ALZHEIMER'S DISEASE IN 2026: FROM SYMPTOMATIC CARE TO EARLY DETECTION AND PREVENTION

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DISCLOSURES

The presenters have no financial disclosures.

Brigid Reynolds is the Memory Disorders Program Site Principal Investigator (PI) for the ADNI Study and the Alzheimer's Clinical Trial Consortium (ACTC) Georgetown Site Co-PI.

Alison Perlberg Coordinated the A4 and LEARN Studies at the Memory Disorders Program.

GEORGETOWN UNIVERSITY MEMORY DISORDERS PROGRAM



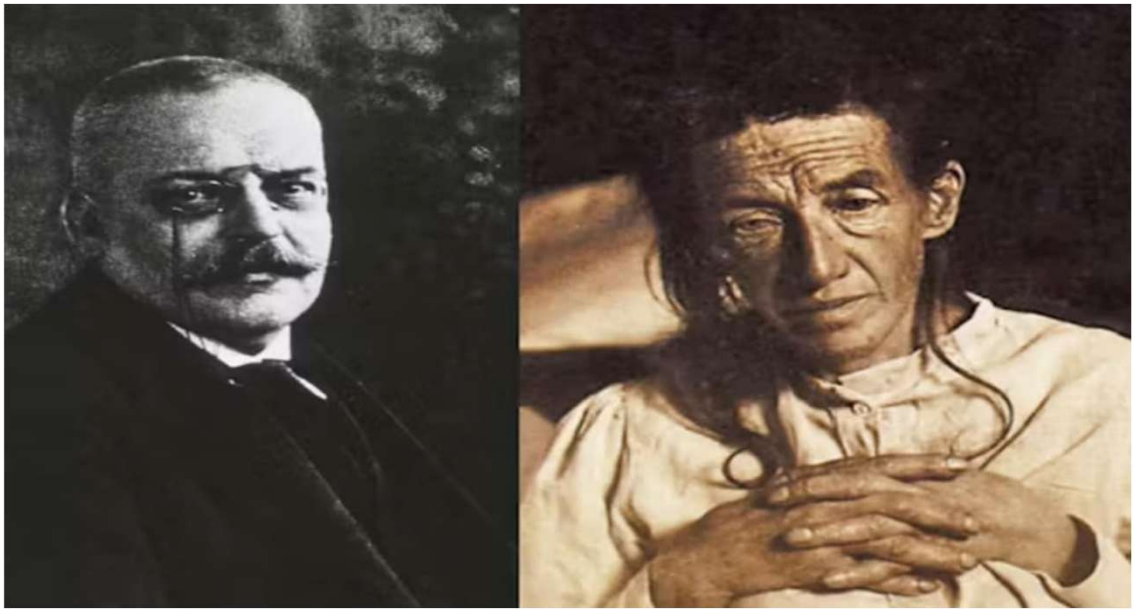
GEORGETOWN UNIVERSITY

PRESENTATION OUTLINE

1. **Case study #1 Auguste's Story- 1906**
2. AD Pathology
3. Dementia and MCI
4. The ADNI Study
5. **Case study # 2 Edith's Story- 2005**
6. **Case Study # 3 Joy's Story- 2015**
7. The Antiamyloid in Asymptomatic Alzheimer's disease study (A4) and LEARN Studies
8. The AHEAD and LEARN Studies
9. The Pointer Study
10. **Case Study #4 Archie's Story- 2025**
11. Blood-Based Biomarkers
12. Amyloid-Reducing Treatments
13. The Alzheimer's Tau Platform Study (ATP)
14. Key Takeaways
15. Websites/Resources

CASE STUDY # 1
AUGUSTE DETER (1906)

In **1906**, German psychiatrist and neuropathologist **Dr. Alois Alzheimer** presented the case of **Auguste Deter**, a 51-year-old woman with profound memory loss and hallucinations.



A Diagnosis in 1906: Auguste's Journey (1850-1906)

The First Signs

BEHAVIOR & MEMORY CHANGES

- Presented with profound memory loss and hallucinations
- Admitted to a Frankfurt psychiatric hospital in 1901
- Died from septicemia due to bedsores and pneumonia at age 55 in 1906

The 1906 Diagnosis

PROCESS OF ELIMINATION

- Following her death, Dr. Alzheimer performed a brain autopsy
- Chemical staining determined Auguste had amyloid plaques and tau tangles
- **Auguste's case defined the hallmark pathologies for Alzheimer's disease**

The Care Plan

MANAGING THE SYMPTOMS

- **No treatments would become available for another 87 years**

Inside the Brain: The 3 Stages of Alzheimer's Disease

How specific protein changes slowly disrupt normal brain function over time.

