# Envisioning the Future of AD/ADRD Research

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Alzheimer's Association

# What May Impact Risk of Cognitive Decline or Dementia


**Constellation of reasons may be fundamental and unique to each individual**

**Social determinants of health may impact some or all of these factors**

**Strength of our understanding is different across risk factors**

**Need to Study Risk from ALL Angles**

# Focus on Risk Reduction

Up to **40%** of global dementia cases could be prevented or delayed by targeting modifiable risk factors

Research suggests combining multiple healthy factors may be the most impactful

**Physical Activity**

**Cognitive & Social Stimulation**

**Healthy Diet**

# U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk

U.S. POINTER
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**Two Year** | Multi-Center (Five U.S. Sites) | Randomized Clinical Trial
**2,000 Participants** | 60-79 Years Old | At Risk for Cognitive Decline

**Self-Guided** and **Structured** Intervention Groups
Physical Activity | Nutrition | Intellectual Engagement | Health Coaching
*Differ in Format, Expectations, and Accountability*

Commitment to **Community-Based** Outreach, Recruitment and Representation

- ✓ ***Completed Recruitment in March 2023***
- ✓ ***~ 30% from Underrepresented Populations***

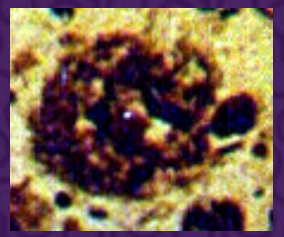
NIA Supported **Ancillary Studies**:

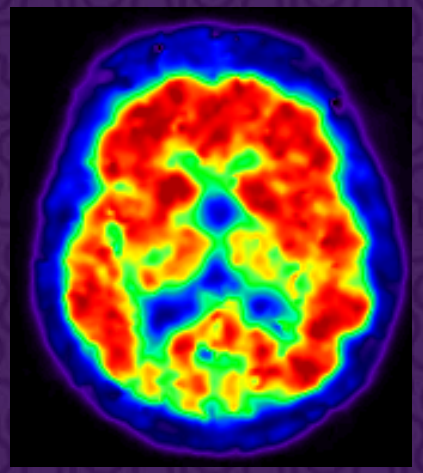
- ✓ **POINTER-Neuroimaging**
- ✓ **POINTER-zzz**
- ✓ **POINTER-Neurovascular**
- ✓ **POINTER-Microbiome**

**If the interventions prove effective, this study will lead the way in the development of an accessible and sustainable community-based program for prevention.**

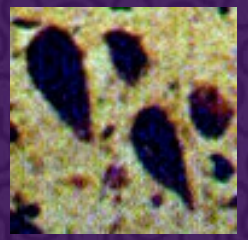
# Aβ and Tau Biomarkers

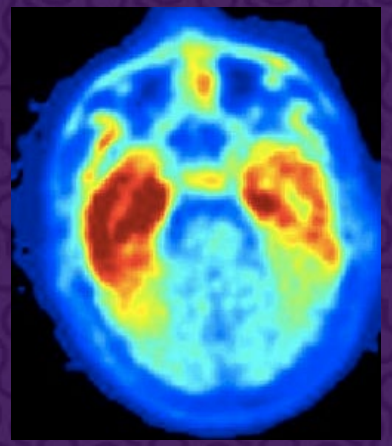
**Late 1990s**
**CSF Aβ, Tau, p-Tau**





**Mid-late 2000s**
**Amyloid PET**





**Mid-late 2010s**
**Tau PET**

**2020s**
**Plasma Aβ, Tau, p-Tau**

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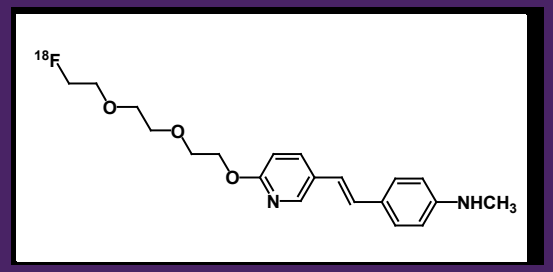
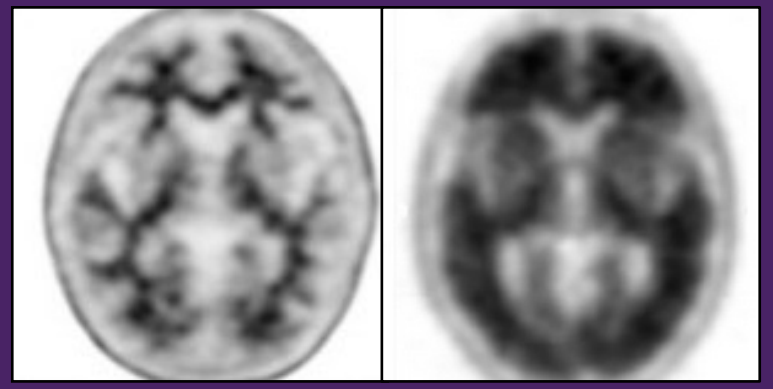
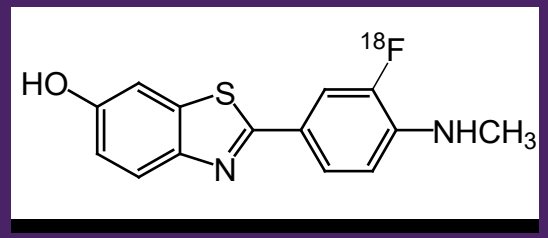
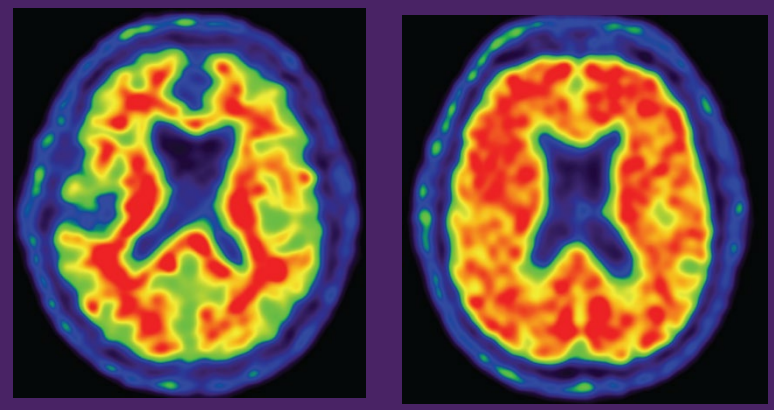
## $^{18}$F-florbetapir (Amyvid™)
## FDA approved April 2012



