Alzheimer's Disease Unmasked
Evaluation, Treatment and Research

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Georgetown University
Memory Disorders Program

Northern VA Caregivers
Conference
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Memory Disorders Program Team, 2022

Our Mission

To provide state of the art clinical care and opportunities for slowing disease through clinical trial participation

Clinical Consultation GUMC Neurology

- Clarification of diagnosis and recommend treatment
- Process starts with records review by our staff to determine appropriate clinic
- Could be a second opinion (limited visits) or ongoing neurology care

Research Participation Clinical Research Unit

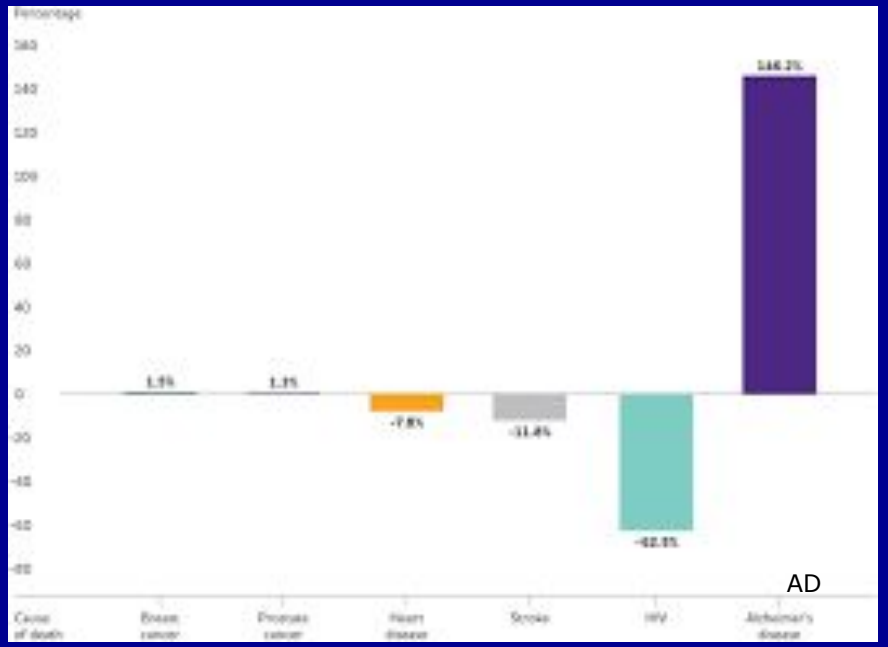
- Cognitively normal, MCI or early-stage Alzheimer's
- Treatment or nontreatment trials are offered
- Seeking diversity
- Must be medically stable with informant
- Autopsy program

Objectives

- Review how Alzheimer's is diagnosed (AD) and current treatments.
- Provide education about Clinical Research.
- Discuss Lecanemab and other anti-amyloid monoclonal antibodies under study for the treatment and prevention of AD.
- Highlight current research opportunities at Georgetown (MGUH) for individuals diagnosed with or at risk for developing AD