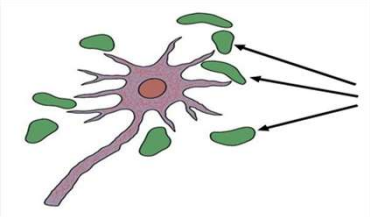
STAGE 1

The "Plaques" (Amyloid)

The External Clumps

Healthy brain cells overproduce small protein fragments called amyloid.

Fragments form sticky **plaques** that build up outside and between brain cells.



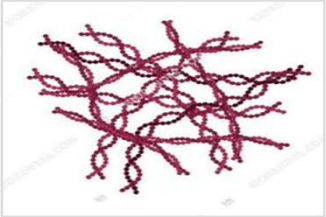
STAGE 2

The "Tangles" (Tau)

The Internal Collapse

Inside brain cells, tau proteins twist into abnormal **tangles**.

Tangles disrupt vital communication between neurons.



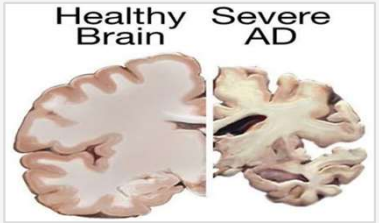
STAGE 3

The "Damage" (Neurodegeneration)

The Communication Loss

External plaques and internal tangles strangle the brain cells.

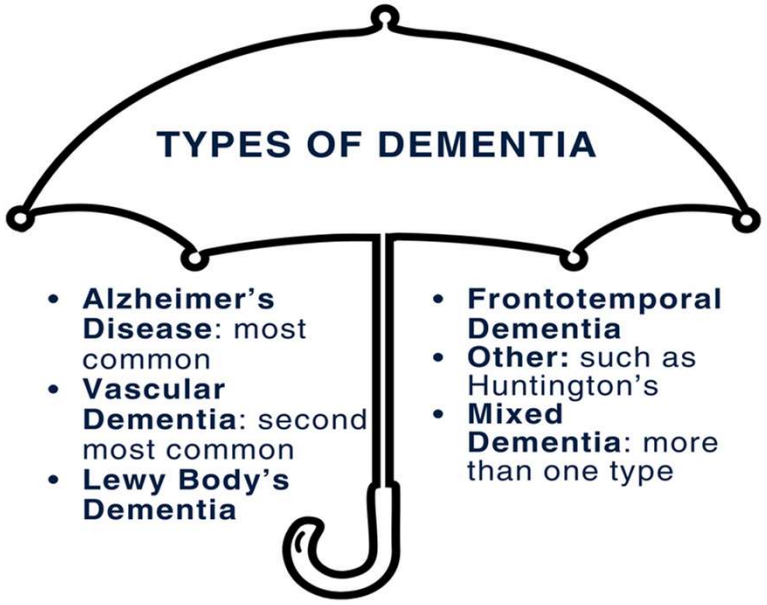
Over time, these cells fail, wither, and completely fade away.