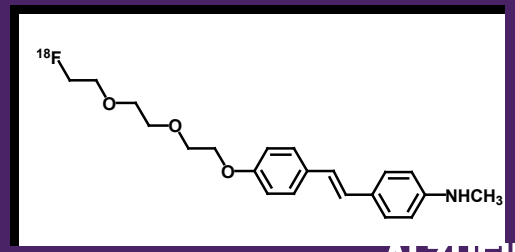



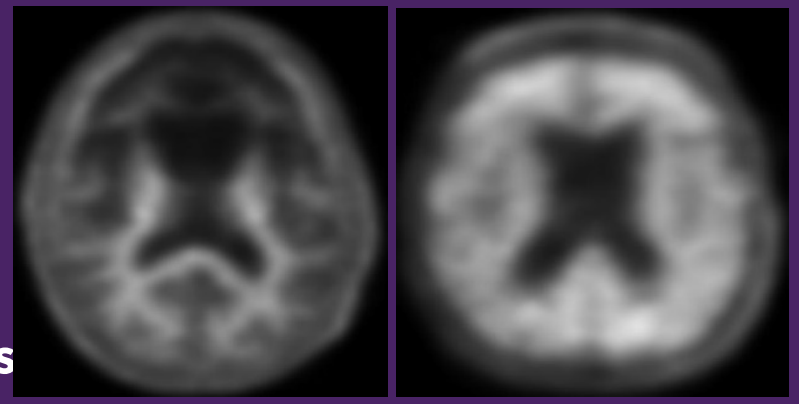
## $^{18}$F-flutemetamol (Vizamyl™)
## FDA approved October 2013



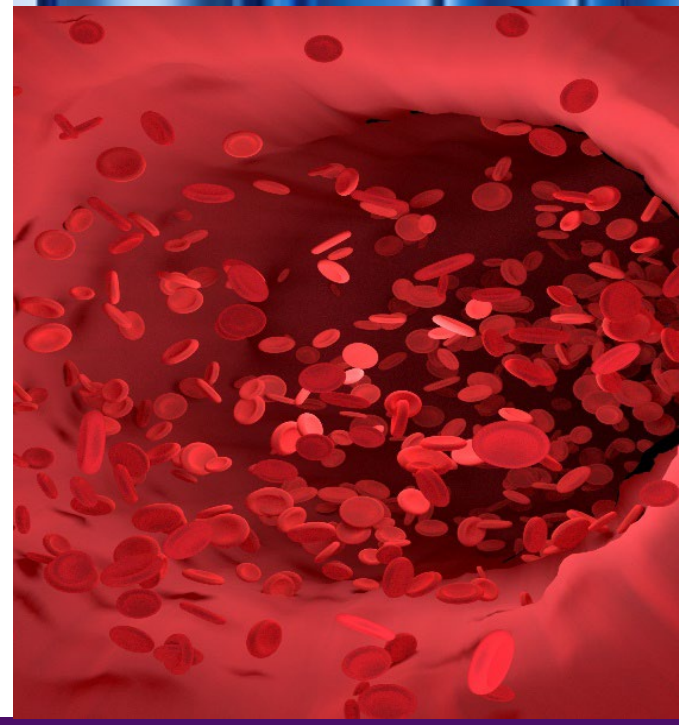
## $^{18}$F-florbetaben (Neuraceq™)
## FDA approved March 2014



# Advances in Biofluid Biomarkers

- Cerebrospinal fluid
  - Appropriate Use Criteria - 2018
  - CSF pre-analytical sample handling guidelines 2021
  - Some reference materials/methods available for standardization
  - 2 FDA cleared Amyloid CSF test on market
- Blood and plasma
  - Global race to uncover and develop blood based biomarkers for Alzheimer's and other dementia
  - Blood pre-analytical sample handling characterization 2021
  - No reference materials/methods available for standardization
  - 3 CLIA approved tests on market. No FDA cleared test on market.
  - Appropriate Use Recommendations (Published- 2022)
    - Focus on current state of field, gaps in knowledge and research priorities.
    - Recommendations for use of blood biomarkers in different settings: 1) clinical trial/research, 2) specialty care, 3) primary care