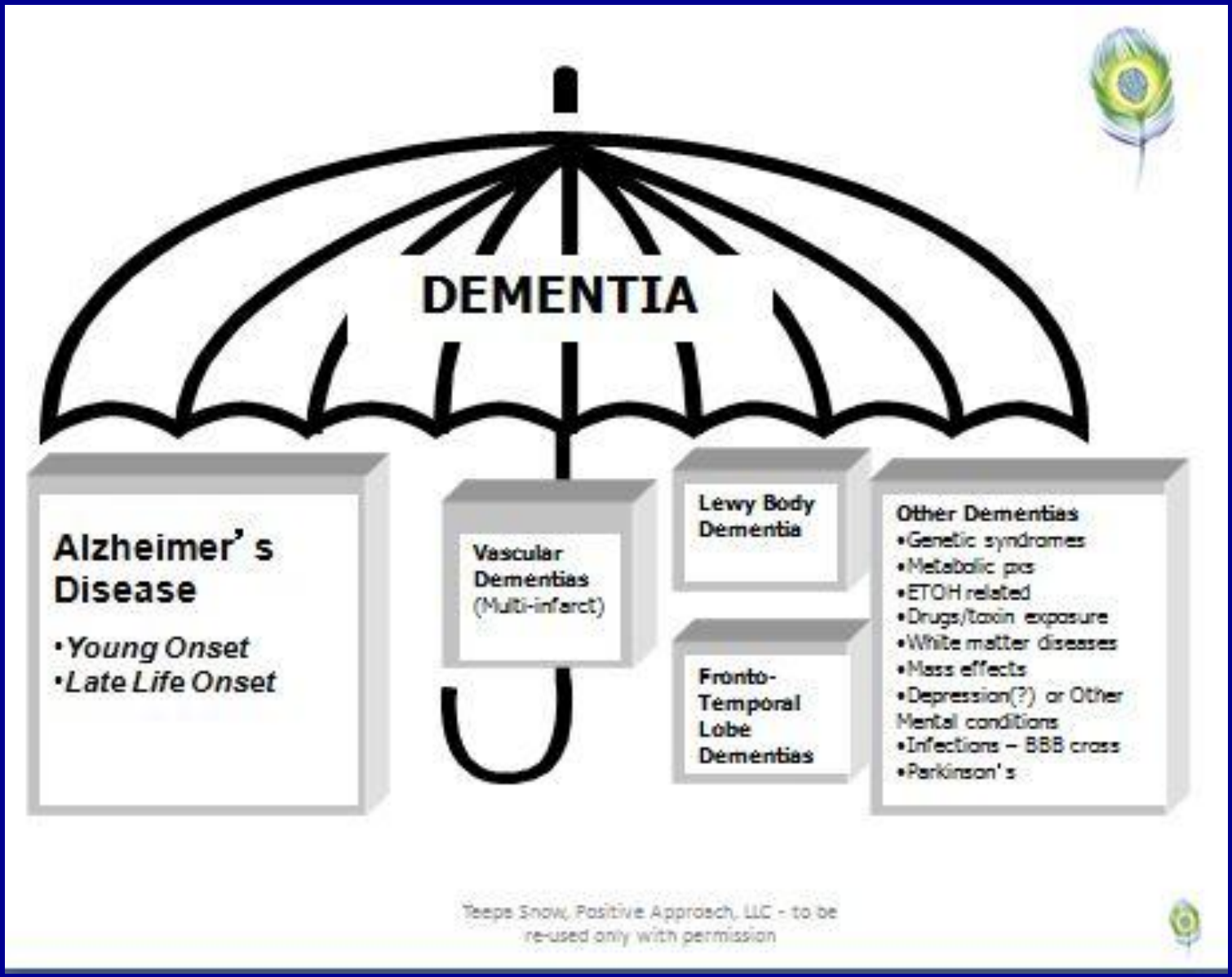
Scope of the Problem

- Every 67 **SECONDS** someone in the U.S. develops the disease.
- Alzheimer's Disease is the 6th **LEADING CAUSE OF DEATH** in America.
- **Lifetime risk** (at age 45) is **20% for women** and 10% for men
- 1 in 3 **SENIORS** dies with Alzheimer's or another dementia.



Percentage changes in selected causes of death (all ages) between 2000 and 2018.
Created from data from the National Center for Health Statistics.

The newer medical term for dementia is Major Neurocognitive Disorder. Dementia is characterized by a decline in intellectual function that significantly impacts ones functional and social abilities. Most forms of dementia are progressive and irreversible.



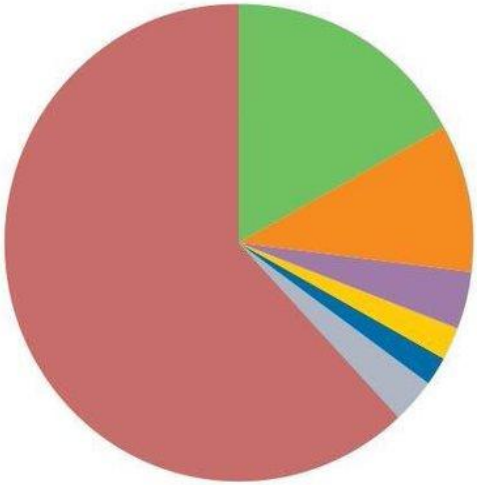
The different kinds of dementia

Dementia is not one thing. There are several routes to similar symptoms

ALZHEIMER'S 62%
Causes problems with memory, language and reasoning. 5% of cases start before age 65

VASCULAR DEMENTIA 17%
Impaired judgement, difficulty with motor skills and balance. Heart disease and strokes increase its likelihood

MIXED DEMENTIA 10%
Several types of dementia contribute to symptoms. Most common in people over 85



OTHER 3%
Conditions such as Creutzfeld-Jacob disease; depression; multiple sclerosis

DEMENTIA WITH LEWY BODIES 4%
Caused by Lewy body proteins. Symptoms can include hallucinations, disordered sleep

FRONTOTEMPORAL DEMENTIA 2%
Personality changes and language problems. Most common onset between the ages of 45 and 60

PARKINSON'S DISEASE 2%
Can give rise to dementia symptoms as the condition progresses

SOURCE: ALZHEIMERS.ORG.UK

Dementia is Underdiagnosed

24-72% of dementia cases are undiagnosed or underdiagnosed.

Cognitive deficits can be dismissed as normal aging.

Denial by family and friends can create an obstacle for diagnosis.

Patients often lack insight.