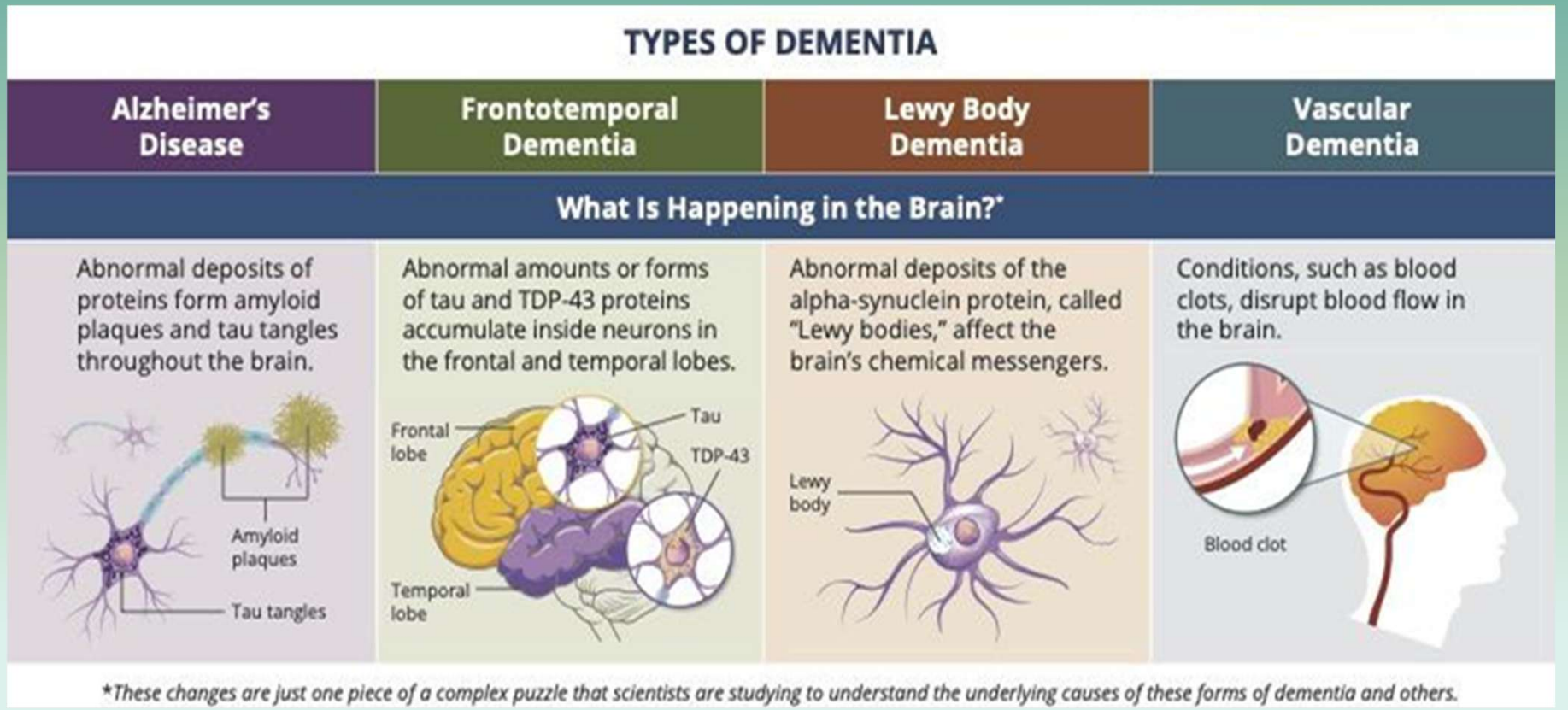


DEMENTIA- AN UMBRELLA TERM

Dementia: progressive, irreversible brain diseases in which a specific neurological process directly destroys brain cells and leads to a loss of function.

Four major types account for the vast majority of all cases.





https://www.nia.nih.gov/health/alzheimers-and-dementia/understanding-different-types-dementia

Understanding Mild Cognitive Impairment (MCI)

The middle ground between normal aging and dementia

What is it?

- A noticeable decline in memory, thinking, or concentration skills
- Changes are clear to the person or family, but do not stop daily independence
- The individual manages daily life on their own
- They can still drive, pay bills, shop, and live safely alone

How it differs

- Normal Aging: Forgetting keys occasionally
- MCI: Forgetting recent events or conversations regularly
- Dementia: Struggles to dress, cook, or live safely without assistance

What comes next?

- It is a warning sign, not a guarantee of dementia
- Some people stay stable or improve; others progress
- Early diagnosis opens doors to lifestyle changes and proactive care.

THE CHOLINERGIC HYPOTHESIS

Alzheimer’s a treatable disease?

Cholinergic hypothesis: dysfunction of acetylcholine in the brain contributes substantially to the cognitive decline observed in Alzheimer's disease.

Key Milestones:

1976: Researchers Peter Davies and A.J.F. Maloney first discovered a major loss of the acetylcholine-synthesizing enzyme in the brains of patients with Alzheimer's disease.

1982: Dr. Raymond T. Bartus and colleagues published a landmark review article in *Science*, titled *"The cholinergic hypothesis of geriatric memory dysfunction,”* - formally established the concept.

CHOLINESTERASE INHIBITORS

Provide symptomatic benefit

Not disease-modifying

Approved for treatment in mild, moderate, and severe Alzheimer's disease:

Aricept (donepezil)- FDA approved in 1996

Exelon (rivastigmine)- FDA approved in 2000

Razadyne (galantamine)- FDA approved in 2001

THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)

A long-term, multi-center study that tracks the progression of Alzheimer's disease using brain scans, memory tests, and biological samples.

Began in 2004 as a private-public partnership supported by the National Institute on Aging, the Alzheimer's Association, and dozens of companies.

- **Study Type:** Observational only (no experimental drugs or medications are given as part of the study)
- **Main Purpose:** To find and validate early-detection biomarkers (such as MRI scans, PET scans, and spinal fluid/blood tests) to help design better clinical drug trials aimed at developing treatments that slow or stop disease progression
- **Data Sharing:** All collected data is shared openly with researchers worldwide. More than 5,000 to 6,000 scientific publications have been produced or facilitated using data from the ADNI study.

ADNI Study Milestones & Timeline

Alzheimer's Disease Neuroimaging Initiative: Shaping biomarker validation since 2004.

ADNI-1

2004 – 2009

Baseline biomarker tracking & standardization across 1.5T MRI, FDG PET, and CSF samples.

Amyloid PET PIB-pilot 2005

ADNI-GO

2009 – 2011

Grand Opportunity expansion adding an early-MCI cohort to catch the earliest signs.