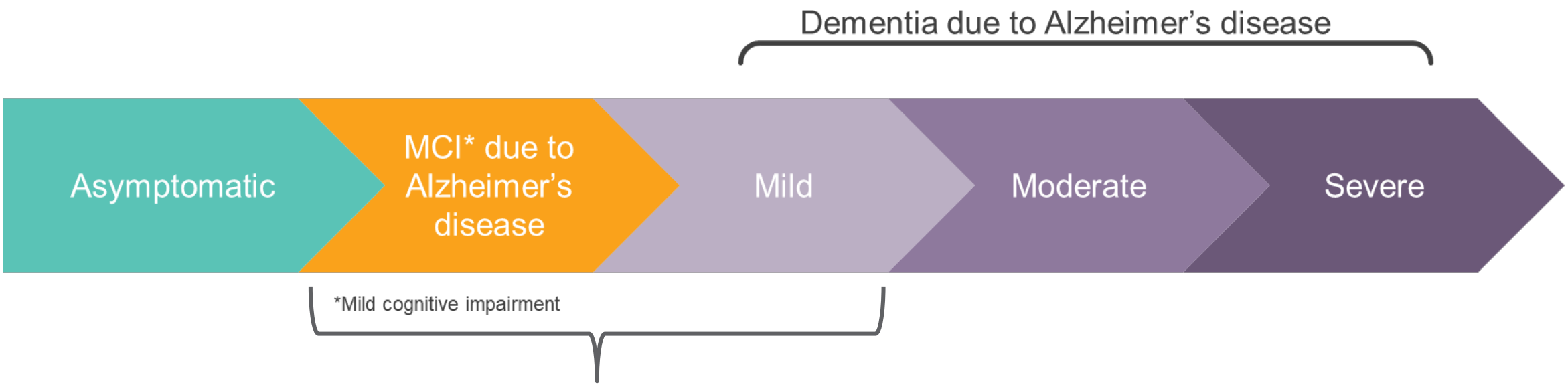
# Deeper Dive:
# A New Phase of Treatment

**Aducanumab (Aduhelm™)**
Approved in 2021
Targets Beta Amyloid

**Lecanemab (Leqembi ™)**
Approved in 2023
Targets Beta Amyloid

**Donanemab**
Reported Phase 3 Trial
Targets Beta Amyloid

# Prescribing Information for Newly Approved Treatments




**Lecanemab & Aducanumab**

- Ages 50-90
- Mild cognitive impairment (MCI) due to Alzheimer's OR mild Alzheimer's dementia
- Evidence of a buildup of amyloid plaques in the brain

# Outcome of Treatment(s)

Slowing of disease progression
(changes in underlying biology)

"I can keep doing what I want to do for a longer period of time"

*Individual response to any treatment or combination of treatments may vary*

# Growing Number of Papers Evaluating Clinical Meaningfulness

VIEWPOINT

## A Step Forward in the Fight Against Dementia—Are We There Yet?

Expectati
controlled

Ronald C. Pete
Brandy R. Matt
Maria C. Carrill

As clinicians who take care of many patients with AD who fit Clarity AD study criteria, we feel these patients and families should have access to this drug. Accessible treatment requires full approval by the FDA and other regulatory agencies, as well as payer coverage, including the US Centers for Medicare & Medicaid Services (CMS). In 2022, the CMS rendered a National Coverage Decision for the class of anti-Aβ monoclonal antibodies, limiting reimbursement to patients in CMS-approved studies. This decision needs to be revisited. Coverage decisions should not be made for the entire class but should evaluate each drug on its own merit given clear differences between antibodies in biological effects and clinical efficacy.


**David A. Wolk, MD**
Penn Alzheimer's Disease Research Center, Perelman School of Medicine, Department of Neurology, University of Pennsylvania, Philadelphia.

**Gil D. Rabinovici, MD**
Weill Institute for Neurosciences, Memory and Aging Center, Alzheimer's Disease Research Center, Department of Neurology, University of California, San Francisco, San Francisco; and Department of Radiology & Biomedical Imaging, University of California, San Francisco, San Francisco.