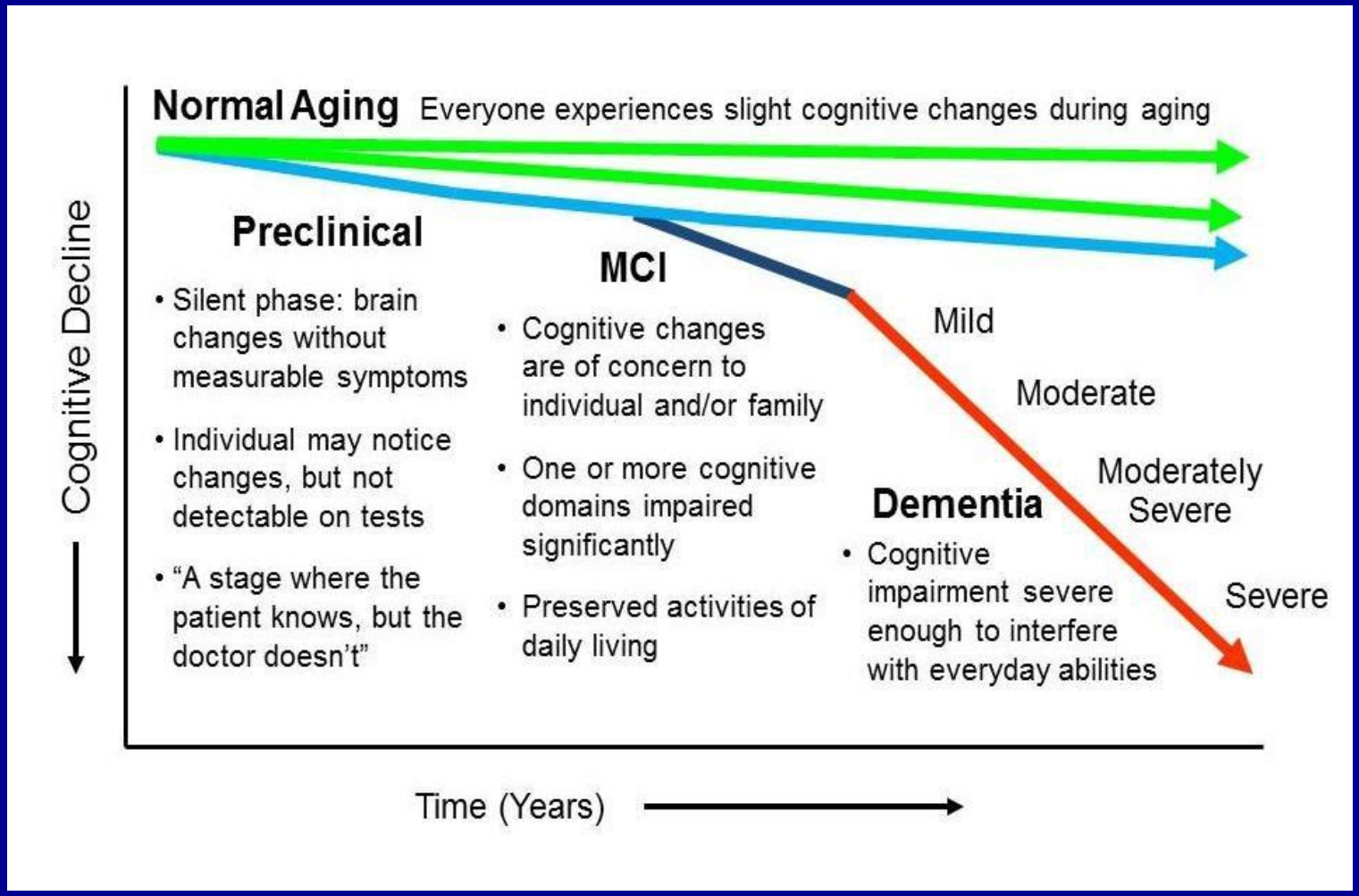
AGE RELATED CHANGES

Normal age-related memory changes	Symptoms that may indicate dementia
Able to function independently and pursue normal activities, despite occasional memory lapses	Difficulty performing simple tasks (paying bills, dressing appropriately, washing up); forgetting how to do things you've done many times
Able to recall and describe incidents of forgetfulness	Unable to recall or describe specific instances where memory loss caused problems
May pause to remember directions, but doesn't get lost in familiar places	Gets lost or disoriented even in familiar places; unable to follow directions
Occasional difficulty finding the right word, but no trouble holding a conversation	Words are frequently forgotten, misused, or garbled; Repeats phrases and stories in same conversation
Judgment and decision-making ability the same as always	Trouble making choices; May show poor judgment or behave in socially inappropriate ways

Conditions that may contribute to memory changes

- Mental health issues- depression, anxiety, alcoholism and drug abuse
- Other illnesses and infections that stress your body (usually a temporary change in memory)
- Endocrine problems that are poorly controlled (hypothyroidism or diabetes)
- Medications- pain, bladder, benzodiazepines (xanax), antianxiety (valium) (assess benefit vs. risk, do not stop suddenly)
- Insomnia- sleep is the7thvital sign!
- Head trauma-avoid falls, wear seatbelts

What is Mild Cognitive Impairment?



Cognitive Evaluation

Primary care clinician, Geriatrician, or Neurologist

- **History of problem, physical exam, bloodwork, vision and hearing referrals**
- **Basic cognitive test (MMSE or MOCA)**
- **CT or MRI Brain (looking for other causes, AD does not show up on these brain scans)**
- Sleep evaluation if indicated
- Psychiatric evaluation if indicated
- Initial referral to Neurologist if indicated
- Neuropsychometric testing if indicated
- In rare cases FDG PET scan or spinal tap if indicated

AD Treatment with Medications

- No readily available FDA approved medications for MCI.
- An acetylcholinesterase inhibitor may be indicated once diagnosed with dementia due to AD
- Three FDA-approved cholinesterase inhibitors with similar efficacy and tolerability (donepezil, galantamine and rivastigmine)
- Memantine (Namenda) may be added with a cholinesterase inhibitor when dementia advances.
- Aduhelm (aducanumab) is now FDA approved for MCI/early AD with evidence of amyloid in the brain. (not covered by insurances and ongoing study of efficacy)

FDA-approved drugs for AD

Drug	Year Approved	Mechanism of Action	Indications
Donepezil Aricept	1996	Cholinesterase inhibitor	Mild-to-severe AD
Rivastigmine Exelon	2000	Cholinesterase inhibitor	Mild-to-severe AD Mild-to-moderate Parkinson's dementia
Galantamine Razadyne	2001	Cholinesterase inhibitor	Mild-to-moderate AD
Memantine Namenda	2003	NMDA antagonist	Moderate-to-severe AD
Memantine + donepezil Namzaric	2014	Fixed-dose combination: NMDA antagonist plus cholinesterase inhibitor	Moderate-to-severe AD
Aducanumab Aduhelm	2021	Anti-Amyloid	MCI/Mild AD with Evidence of elevated Amyloid in brain

Other Treatments

Pharmacologic

- Antidepressants

  apathy, irritability, anxiety, insomnia, restlessness, hoarding, hypersexuality

- Antipsychotics

  agitation, aggression, frightening hallucinations, resisting care

Nonpharmacologic

- routine heath care to manage other health problems
- adequate sleep
- supervision to prevent accidents, wandering, fall prevention, assess driving
- maintain nutrition
- structured routine including exercise and some enjoyable activities

Supplements and New Therapies

- The FDA does NOT approve dietary supplements for safety and effectiveness or approve their labeling before marketing.
- No supplement seal guarantees the safety or effectiveness of the ingredients in the bottle.
- A drug + a supplement together may increase the drug's effects.
- Effectiveness of new therapies should be supported by peer reviewed scientific literature with results from controlled clinical trials.