ADNI-2

2011 – 2016

Full clinical spectrum validation, splitting MCI into early and late stages.

Amyloid PET- florbetapir, florbataben

Tau Pet- flortaucipir, introduced during the later phase of ADNI 2

ADNI-3

2016 – 2023

Transition to 3T scanners, adding advanced fMRI sequences and revolutionary Tau PET.

ADNI-4

2023 – Present

Modern digital focus on highly sensitive blood-plasma testing and minority cohort diversity.

CASE STUDY # 2 - EDITH



Edith, is a 68-year-old retired teacher.

Her spouse began noticing changes such as Edith's misplacing her keys, and repeating questions.

The onset of gradually progressive symptoms were first noticed by her spouse approximately two years ago.

Edith was unaware of her memory and thinking changes and was resistant to come in for an evaluation.

Edith stopped driving after getting lost on a familiar route twice.

She screened for enrollment in ADNI-1. Her spouse served as her Study Partner.

A Diagnosis in 2005: Edith’s Journey

What finding out you had Alzheimer's looked like over two decades ago, before modern biomarkers.

The First Signs

MEMORY CHANGES

- Presented with noticeable changes to her memory such as repeating questions and misplacing personal belongings
- Functional changes included no longer driving due to getting lost
- Enrolled in the AD cohort of ADNI-1

The 2004 Diagnosis

PROCESS OF ELIMINATION

- Pen-and-paper tests of memory and thinking
- Medical history and physical exam
- MRI performed to rule out stroke, tumor, or other causes for thinking changes
- Spinal fluid (CSF) analysis for Amyloid-beta (Aβ) and Tau Proteins
- Given a diagnosis of probable Alzheimer’s disease

The Care Plan

MANAGING THE SYMPTOMS

- Encouraged to make lifestyle interventions
- PCP prescribed donepezil (Aricept) for symptomatic management
- Encouraged to initiate long-term care planning
- No disease-modifying treatments were available

LIFESTYLE INTERVENTIONS- 2005

In 2005, the understanding of lifestyle interventions for brain health was in a transitional phase. Medical consensus still overwhelmingly favored the **cholinergic hypothesis** and the search for a pharmaceutical "silver bullet."

Neuroplasticity- From the late 20th century onward, scientists first began proving that the adult brain could change, grow, and protect itself through behavior.

Healthy lifestyle interventions including engagement in physical, social, and mentally stimulating activities were recommended.

The absence of clinical biomarkers to detect and measure change made it difficult to quantify and characterize the impact of lifestyle interventions.

CASE STUDY # 3 - JOY (2015)



Joy, a 71-year-old retired accountant noticed changes in her memory, such as forgetting names and conversations.

She first noticed changes approximately one year ago.

She maintained independence with her daily activities at home.

Her medical history was significant for high blood pressure and diabetes.

She screened for enrollment in ADNI-2. Her sister served as her Study Partner.

A diagnosis in 2015: Joy's Journey

How joining the Alzheimer's Disease Neuroimaging Initiative (ADNI) in 2015 shifted toward advanced biomarker tracking.

The ADNI Screening

CLINICAL & STRUCTURAL BASELINES

- Screened for the ADNI study using extensive testing and standardized functional assessments
- Enrolled in the MCI cohort of ADNI-2

