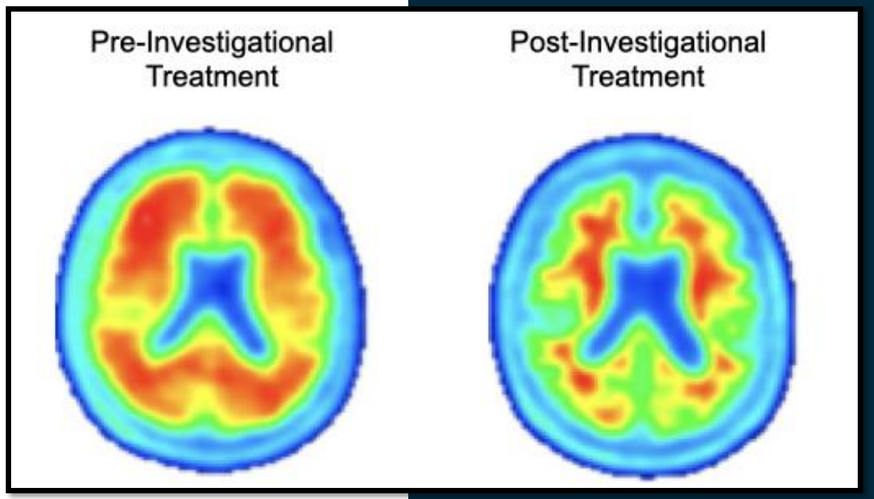
Two Approved Therapies: What We See

Therapy	Approved	Target	Dosing	Centiloid reduction
Lecanemab (Leqembi)	2023	Soluble protofibrils	Q2weeks	50–60
Donanemab (Kisunla)	2024	Insoluble plaques	Q4weeks	80–90

- First FDA Approved treatment for Alzheimer **in 20 years**

- First therapies that **directly target** the underlying biology:
  - Substantial amyloid clearance
  - Slowing of downstream tau accumulation

Amyloid removal is associated with **slower tau spread**, which more closely tracks clinical progression – **real disease modifying properties**