Causes
Aging
ApoE4 > 3 > 2
Downs syndrome
Familial AD mutations

Treatments
donepezil
rivastigmine
galantamine
memantine

APP turnover

Aβ accumulation
Aβ oligomers, fibrils
amyloid plaques

Biomarkers
low Aβ, high tau in cerebrospinal fluid

positive amyloid-PET

neurotoxicity
neurofibrillary tangles

mild cognitive impairment
microgliosis and astrocytosis
inflammation
focal encephalopathy
neuronal morbidity
synaptic and neurotransmitter loss

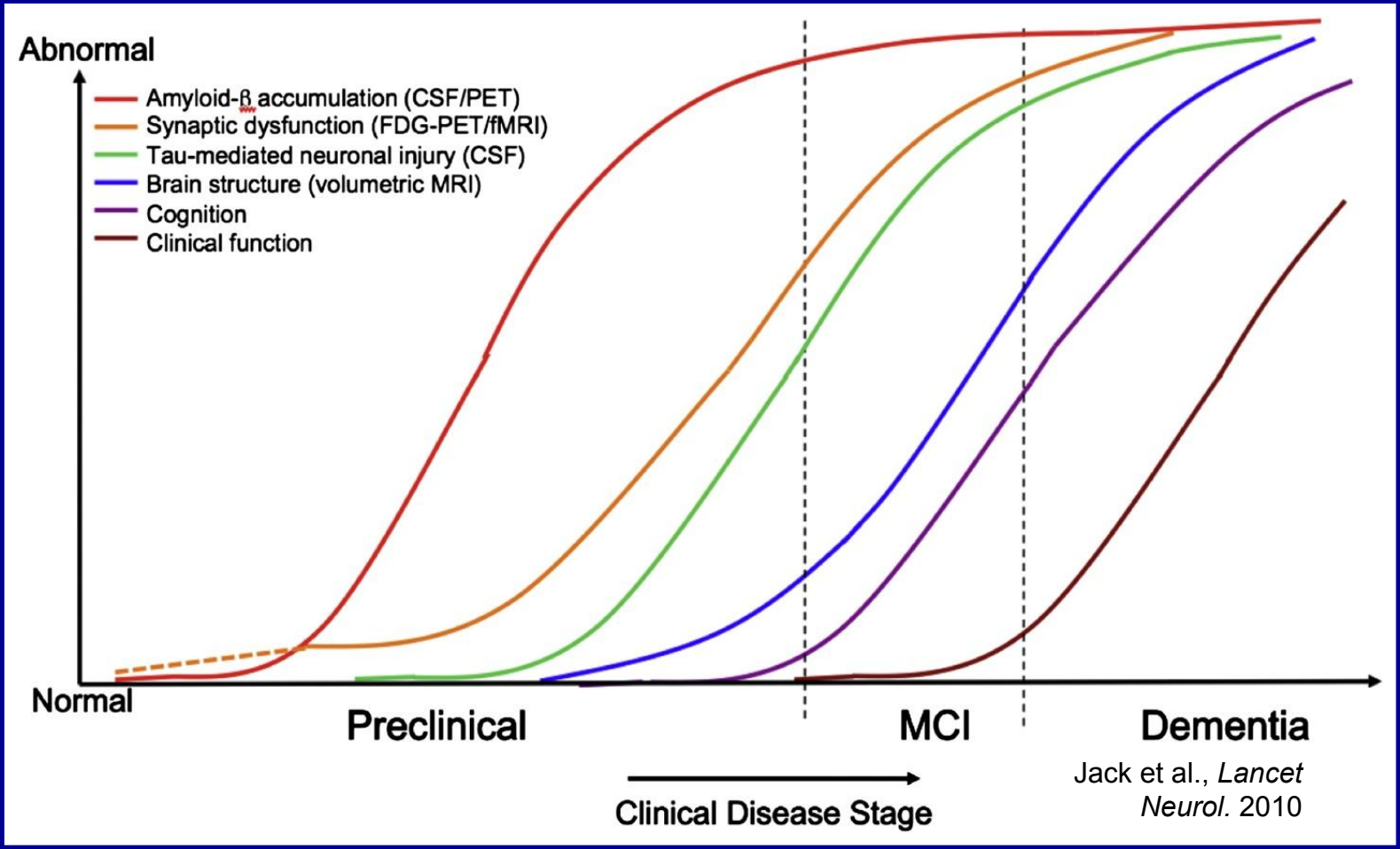
focal hypometabolism on FDG-PET

neuronal mortality
brain atrophy
white matter rarefaction
dementia
death

atrophy, white matter changes on MRI

from Turner, Alzheimer's Disease, 2012

Course of AD Biomarker Changes



Jack et al., *Lancet Neurol.* 2010

Is **CLINICAL RESEARCH** right for me?