The 2014 Biomarkers

ADVANCED IMAGING & PATHOLOGY

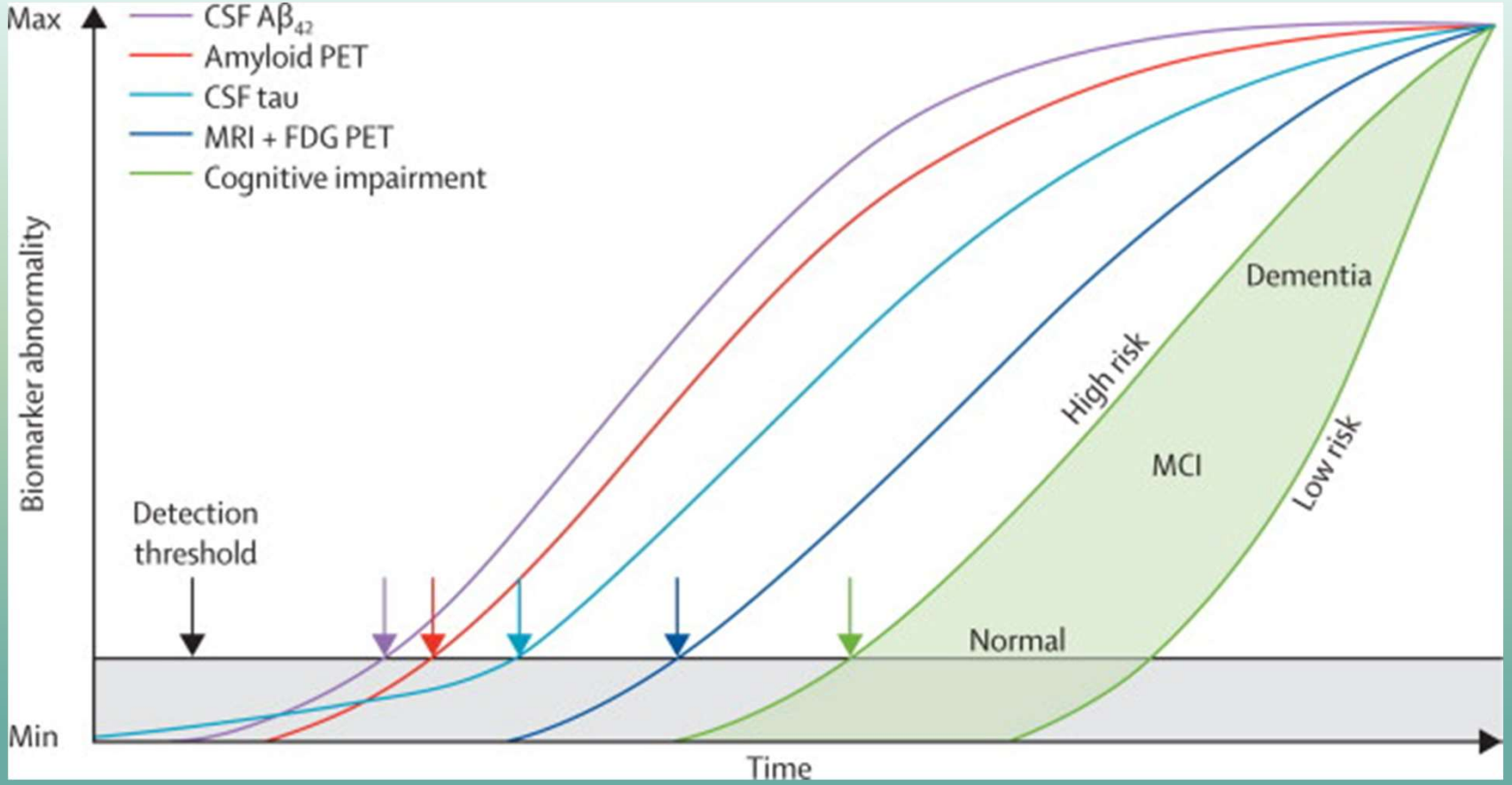
- In addition to paper-and-pencil testing, Joy's evaluation included:
- Amyloid PET scan- visualize amyloid plaques
- FDG PET Scan
- Volumetric MRIs - visualize structural brain changes
- Spinal tap- CSF fluid analysis for Amyloid-beta (Aβ) and Tau Proteins

The Care Plan

LONGITUDINAL TRIAL PARTICIPATION

- Encouragement to make lifestyle changes including physical, social, and cognitive engagement
- Control diabetes and hypertension
- FDA approved medications for the treatment of MCI remained unavailable

THE JACK CURVE- 2010



- https://pubmed.ncbi.nlm.nih.gov/20083042/#&gid=article-figures&pid=figure-2-uid-1

A4: A LANDMARK PREVENTION TRIAL
ANTI-AMYLOID IN ASYMPTOMATIC AD

The A4 Study
Now is the time

ACTC
ALZHEIMER'S
CLINICAL TRIALS CONSORTIUM

Duration: The landmark trial **launched in 2013.** Results were announced in **March 2023.**

- **First-of-its-kind Phase 3 secondary prevention** trial designed to see if an anti-amyloid treatment could slow cognitive decline in individuals at risk for Alzheimer's disease before symptoms appear
- **Participants:** Tracked **1,169 cognitively normal adults** (ages 65–85) over 4.5 years of continuous monthly evaluation
- **Results:** The investigational drug, *solanezumab*, **did not slow memory loss** or lower the risk of progressing to symptomatic Alzheimer's compared to a placebo
- **Amyloid linked to memory:** Proved higher amyloid plaque burden led to more rapid cognitive decline which confirmed plaque buildup is a direct, early driver of the disease
- **Paving the way forward:** While the drug itself failed, the A4 Study successfully proved that pre-symptomatic clinical trials are entirely possible

LEARN THE LEARN STUDY

ACTC ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

- **The "Screen-Fail" Strategy:** Enrolled individuals who did not qualify for the A4 trial due to *negative* screening on amyloid PET scans (low brain amyloid levels).
- **The Control Value:** Serves as a vital, direct longitudinal baseline comparison group to understand true preclinical neurodegeneration absent early amyloid accumulation.
- **No Cognitive Decline:** Over the course of the 240+ week monitoring period, LEARN participants (who were amyloid-negative at baseline) **did not demonstrate cognitive decline.**
- **Biomarkers as Predictors:** Data combining both studies confirmed that higher baseline levels of amyloid-beta and tau are the strongest predictors of subsequent memory loss.