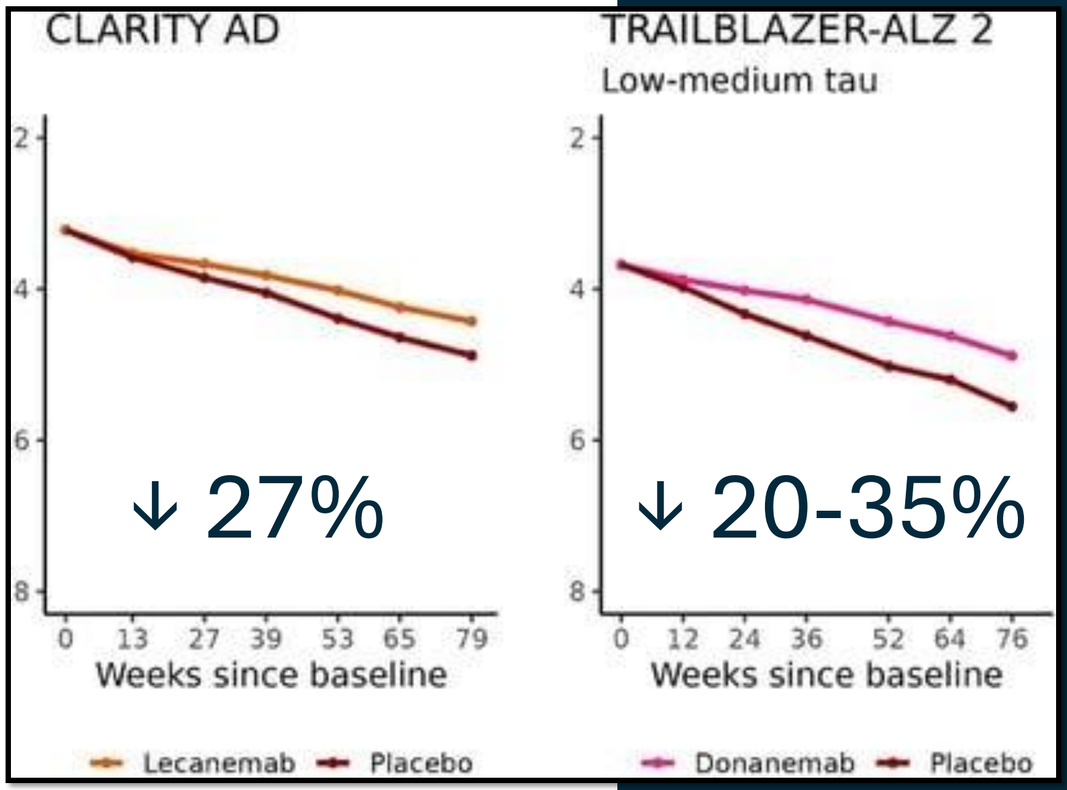


Luna-Muñoz et al., 2013;
Olsson et al., 2016;
Hansson., 2021
Vossel et al., 2021;
Mohs et al., 2024;
Mohamadi et al., 2025

Disease Modification Is Real — But Modest

- Therapies **slow clinical decline**, rather than restore function.
  - Does **not restore memory**
  - **Delays worsening** of cognition/daily function
  - Benefit is **meaningful, but limited**

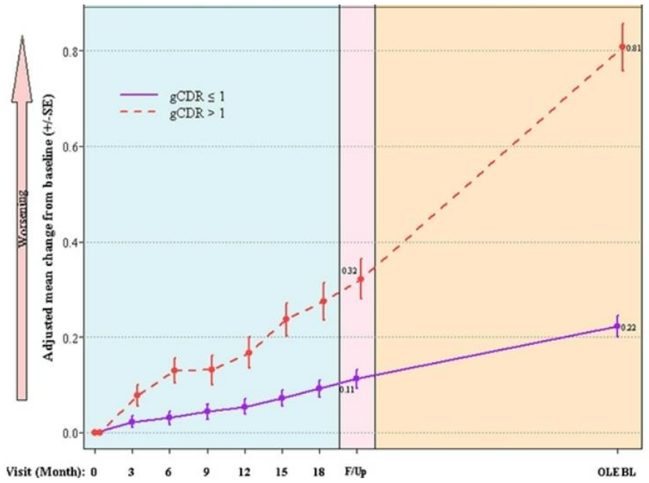
- **Important nuance:**
  - Results reflect group averages
  - Some patients show stronger response
  - Some show minimal response

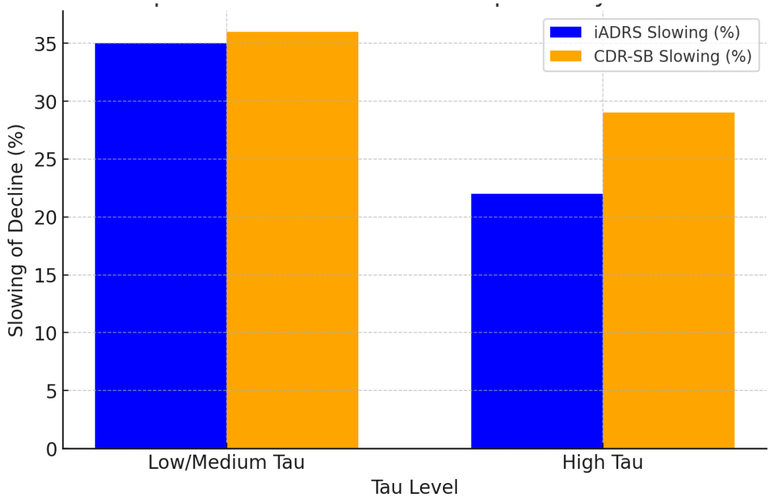


Greatest benefit occurs **early and mild disease**

Hansson., 2021
Swanson et al., 2021;
Mcdade et al., 2022;
Sims et al. 2022;
Mahase et al., 2023
Van Dyck et al. ,2022; 2023

Who Benefits Most From Therapy





- Greatest benefit occurs in early, low-tau disease
  - Early treatment
  - Mild symptoms
  - Lower tau