**Bradford C. Dickerson, MD**
Frontotemporal Disorders Unit, Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston.

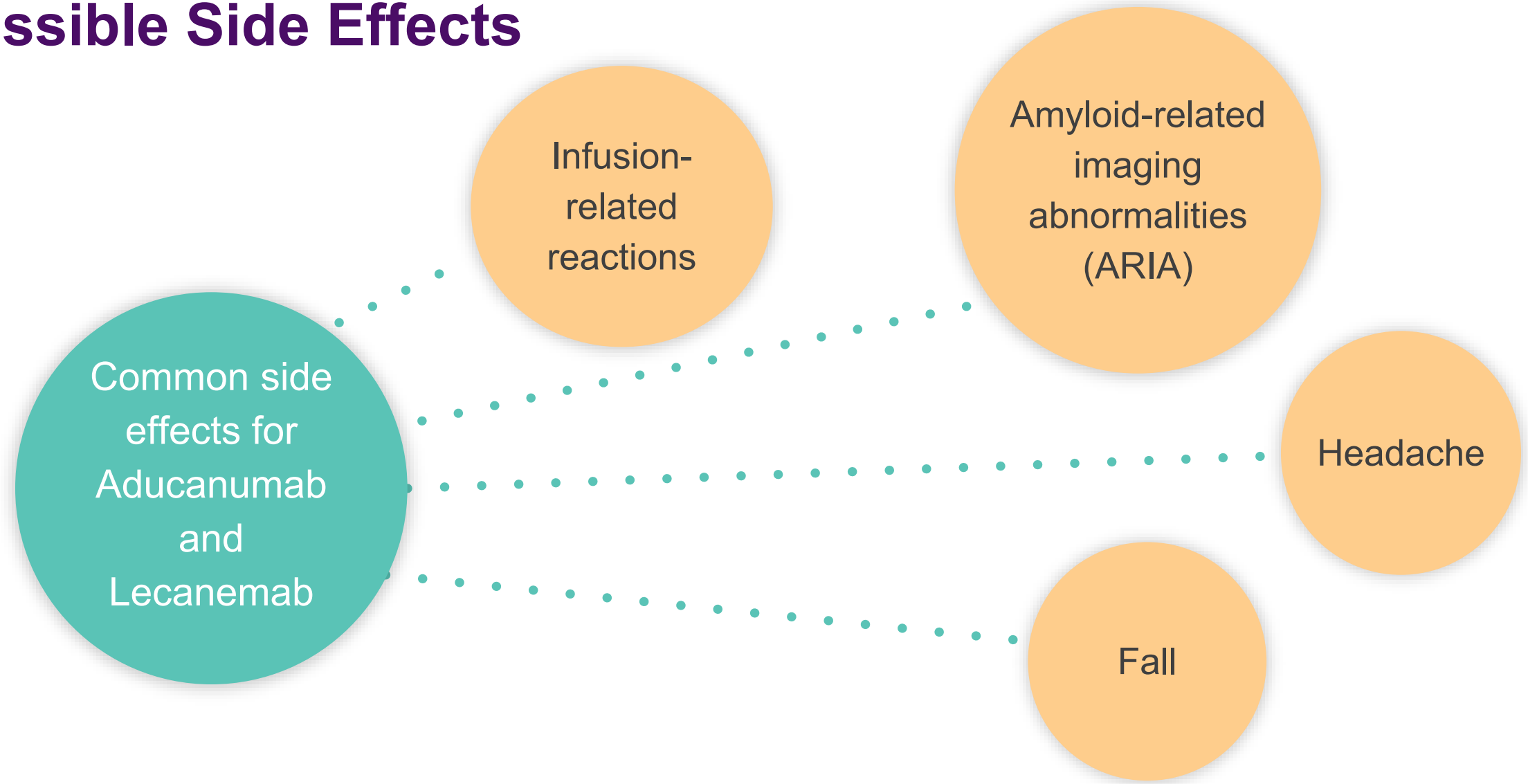

and Stephen Salloway[7]

URE 2 Adapted from As lening

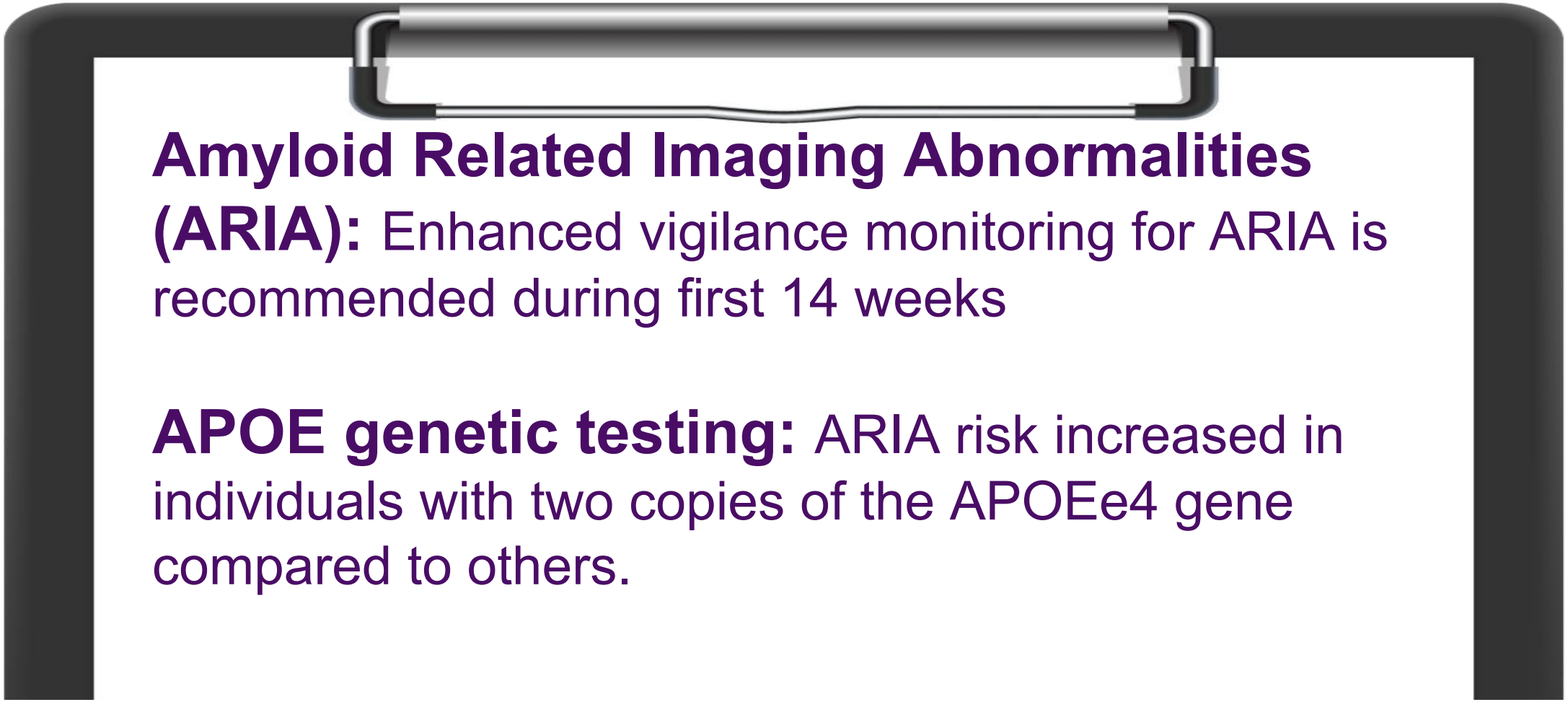
-placebo difference shows t lative benefit with