THE AHEAD STUDY

Funding: A public-private partnership- the National Institute on Aging (NIA) and Industry and Philanthropic Sponsors

Sponsor: The Alzheimer's Clinical Trials Consortium (ACTC) provides scientific leadership, trial management, and infrastructure

Purpose: Test whether lecanemab clears brain amyloid plaques and reduces Alzheimer's risk before memory loss starts

Target Population: Adults aged 55 to 80 who are cognitively normal but show elevated or intermediate brain amyloid levels

Study Design: 4-year double-blind, placebo-controlled trial split into two sister studies (A3 for intermediate amyloid; A45 for elevated amyloid)

Study Timeline: First patient infusions began in September 2020

Projected End Dates:

- **Primary Completion: December 21, 2028**
- **Full Study Completion: January 16, 2031**

U.S.POINTER
ALZHEIMER'S ASSOCIATION

A two-year randomized clinical trial sponsored by the Alzheimer's Association evaluated whether multidomain lifestyle interventions can protect brain function and reduce the risk of cognitive decline in older adults.

- **Participants:** 2,111 older adults aged 60 to 79 who were at increased risk for cognitive decline and did not exercise regularly

- **Core Interventions:** The trial tested four main lifestyle areas:
  - **Physical Exercise:** Aerobic activity (30–35 minutes, 4 times per week) plus strength and flexibility training (2 times per week)
  - **Nutrition:** The **MIND diet** (focusing on leafy greens, berries, nuts, whole grains, and lean proteins while limiting red meat and saturated fats)
  - **Cognitive & Social Engagement:** Computerized brain training and group activities
  - **Cardiovascular & Health Monitoring:** Regular checks for blood pressure, weight, and blood sugar

Universal Improvement: Both the self-guided and structured groups showed marked cognitive improvement over baseline.

Structure Drives Success: The structured group achieved a significantly higher benefit in memory and thinking capabilities than the self-guided cohort.

Turning Back the Clock: Highly structured accountability effectively slowed the cognitive aging clock, yielding test scores on par with adults **1 to 2 years younger**.

Broad Demographic Impact: Cognitive resilience improved across all groups, independent of sex, race, ethnicity, heart health status, or genetic risk factors like the APOE4 allele.

CASE STUDY # 4 - ARCHIE (2025)



Archie, a 59-year-old retired accountant, began noticing changes in his memory, such as forgetting his home address and disorientation while driving. He had recently been involved in a “fender bender”.

His son reported memory loss symptoms were first noted about one year ago and were gradually progressive.

He had missed paying some bills which he had never done before. The debt collectors were calling.

Archie wasn’t concerned about his memory but was unopposed to being evaluated. He and his family had heard about research involving new blood tests that could detect Alzheimer's disease in its earliest stages.

He screened for enrollment in ADNI-4. His son served as his Study Partner.

A diagnosis in 2025: Archie's Journey

What finding out you have Alzheimer's disease looks like today

The ADNI Screening

CLINICAL & STRUCTURAL BASELINES

- Screened for the ADNI study using extensive testing and standardized functional assessments
- Enrolled in the AD cohort of ADNI-4 with a diagnosis of mild, **early-onset** Alzheimer's disease

The 2014 Biomarkers

ADVANCED IMAGING & PATHOLOGY

- In addition to paper-and-pencil testing, Archie's evaluation included:
  - Amyloid PET scan
  - Volumetric MRIs
  - Tau PET scan
  - Blood-based biomarkers

The Care Plan

LONGITUDINAL TRIAL PARTICIPATION

- Archie was diagnosed with Alzheimer's disease
- The POINTER study results motivated Archie to adhere to lifestyle changes to maintain his brain health
- Archie's Neurologist initiated treatment with Aricept
- Archie will consider treatment with Kisunla or Leqembi to help slow disease progression

BLOOD-BASED BIOMARKERS

- **p-tau (Phosphorylated Tau): p-tau217** or **p-tau181;** these proteins track tau tangles and amyloid plaque pathology in the brain. **p-tau217** is currently one of the most reliable markers and is used in FDA-cleared blood tests.
- **Amyloid-beta (Aβ42 / Aβ40 ratio):** A lower ratio of amyloid-beta 42 to 40 in the blood indicates that amyloid plaques are depositing in the brain.
- **NfL (Neurofilament Light Chain):** A general marker of nerve cell (axon) damage and degeneration, though it elevates in many neurological conditions (like ALS or multiple sclerosis) rather than just Alzheimer's.
- **ATN: A** stands for **Amyloid, T** stands for **Tau, N** stands for **Neurodegeneration**

  A: Blood tests look for the **Aβ42/Aβ40 ratio**.