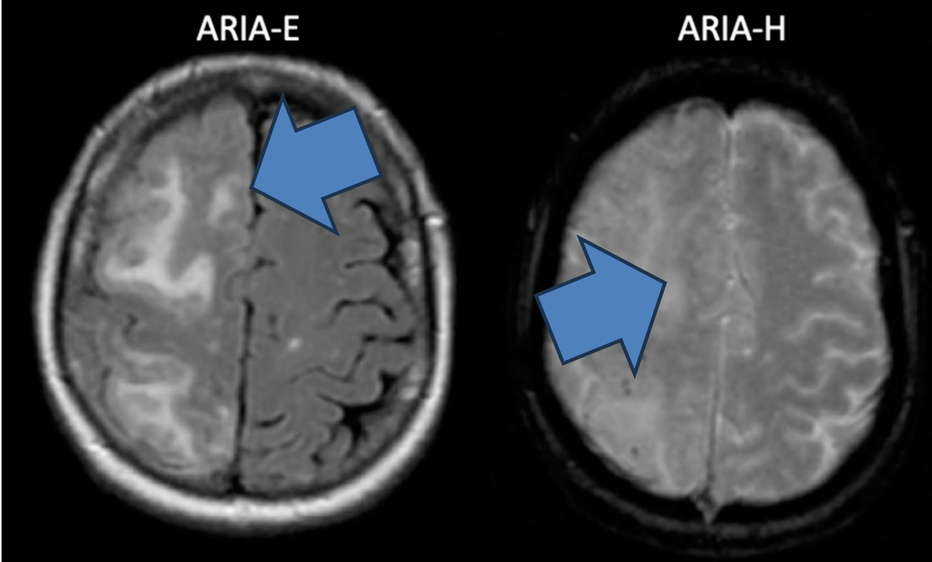
Earlier intervention → greater slowing of decline

Hansson., 2021
Swanson et al., 2021;
Mcdade et al., 2022;
Sims et al. 2022;
Mahase et al., 2023
Van Dyck et al. ,2022; 2023

Safety and Monitoring of

ARIA

Amyloid Related Imaging Abnormalities

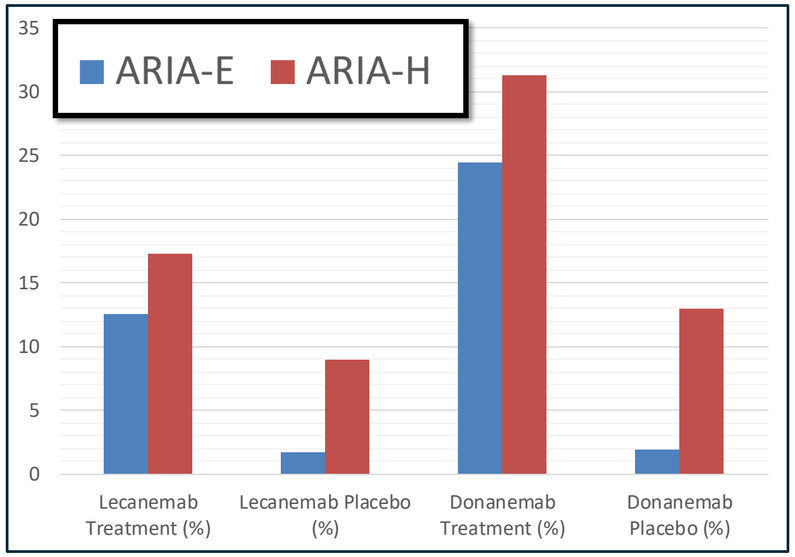


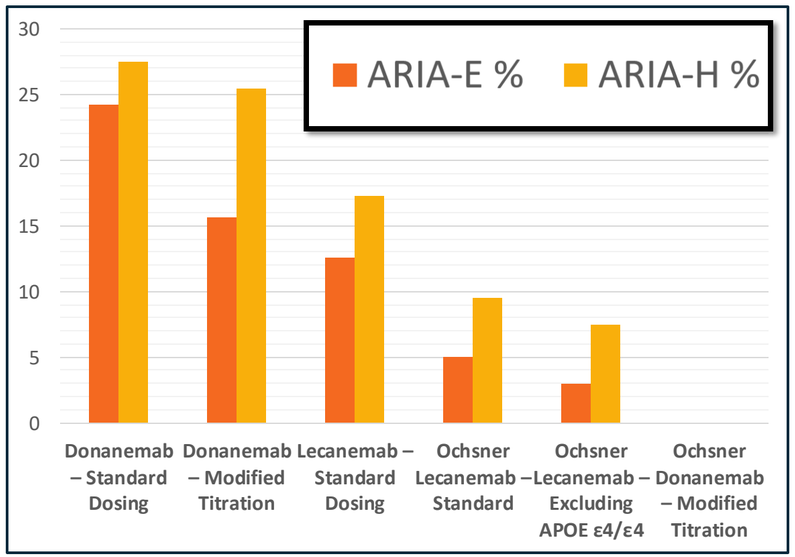
- Most common side effects:
  - Infusion reactions
  - Headache
- The most important risk is ARIA
  - ARIA-E – brain swelling
  - ARIA-H – microhemorrhage
- Most ARIA cases:
  - Asymptomatic
  - Resolve with monitoring