Clinical research is medical research that involves **people.**

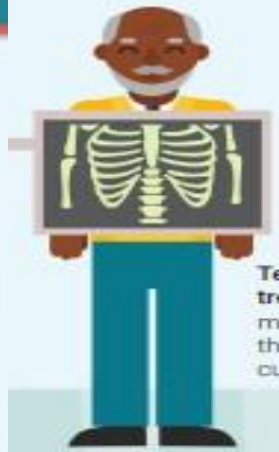
It's led to the **DISCOVERY** of every disease treatment prescribed today.

Study volunteers play a critical role in this process.

Are you interested in joining a study or trial?

CLINICAL RESEARCH may be right for you if you want to:

Help others, including future family members, who may be at risk for certain diseases



Receive regular monitoring by medical professionals

Test new disease treatments that might work better than those currently available

Be part of the **BREAKTHROUGH.**

Learn more about participating in research at www.nia.nih.gov/clinical-trials-and-older-people.

NIH National Institute on Aging

PHASES of a CLINICAL TRIAL

Preclinical
LABORATORY STUDIES
Duration: Several years
- ✓ Provide information on dosing and toxicity levels

Phase 1
SAFETY
Duration: Several months
- ✓ Evaluate safety
- ✓ Gather information about how a drug interacts with the human body

Phase 2
SAFETY AND DOSING
Duration: Several months
- ✓ Further evaluate safety
- ✓ Monitor side effects
- ✓ Check which dose works best
- ✓ Check effectiveness

Phase 3
SAFETY AND EFFICACY
Duration: Several years
- ✓ Confirm effectiveness
- ✓ Monitor safety

FDA APPROVAL

Phase 4
POST MARKETING SAFETY AND EFFICACY
- ✓ Gather information on the drug's effect in various populations and any side effects associated with long-term use

To search the national registry for trials, go to Clinicaltrials.gov

Active NIA AD/ADRD Clinical Trials

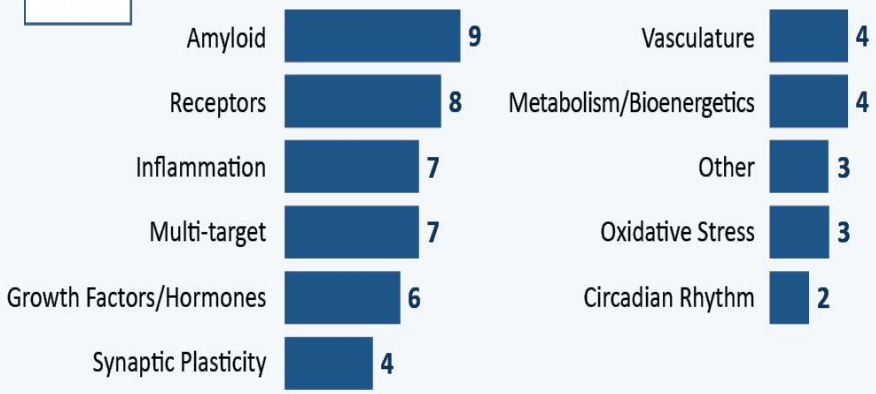
Pharmacological Interventions

65 TRIALS

57 trials

Early Stage Trials (Phase I & Phase II)

Targeted Disease Process



8 trials

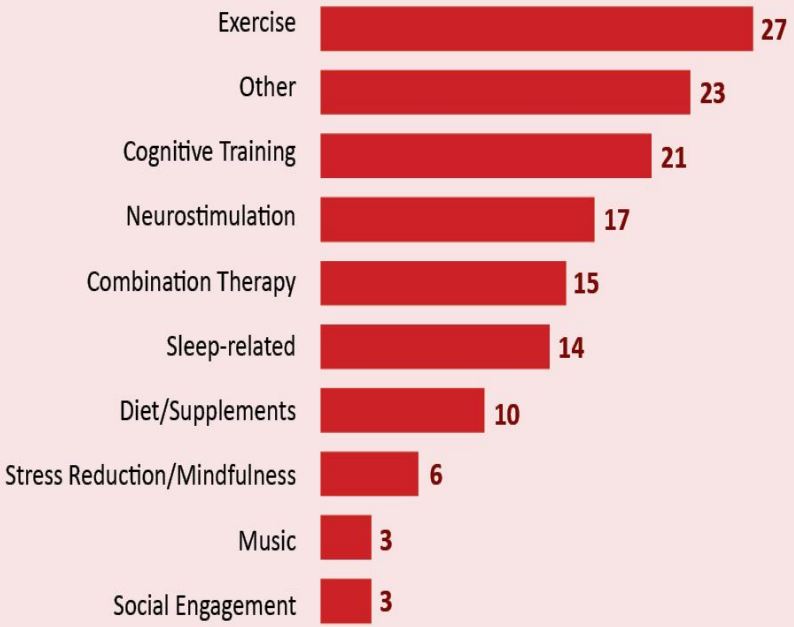
Late Stage Trials (Phase II/III & Phase III)

Targeted Disease Process

Non-Pharmacological Interventions

139 TRIALS

Intervention Modality



For more information please visit
www.nia.nih.gov/research/ongoing-AD-trials

NIH National Institute on Aging

Data last updated: July 2022.