  T: Blood tests look for **p-tau217** or **p-tau181**.

  N: Looks for **NfL (Neurofilament Light)** or **GFAP**.



AMYLOID REDUCING ANTIBODY TREATMENTS

Leqembi (lecanemab) -Eli Lilly and Company—FDA approved in 2023

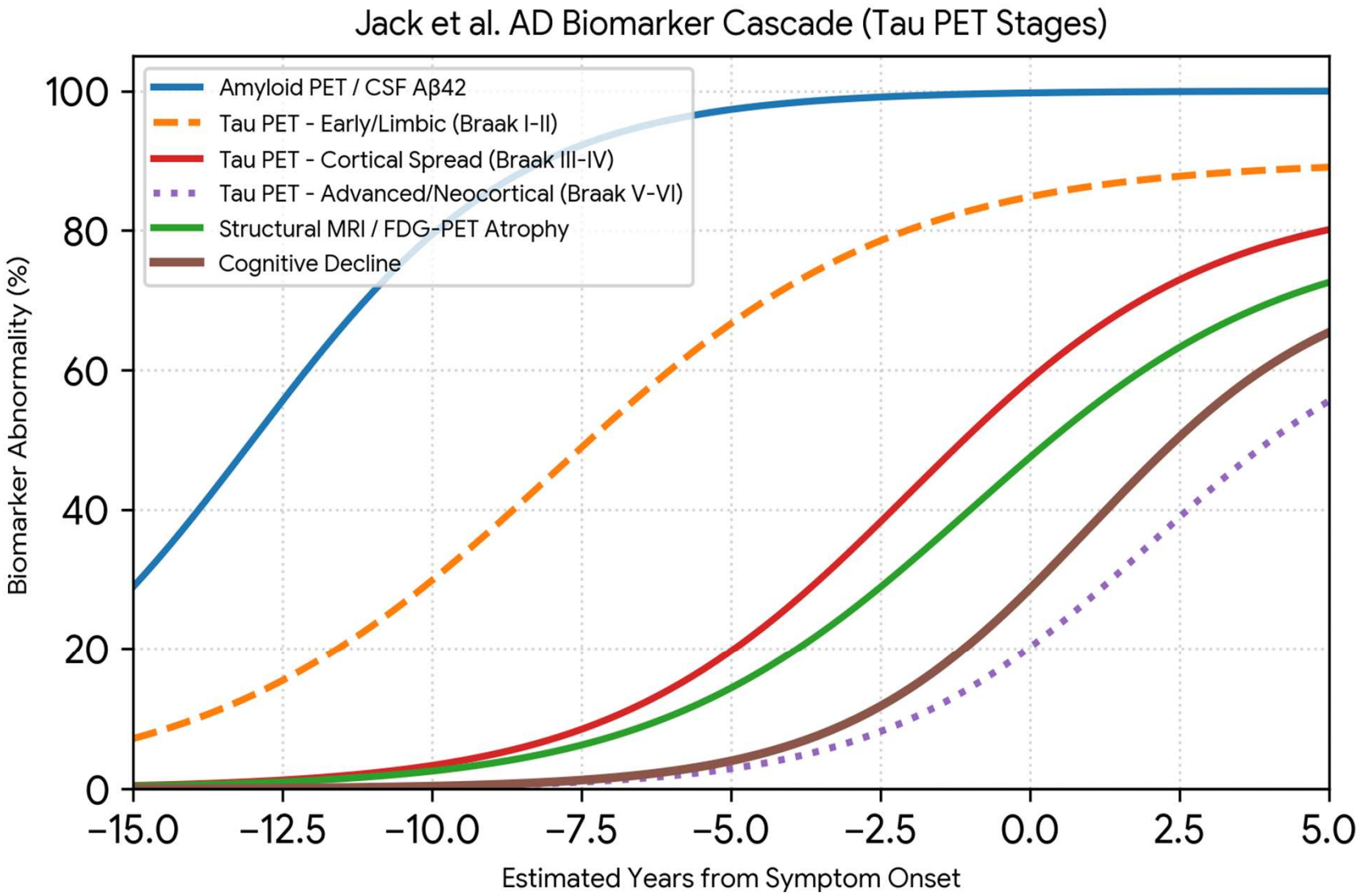
- **Clarity AD- 2019-2022 - November 2022** *The New England Journal of Medicine*

Kisunla (donanemab) -Eisai- FDA approved in 2024

- **Trailblazer Alz 2- 2020-2023 - July 2023** *The Journal of the American Medical Association*

- **Slow down the disease:** By targeting amyloid plaques, slow down memory decline and thinking problems by about 27% to 35%
- **Not a cure:** Cannot reverse existing brain damage or restore memories that are already lost
- **Early stages only:** Only for people with mild cognitive impairment or early-stage Alzheimer's dementia
- **Not for advanced stages:** It does not help, and can be unsafe for, people with moderate or severe Alzheimer's

All medications carry risks and no medication is right for everyone. Speak with your provider about the risks of a antibody treatments and all other medications you are taking!