-term treatment, and this is critical to meaningful benefit

# Possible Side Effects



# Prescribing Information for Newly Approved Treatments: Warnings & Precautions (Lecanemab label)



**Amyloid Related Imaging Abnormalities (ARIA):** Enhanced vigilance monitoring for ARIA is recommended during first 14 weeks

**APOE genetic testing:** ARIA risk increased in individuals with two copies of the APOEe4 gene compared to others.

# Donanemab Trial Shows Clear Slowing of Cognitive Decline

ALZHEIMER'S ASSOCIATION AAIC 23

## Unique aspects

1736 participants with early symptomatic AD with amyloid & low/medium or high tau

Half of participants met threshold of amyloid reduction to stop taking donanemab at 12 months

## Key Results

Study met primary and secondary endpoints

Slowed clinical decline by 35% and 40% in ability to perform activities of daily living

Greater benefit in participants with low-medium tau (earlier stage of disease)

## Learnings

Early detection & intervention leads to greater benefit

Donanemab will significantly change the course of the disease

**Take home message**: First ever deep dive of TRAILBLAZER-ALZ 2 clinical trial results of donanemab showed **significant slowing** of **cognitive** and **functional decline** in **early** symptomatic **Alzheimer's disease**

# Treatment Related Amyloid Clearance TRAC

**Renaud La Joie**
University of California, San Francisco

**Claire Sexton**
Alzheimer's Association

# Workgroup members

| | |
|---|---|
| **Maria Carrillo** | *Alzheimer's Association* |
| **Jeffrey L Cummings** | *University of Nevada Las Vegas* |
| **Douglas Galasko** | *University of California, San Diego* |
| **Milos D Ikonomovic** | *University of Pittsburgh School of Medicine* |
| **Susan M Landau** | *University of California, Berkeley* |
| **Jorge Llibre-Guerra** | *Washington University in St. Louis School of Medicine* |
| **Catherine Mummery** | *University College London* |
| **Rik Ossenkoppele** | *Amsterdam University Medical Center* |
| **Julie Price** | *Massachusetts General Hospital* |
| **Shannon Risacher** | *Indiana University School of Medicine* |
| **Ruben Smith** | *Lund University* |
| **Christopher H. van Dyck** | *Yale School of Medicine* |

# Background & Objective

Disease Modifying Treatments (DMT) have a major effect on Aβ-PET

- In phase 2 and 3 trials, many patients became Aβ-PET negative
- Measurable effect on Aβ-PET is thought to underpin clinical benefit
- Reach Aβ-PET negativity: switch to placebo in donanemab phase 3

- **Goal** - Summarize current knowledge @“amyloid-depleted” cases & define a framework
  - a harmonized definition and operationalization for future studies
  - a nomenclature for this new entity | *would complement AT(N)/Revised criteria*

Our current focus is on

- data available in DMT in cognitively impaired patients (not preclinical AD)
- defining group based on amyloid-PET (no other amyloid biomarkers)

# Treatment Related Amyloid Clearance (TRAC)

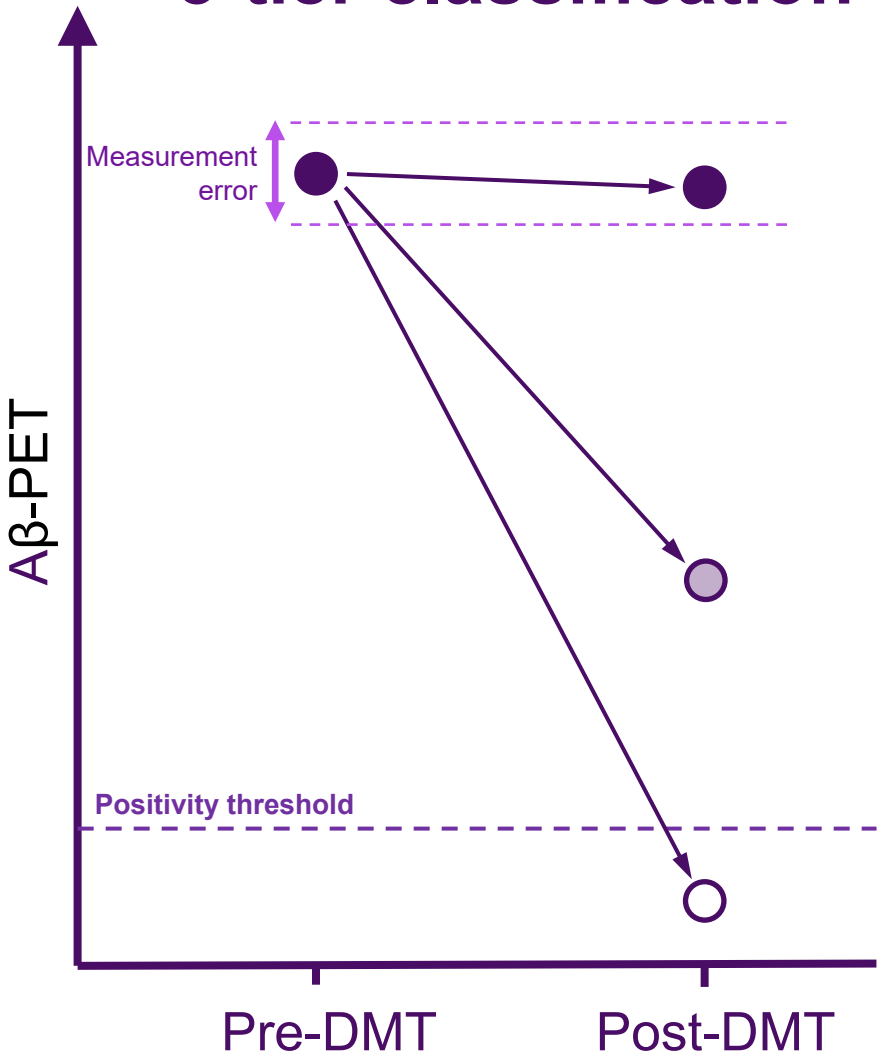
Signifies that natural history of disease has been altered