AD clinical trials (phase 1,2,3) in progress

Target type (major only)	Total Number	Phase 3
Other	92	5
Amyloid-related	69	9
Other neurotransmitters	52	8
Inflammation	40	2
Cholinergic system	31	0
Tau	25	1

Therapy type (major only)	Total Number	Phase 3
Small molecule	199	15
Passive immunotherapy	36	5
Dietary supplement	19	1
Other	14	1
Active immunotherapy	13	1
Combination	9	2

Alzforum.org, June 2022

Progress in AD Research

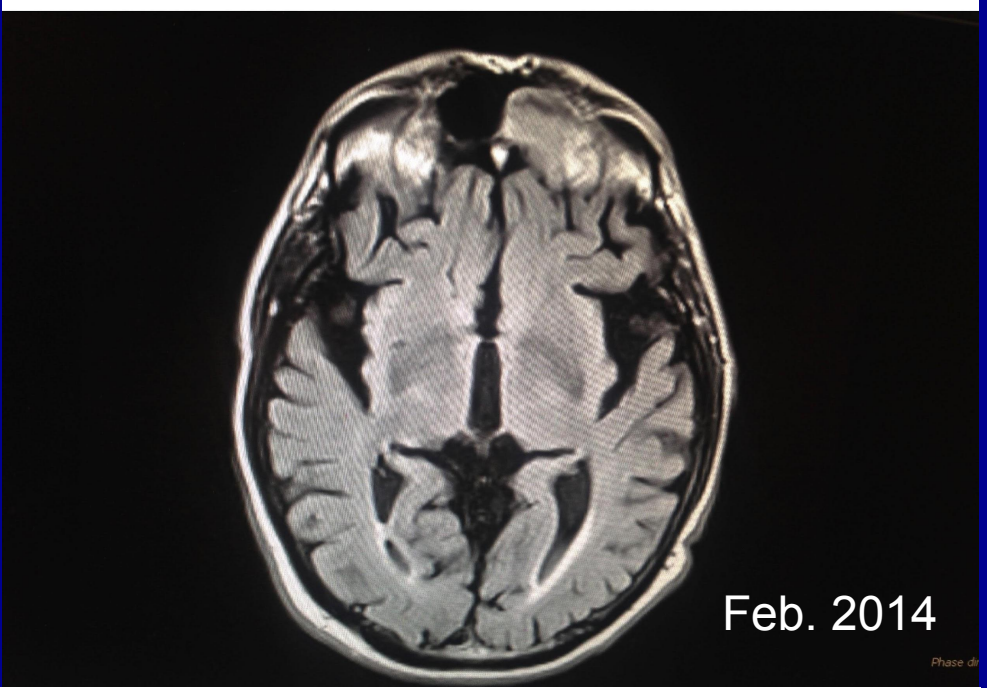
- Better understanding of risks and prevention
- Abeta/amyloid and tau/tangle PET imaging
- Spinal fluid and blood protein biomarkers
- Defined a new prodromal stage of AD
- AD prevention trials - with anti-amyloid antibodies
- First tau/tangle immunotherapy studies
- Increased NIH funding
- Better understanding of non-AD dementias – Lewy body, frontotemporal, HIV dementia…
- Growth of national/international research consortia
- First anti-amyloid disease modifying drug approved (with caveats) Aduhelm

2nd generation anti-amyloid antibodies

Antibody, sponsor	Route of administration, frequency	Treatment trials (MCI and mild AD)	Prevention trials (normal, at-risk)
Aducanumab, Biogen	IV, Q4 weeks	EMERGE, ENGAGE, completed EMBARK, in progress	
Lecanumab, Eisai, Biogen	IV, biweekly	CLARITY completed	AHEAD 3-45, enrolling, also in DIAN
Gantenerumab, Roche	SQ, Q4 weeks	GRADUATE/ POST-GRADUATE in progress	SKYLINE, enrolling, also in DIAN
Donanemab, Lilly	IV, Q4 weeks*	TRAILBLAZER-ALZ2, in progress	TRAILBLAZER- ALZ3, enrolling