Jack et al. AD Biomarker Cascade (Tau PET Stages)
Amyloid PET / CSF Aβ42
Tau PET - Early/Limbic (Braak I-II)
Tau PET - Cortical Spread (Braak III-IV)
Tau PET - Advanced/Neocortical (Braak V-VI)
Structural MRI / FDG-PET Atrophy
Cognitive Decline
Biomarker Abnormality (%)
0
20
40
60
80
100
−15.0
−12.5
−10.0
−7.5
−5.0
−2.5
0.0
2.5
5.0
Estimated Years from Symptom Onset

THE ALZHEIMER'S TAU PLATFORM STUDY

Purpose: To evaluate whether tau-directed therapies—either alone or combined with an anti-amyloid drug—can slow down the biological and clinical progression of early Alzheimer's disease

Design: A multicenter, randomized, double-blind Phase 2 trial to test multiple investigational products simultaneously or sequentially

Target Population: Adults aged **50 to 80** showing amyloid and tau changes via PET scans and blood tests, with no or very mild symptoms

Screening and Enrollment: Already underway at several clinical trial sites

We’ve Come a Long Way

- **The Old Way (Expensive & Invasive):** Historically, confirming Alzheimer's pathology required expensive PET brain scan or an invasive lumbar puncture (spinal tap).
- **The New Way (Simple & Accessible):** Highly accurate blood tests can now detect microscopic Alzheimer's proteins at the earliest stages.
- **How It Works (The Biological Clocks):**

p-tau217 (The Early Warning Light): This specific blood marker spikes dramatically during the "incubation period," warning doctors that amyloid plaque is building up in the brain.

Predicting the "caTAUstrophe": By tracking the exact levels of p-tau in the blood, scientists can accurately predict when a patient is approaching the critical tipping point where toxic tau tangles begin to aggressively spread across the brain.

Catching It Early: This gives clinicians a head start to intervene with treatments at early stages of the disease.

THE ALZHEIMER PREVENTION TRIALS WEBSTUDY



RESEARCH OPPORTUNITIES

Georgetown University
Memory Disorders Program

apt webstudy
ALZHEIMER PREVENTION TRIALS

The APT Webstudy follows healthy older adults (ages 50+) through periodic online memory testing and connect eligible participants with Alzheimer's clinical trials.

- There is no cost to participate.
- Complete your first set of online memory tests in about 20 minutes.
- Re-take your online memory tests every 3 and 6 months.

Healthy adults ages 50+ are eligible to participate. Complete online tests every 3 and 6 months. Available languages: English and Spanish. Open to participants worldwide.

KEY TAKEAWAYS



- **Lifestyle is medicine:** Daily healthy habits are vital for patients, caregivers, and everyone who is aging.
- **Early action builds options:** Spotting signs early unlocks access to treatments and gives patients and families time to plan.
- **Science has evolved:** Breakthroughs like simple blood tests can now detect Alzheimer's disease in its earliest stages. Advanced tools mean faster and easier screening.
- **Improved treatments and prevention are the goals:** Many avenues are being explored to develop more effective treatments, and clinical trials are bringing us closer to preventing the disease before it starts.
- **Every voice matters:** We are far from finished, and there is a place for everyone to get involved in Alzheimer's disease and related dementias (ADRD) research.

KEY CAREGIVER TAKEAWAYS



- **Taking care of yourself** is essential to caring for someone else.
- **Ask for help** from friends, family, and the community, and avoid isolating yourself or trying to handle everything alone.
- **Stay engaged** by connecting with local resources including support groups to share experiences and reduce emotional isolation.
- **Knowledge is power** so please stay tunned because advances in clinical care and research are accelerating at a rapid pace.
- **Advances in clinical trial research** are not possible without you because every clinical trial participant requires a “Study Partner”.

RESOURCES

- National Clinical Trials Registry - https://clinicaltrials.gov/
- The Alzheimer's Association- https://www.alz.org/
- The National Institute on Aging https://www.nia.nih.gov/about/alzheimers-and-dementia/about-adear-center
- Local Clinical Trial Research Programs
  - The Memory Disorders Program- https://memory.georgetown.edu/
  - Sana Research- https://www.sanaresearch.com/
  - Re:Cognition Health- https://www.recognitionhealthusa.com/location/fairfax-center/



Thank You