ARIA is the key risk — but manageable

Hansson., 2021
Swanson et al., 2021;
Mcdade et al., 2022;
Sims et al. 2022;
Mahase et al., 2023
Van Dyck et al. ,2022; 2023

Screening Reduces Risk

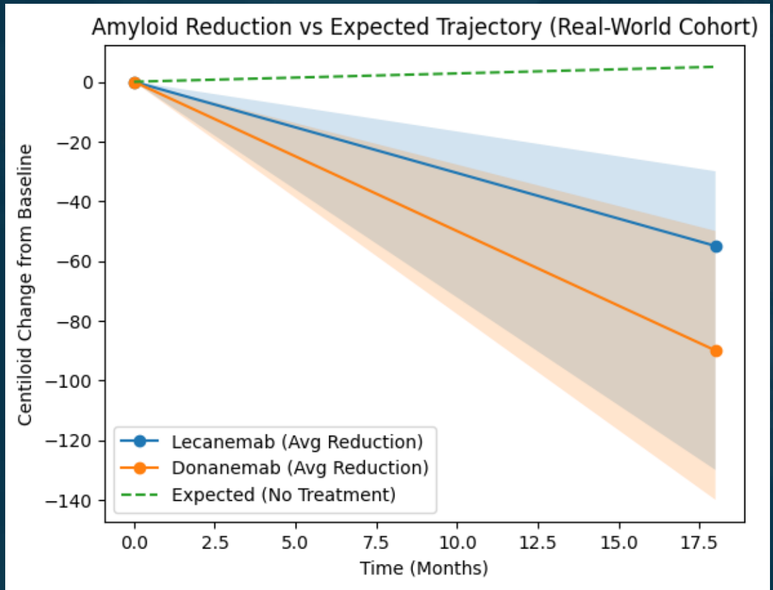


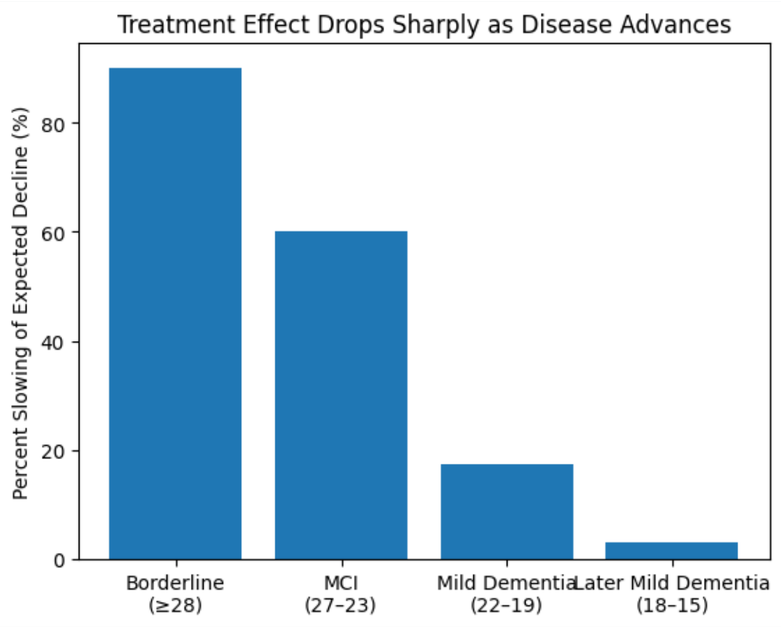


- **Much of ARIA risk reflects underlying CAA — and can be reduced with effective screening**
- **Key insight:**
  - Placebo groups show **meaningful <u>spontaneous</u> microhemorrhage rates**
  - Suggests underlying **CAA-related vulnerability**
- **Clinical interpretation:**
  - ARIA risk is **not random**
  - Reflects **baseline cerebrovascular biology**
- **Our approach:**
  - Structured **CAA screening protocol**
  - Pre-treatment **risk stratification dramatically reduces risk**