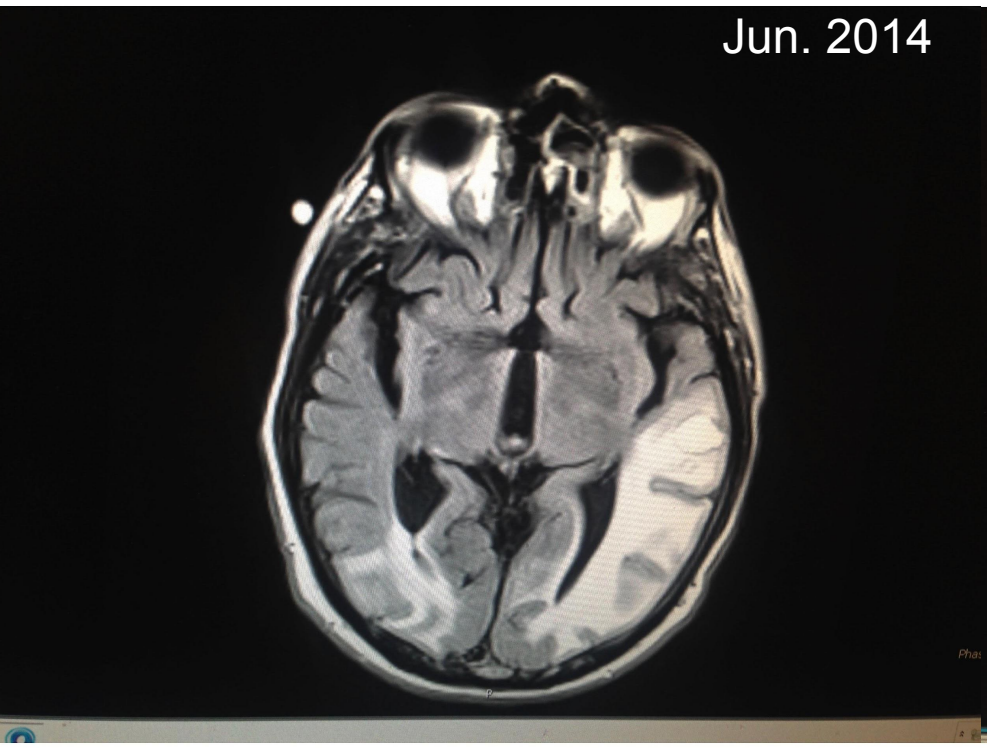
Aducanumab (Aduhelm), Biogen

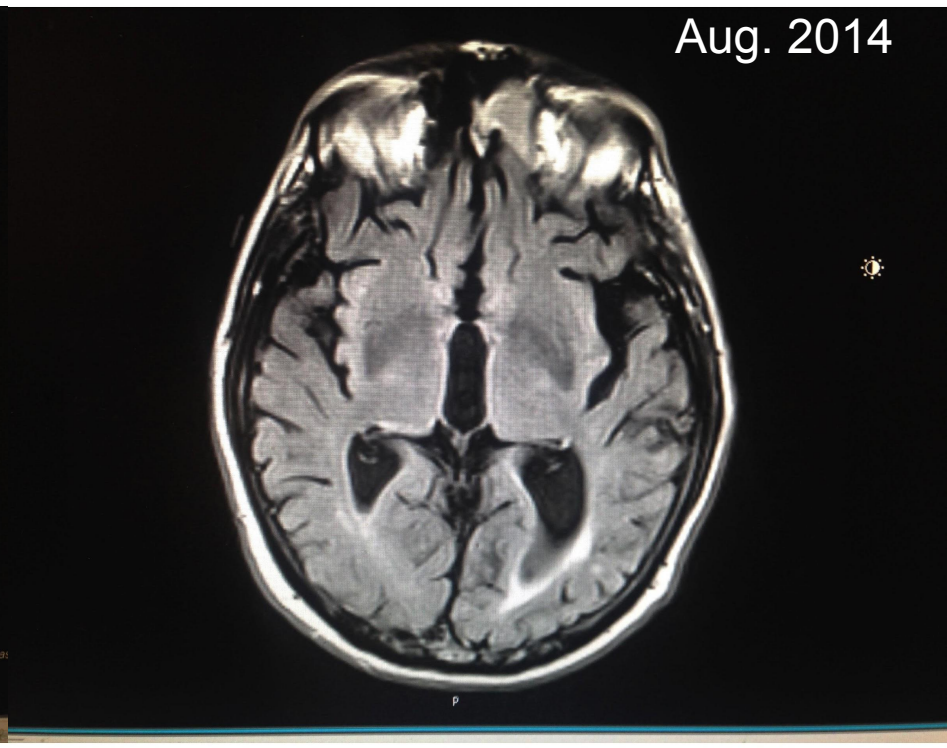
- March 2019: Two phase 3 trials (ENGAGE, EMERGE) discontinued March 2019 after a futility analysis; Continued data collection
- October 2019: Positive outcome of EMERGE - met primary outcome; Supportive results from high-dose subset in ENGAGE
- June 2021: FDA-approval in accelerated pathway
- April 2022: CMS decision - coverage only for evidence-development
- Limited uptake due to questionable efficacy, high cost, and risk of side-effects (infusion reactions, ARIA-amyloid related imaging abnormalities)



ARIA-E and ARIA-H case in the aducanumab Phase 2 trial

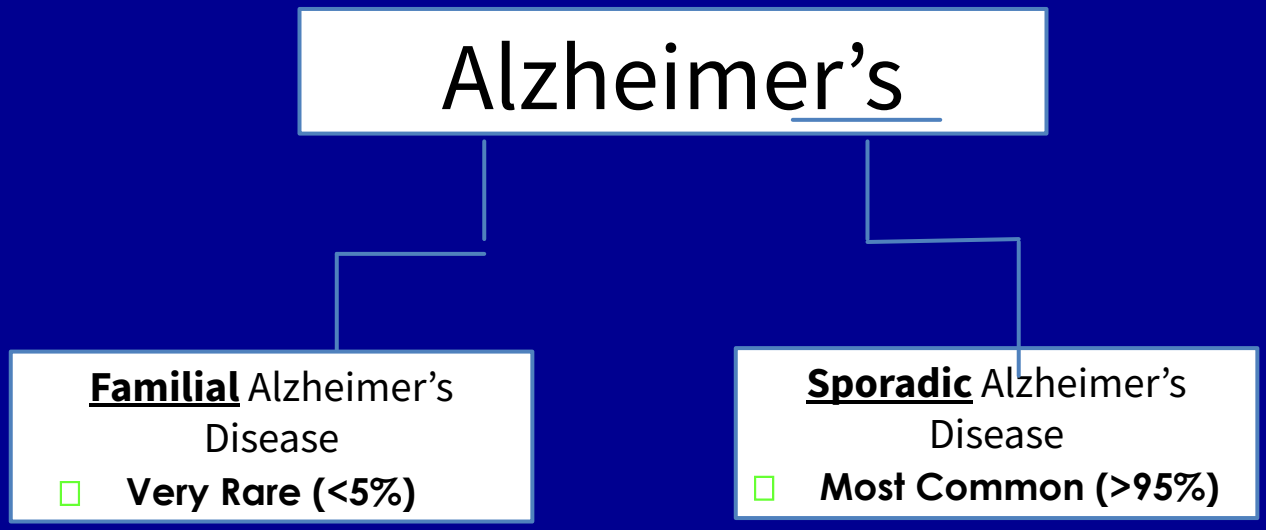
FLAIR images





Symptoms of ARIA
(amyloid related imaging abnormalities)

- Most ARIA is asymptomatic, seen only on brain MRI
- Headache
- Dizziness
- Confusion/altered mental state
- Visual disturbance/eye disorders
- Nausea
- New onset seizures ? (incidence not known yet)



Sporadic is the MOST COMMON type of Alzheimer's disease

- Onset age 65 or before = early onset; over 65 = late onset
- Cause: complex, likely multiple factors including genetic and environmental/lifestyle influences.
- Risk Factors: age, cardiovascular disease, head trauma with LOC, lower socioeconomic status, fewer years of education

APOE4 Increases risk

- APOE is the most common gene associated with late onset AD. One APOE gene is passed on from each parent.