→ Modified relationships between biomarkers, clinical measures, and pathology

Applies to patients who:

- had confirmed A+ biomarker status prior to treatment
- AND have undergone anti-amyloid treatment
- AND have a follow up A biomarker testing

# 3-tier classification




## Complementary to AT(N) Post-DMT A status

### No TRAC
Change within test-retest error
(or Aβ-PET increase)

**A+**

### Partial TRAC
Significant decrease beyond test-retest error but scan is still positive

**A+**

### (Full) TRAC
Signal drops below positivity threshold

**A-**

# Implementation beyond PET

## $TRAC_{PET}$ / $TRAC_{CSF}$ / $TRAC_{plasma}$

## Focus currently is on amyloid-PET

- PET gold standard in trials
- PET quantification is more harmonized than CSF/plasma measures
- Changes in biofluid have been reported, but not with the same level of detail

  e.g. group level average changes but no report on % cases with values in the ‘normal range’

## Known relationships between PET and fluid biomarkers

- based on observational studies (natural disease history)
- might not apply to this modified disease state

# Current evidence & gaps in knowledge – to be investigated

- Underlying neuropathological changes? very limited data
  partial TRAC only (*Plowey Acta Neuropath 2022 ,VandeVrede Acta Neuropath 2023*)
- Predictors of TRAC?
  treatment factors (dose, duration) versus patients factors (baseline CL)
- Downstream effects of TRAC
  clinical response, future change in (other) biomarkers
- Management of patients with TRAC?
  adapt treatment duration?
  enrollment in other trials?
  relevance to combination approach?
- Communication with patients will be necessary

# The Future of Alzheimer's and Dementia Diagnosis, Treatment and Care

ALZHEIMER'S NETWORK

## Alzheimer's Network for Treatment and Diagnostics (ALZ-NET):

A Real World Network to Inform the Future of Alzheimer's Research, Treatment and Care

**LAUNCHED AUGUST 2022**


ALZHEIMER'S ASSOCIATION®

# ALZHEIMER'S NETWORK

## ALZ-NET is building an integrated care network for ALL communities supported by real-world data.

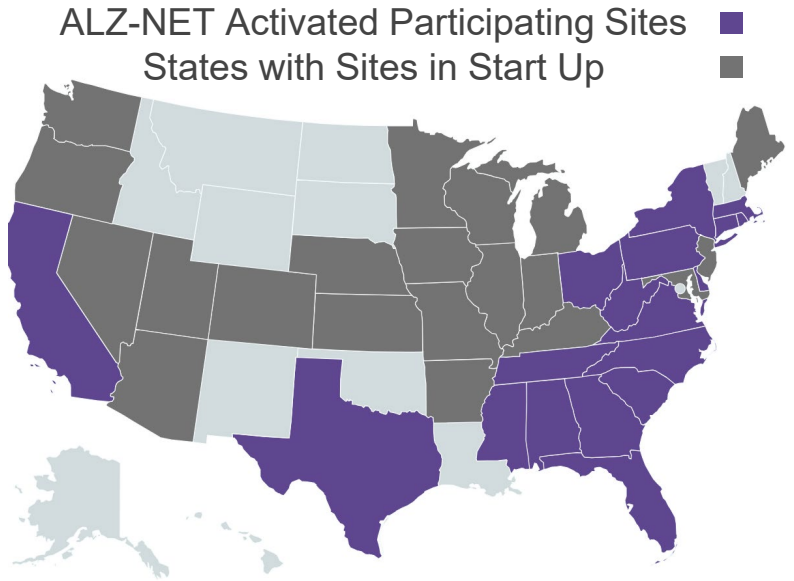
A **voluntary health care provider-enrolled patient network** that collects longitudinal data on patients being evaluated or treated for Alzheimer's disease.

Currently **enrolling patients being evaluated for or treated with novel Alzheimer's treatments** approved by the FDA in 2021 or after, including treatments that slow disease progression, or address cognition/function, or address neuropsychological/ behavioral symptoms.