Hansson., 2021
Swanson et al., 2021;
Mcdade et al., 2022;
Sims et al. 2022;
Mahase et al., 2023
Van Dyck et al. ,2022; 2023

Our Real-World Experience





Emerging Therapies

- **Safety**
  - Infusion reactions ~7%
  - ARIA-E ~4% | ARIA-H ~8%
- **What We're Seeing**
  - ↓ amyloid over time consistent with trials
  - ↓ serum tau over time
  - Slowing of clinical decline
- **Key Insight**
  - Treatment effect is strongly stage-dependent
  - **Greatest benefit early**
- **What Still Matters**
  - Lifestyle: Sleep, Diet, Exercise
  - Comorbidities: vascular, hypertension etc.
  - Longitudinal support

Real-World Treatment Is a Process, Not a Drug

Emerging Therapies

Successful treatment depends on infrastructure: counseling, imaging, infusion access, MRI surveillance, and close follow-up with patients and families.

- Requires multidisciplinary coordination
- Counseling and expectation-setting are essential
- MRI and infusion logistics matter
- Insurance logistics

The system around the drug is part of the treatment

Ask your neurologist about AAT!

Bakker et al., 2012;
Vossel et al., 2021;
Mohs et al., 2024;
Mohamadi et al., 2025

Setting Expectations

- Anti-amyloid therapy represents real progress.

- But it is **not**:
  - A cure
  - A treatment for advanced dementia
  - Appropriate for every patient

- Best results occur with
  - Early diagnosis
  - Mild Disease
  - Biomarker-guided care
  - Close monitoring

Hansson., 2021
Swanson et al., 2021;
Mcdade et al., 2022;
Sims et al. 2022;
Mahase et al., 2023
Van Dyck et al. ,2022; 2023

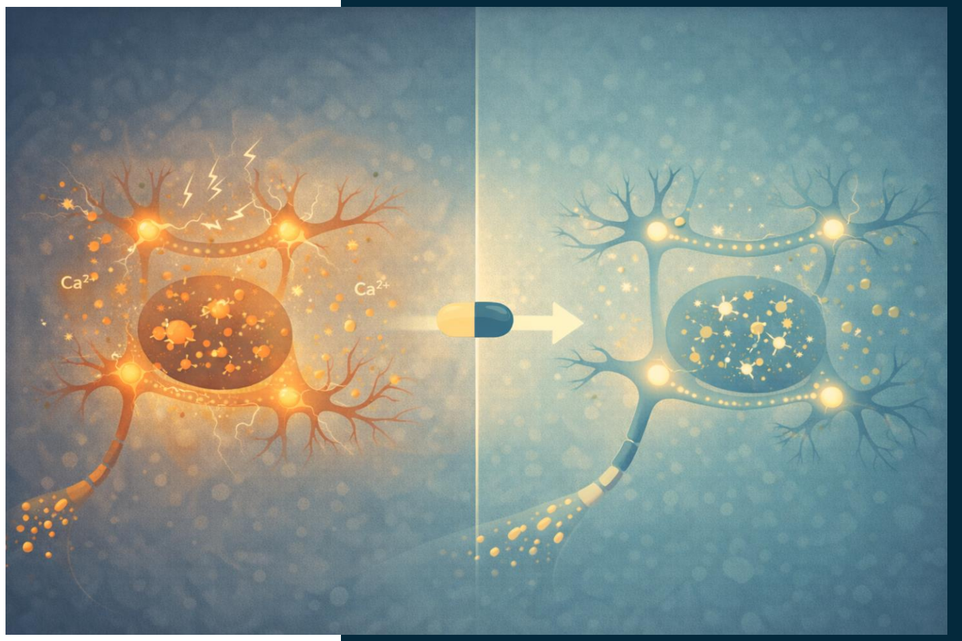
Next Phase Will Go Beyond Amyloid

- Amyloid is important, but not sufficient to explain the whole disease
- Circuit dysfunction, synaptic failure, inflammation, and other proteinopathies matter
- Future treatment will likely be multi-target and stage-specific

Emerging therapies reflect this broader biologic view

Levetiracetam

- Early AD/aMCI can show hippocampal hyperactivity and epileptiform network instability
  - Linked to faster decline in some patients
- Low-dose levetiracetam may stabilize vulnerable memory circuits
  - Reduced hippocampal hyperactivity and improved memory task performance in aMCI
  - Overall mild AD trial neutral, but subgroup benefit appeared with epileptiform activity
- Best viewed as phenotype-specific neuromodulation
  - Most compelling in physiology-enriched subgroups
  - Not a broad cognitive enhancer for all dementia



Levetiracetam may help a hyperexcitable AD subtype by calming vulnerable memory circuits

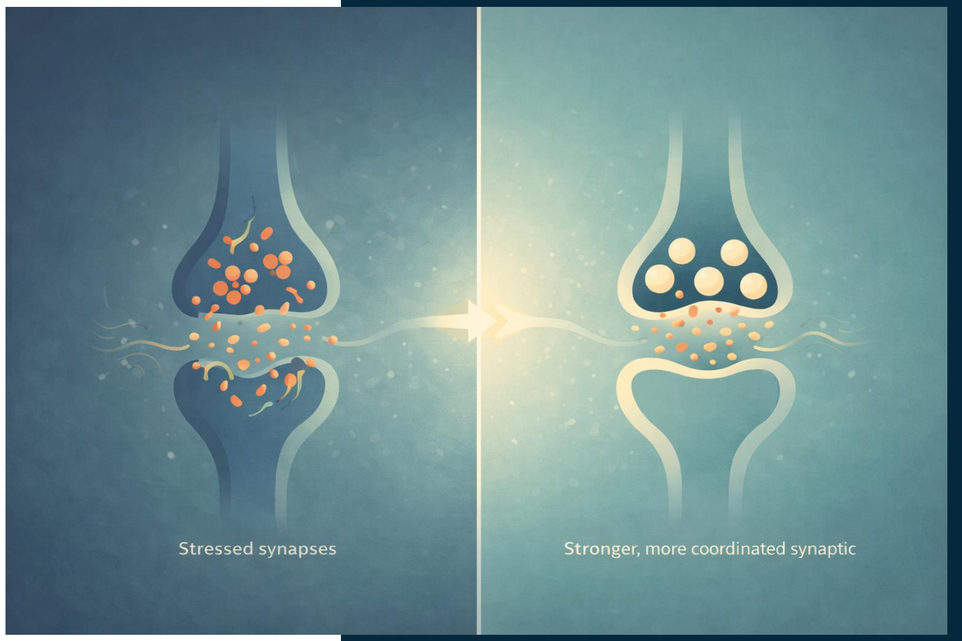
Bakker et al., 2012;
Vossel et al., 2021;
Mohs et al., 2024;
Mohamadi et al., 2025

Neflamapimod

Emerging Therapies

- Chronic α-synuclein–related injury in DLB/PD
  - → chronic stress
  - → chronic p38α activation
  - → disruption of normal cell signaling

- Most encouraging treatment to date in DLB
  - p38α inhibitor targeting synaptic stress biology
  - Phase 2 DLB data showed improvement in dementia severity and mobility
  - Attention/executive may be most responsive
  - Benefit greater in biomarker-defined “purer” DLB