Implemented in real-world clinical practice.
ALZ-NET is **not a clinical trial.**

## ALZ-NET will expand and evolve over time

## Over 170 sites in various stages of activation and start up




**Active Sites**
33

**Sites in Start Up**
116

**Sites in Queue**
23

**Patients Registered**
81

**Next Invitation Cycle**
January 2024

**As of 1/8/24*

ALZHEIMER'S ASSOCIATION

For more information visit
**alz-net.org**

# ALZ-NET is Collaborating on Affiliated Studies:

- 'ALZ-NET Affiliated Coverage with Evidence Development (CED) Study'
  - CMS requires individuals to be registered in a CMS-approved study or registry to allow for Medicare coverage of traditional FDA- approved anti-amyloid therapies for AD.
  - Study will address issues that may be barriers to access to new amyloid lowering treatments for Medicare beneficiaries and will track clinical and safety outcomes.
  - Protocol approval anticipated week of Jan 8.

- 'Lecanemab Post Marketing Requirement (PMR) Study'
  - Eisai must conduct the FDA required 'Lecanemab PMR Study' which will launch in 2025, in collaboration with ALZ-NET
  - Will be an FDA-approved 10 year registry-based, prospective, observational study to evaluate clinical safety outcomes among AD patients treated with lecanemab.
  - Protocol is in development

# Private Payers Also Including ALZ-NET as Registry Example

aetna®

## Leqembi™ (lecanemab-irmb) Medication Precertification Request

**Page 2 of 3**
(All fields must be completed and legible for precertification review.)

**Aetna Precertification Notification**
**Phone:** 1-866-752-7021 (TTY: 711)
**FAX:** 1-888-267-3277

**For Medicare Advantage Part B:**
Please Use Medicare Request Form

| Patient First Name | Patient Last Name | Patient Phone | Patient DOB |
|---|---|---|---|
| | | | |

**G. CLINICAL INFORMATION *(continued)*** – Required clinical information must be completed in its entirety for all precertification requests.

**For Initiation New Start Requests (clinical documentation required for all requests):**

**Alzheimer's Disease**

☐ Yes ☐ No Is the patient or provider currently participating in a provider-enrolled patient registry that collects information on treatments for Alzheimer's disease (e.g., Alzheimer's Network for Treatment and Diagnostics (ALZ-NET))?

Please indicate name of provider-enrolled patient registry: _____

United Healthcare®

- Prescriber attests that the prescriber's site is currently registered or will seek registration with the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) or other comparable patient registry that collects information on treatments for Alzheimer's disease, including Leqembi; **and**
- Leqembi dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no more than 6 months

For **continuation of therapy**, **all** of the following:

- Patient continues to have one of following diagnoses based on National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria[22,55]:
  - Mild cognitive impairment (MCI) due to Alzheimer's disease; **or**
  - Probable Alzheimer's disease dementia

# A New Phase of Treatment

**Targets *amyloid***

**2021**

Aducanumab (Aduhelm™)

**Targets *amyloid***

**2023**

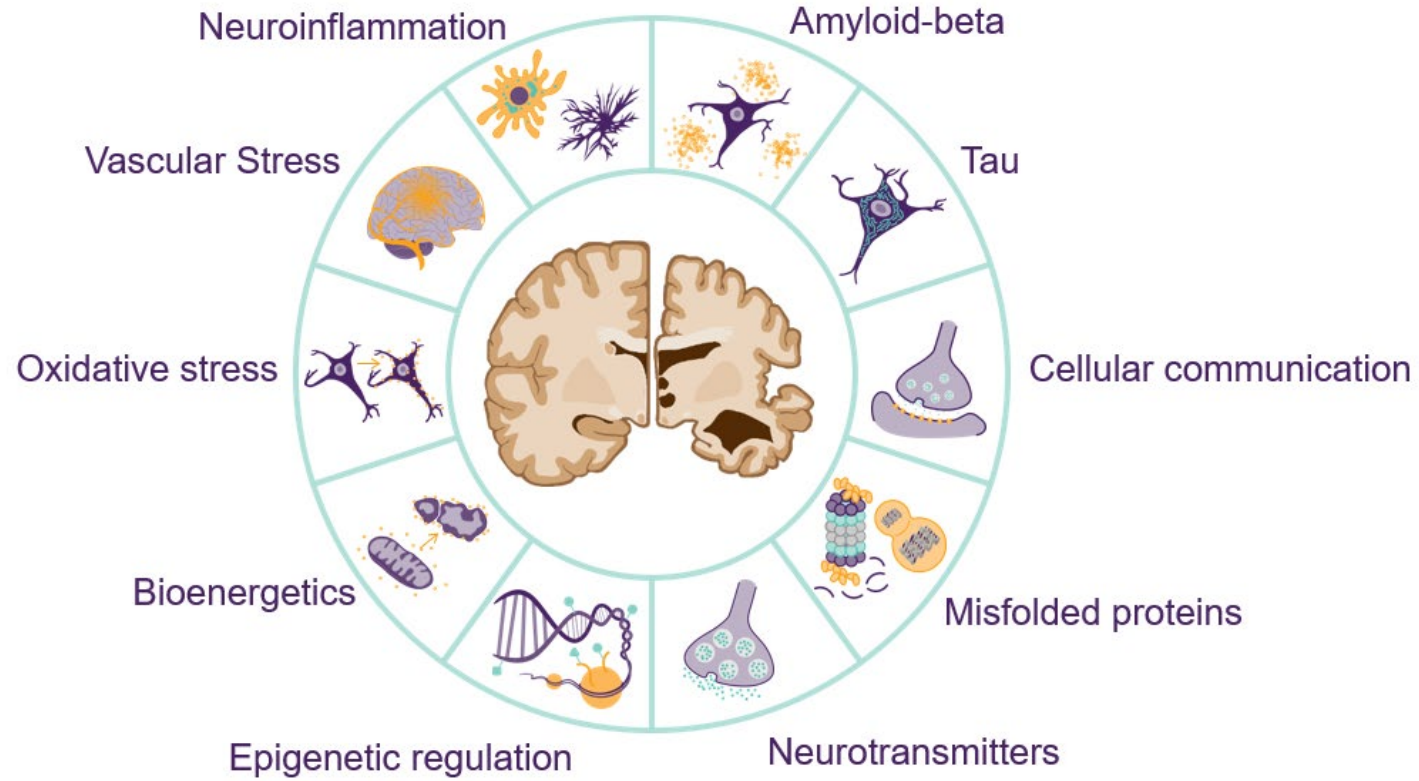
Lecanemab (Leqembi™)