Synaptic-support therapy

- Synaptic preservation may become a major therapeutic goal

Still investigational, but among the more advanced non-amyloid agents

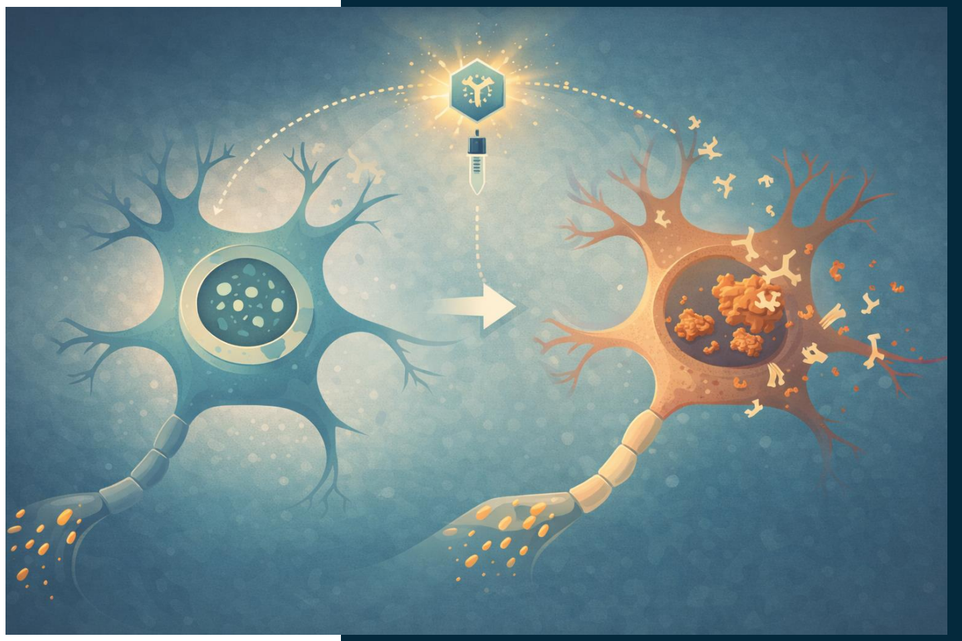
AscenD-LB; RewinD-LB;
Jiang et al., 2022.
Alam et al., 2023.
Julayunont et al. 2026.

VTX-002

- TDP-43 is core ALS/FTD proteinopathy
  - TDP-43 shifts from nucleus into the cytoplasm and forms toxic aggregates
  - ~97% of ALS shows TDP-43 aggregation

- VTX-002 represents a next-generation precision therapy
  - Uses an AAV-delivered vectorized antibody platform
  - Incorporating anti-TDP-43 DNA into neurons via viral transmission
  - The neurons then produces intrabodies specific to these misfolded proteins

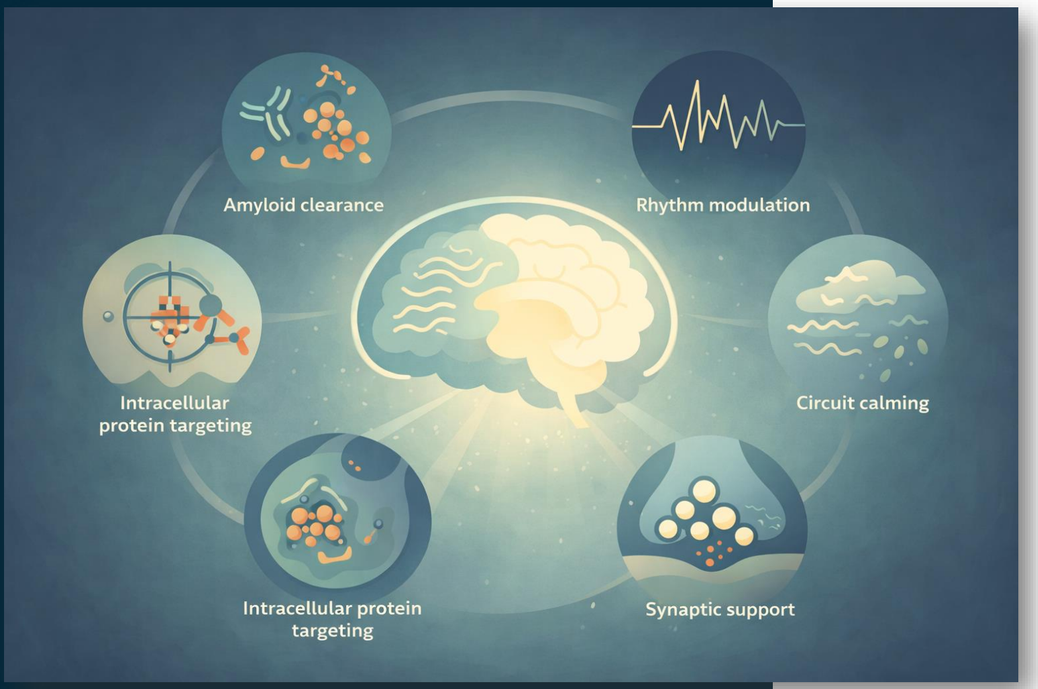
- PIONEER-ALS: Phase 1/2, open-label
  - Early clinical development, but highly important conceptually.
  - There are no public human efficacy results yet.



VTx-002 is a biologically important therapy — but at this stage it is a first-in-human platform story, not a proven clinical treatment.

Uspenskaya et al., 2025;
de Sabbata et al., 2025;
VectorY Therapeutics, 2025; 2026

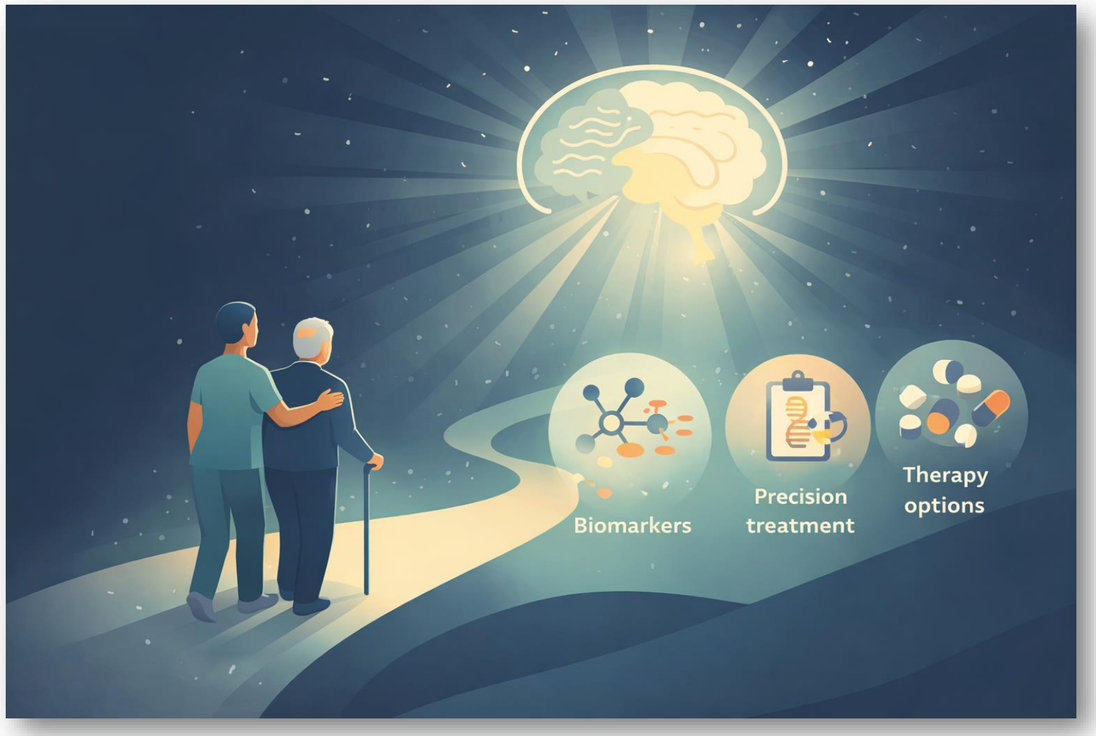
The Future Is Combination Therapy



- Different biologic stages may require different therapies
- Some patients may need plaque removal plus network support
- Others may need protein-specific or inflammation-focused strategies
- Precision medicine will depend on biomarkers and timing

The future of dementia treatment will likely resemble oncology more than a single one-size-fits-all drug.

What Patients and Families Should Hear



These therapies offer cautious hope, but they require honest discussion about benefit, burden, safety, and fit.

- There is real progress, but not a cure
- The benefit is slowing, not restoring
- Some patients are good candidates and some are not
- The right decision depends on biology, goals, values, and risk tolerance

Innovative and exciting treatments are emerging to tackle previously untreatable diseases in neurology and taken current treatments to the next level

Take-home message

The treatment and research landscape in neurology is steadily growing

1. Anti-amyloid therapy is a real advance, but it is best understood as slowing, not curing.

2. Patient selection, safety monitoring, and care infrastructure matter just as much as the drug itself.

3. The future of dementia treatment will likely be more precise, more biologically guided, and more personalized.

The goal is not just longer life, but more clear and meaningful time.

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