**Targets *amyloid***

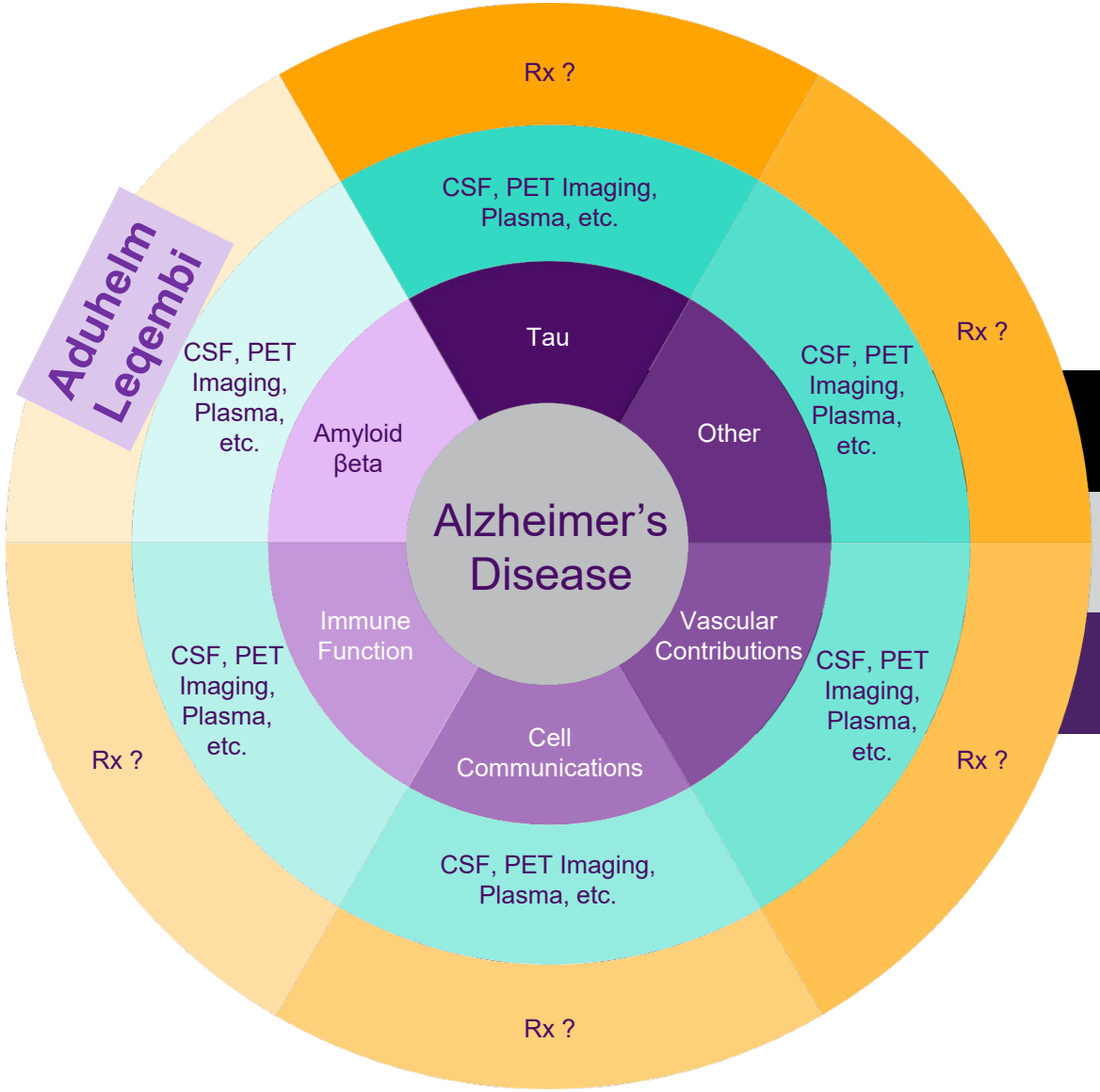
Donanemab

FDA review pending Q1 2024

## Today, Over 140 Unique Therapies Being Tested in Clinical Trials that Target Multiple Aspects of Alzheimer's Biology



Modifiable Risk Factors




Brain Changes

Biomarkers

Therapies



*Adapted from R. Petersen, Neurology 2018 91(9)*