- 3 types of the APOE gene
  - **e2** = the **LEAST** common, reduces risk
  - **e3** = the **MOST** common, doesn't seem to affect risk
  - **e4** = the **SECOND MOST** common, increases risk
  - **e4 gene increases your risk of developing Alzheimer's Disease**

Memory Disorders Program Studies

Biomarker discovery/validation (normal, MCI, AD)

- LEARN (amyloid PET negative)
- Alzheimer's disease neuroimaging initiative (ADNI)
- Trial ready cohort for the prevention of Alzheimer's dementia (TRC-PAD)
- Early onset AD consortium (LEADS)
- Functional MRI, visual task (with Dr. Jiang, GU)
- Language changes in AD (with Dr. Diaz-Asper et al., Marymount Univ.)
- Imaging neuroinflammation in dementia by PET (COX1, COX2) (with Dr. Innis et al., NIMH)

- Yellow indicates currently enrolling
- White indicates fully enrolled

Memory Disorders Program Studies

Therapeutic trials (MCI/prodromal AD or AD)

- aducanumab (anti-amyloid antibody) (EMBARK)
- lecanemab (anti-amyloid antibody) (CLARITY)
- gantenerumab (anti-amyloid antibody) (POST-GRADUATE)
- donanemab (anti-amyloid antibody) (TRAILBLAZER2)
- AL002 (anti-TREM2 antibody) (INVOKE)
- pepinemab (anti-sema4D antibody) (SIGNAL-AD)
- JNJ-63733657 (anti-tau antibody) (AUTONOMY)
- nicotine patch (MIND)
- metformin for AD prevention (MAP)

- Yellow indicates currently enrolling
- White indicates fully enrolled

Lecanemab (Clarity study)

- Anti-amyloid compound (reduces brain plaques), IV infusion bi-weekly x 18 mos
- Enrolled 1795 volunteers with MCI and early AD

  +confirmed evidence of AD pathology in the brain
- Side Effects: ARIA (total 21.3% most asymptomatic)
- Completed phase III trials met endpoints
- Claims: slowed clinical progression
- Biogen/Esai submitted results to FDA
- Expect coverage decision early January 2023

Lecanemab Considerations
(if approved)

- Will the center for medicare and medicare services (CMS) provide coverage?
- What will Appropriate Use Guidelines recommend?
- What effect would use of this drug have on ongoing treatments under study?
- What factors would affect clinical use?

Gantenerumab (Graduate study)

- Acts centrally to disassemble and degrade amyloid plaques
- Phase 3 Anti-amyloid compound sponsored by Roche given by subcutaneous injection bi-weekly
- Side effects include skin reactions at the injection site and ARIA
- Results from completed phase 3 trials expected next year.

Donanemab (Trailblazer study)

- Aggressive anti-amyloid compound, 2/3 of volunteers were amyloid negative by end of trial
- Phase 3, sponsored by Lilly, IV infusion every 4 wks
- Side effects of ARIA and nausea
- ARIA-E developed in 27 percent of treated patients, with 6 percent becoming symptomatic
- FDA granted Breakthrough therapy designation 6/21 based on phase 2, Efficacy results expected 2023

Currently enrolling for MCI and AD

Autonomy Janssen. Phase 2. Assessing the efficacy and safety of JNJ-63733657, anti-tau monoclonal antibody. IV infusion every 4 wks x 4.5 yrs. 1/3 chance of placebo.

Signal AD Vaccinex. Phase 1b/2a. Testing pepinemab, a monoclonal antibody to semaphorin 4D. In pre-clinical work slowed brain atrophy and improved some behaviors in mice. IV Infusion every 4 wks x 52 wks. 50% chance of placebo.

INVOKE Alector. Phase 2. Testing a monoclonal antibody, AL002, that binds to TREM2 receptors, induces microglia proliferation, and reduces amyloid deposits. Infusions every 4 wks for 48-96 wks. 1/4 chance of placebo. APOE 4/4 genotype excluded.

MIND study
(memory improvement through nicotine dosing)

- Enrolling 300 volunteers with MCI/excludes smokers for 24 months
- 50% chance drug/50% chance placebo
- daily transdermal nicotine patch
- Aim: evaluate if nicotine is able to produce a significant cognitive, clinical and functional improvement. Neuronal nicotinic receptors have long been known to play a critical role in memory function in preclinical studies, with nicotine improving attention, learning, and memory function.

MAP Study
(metformin for alzheimer's prevention

- Enrolling 380 volunteers with MCI/no diabetics
- 50% chance drug/50%chance placebo
- 2-year study
- Daily extended-release Metformin tablet
- Aim: This study will test the effects of metformin, an FDA-approved medication to treat diabetes, on memory and other indicators of Alzheimer's disease in older adults who are overweight or obese and have mild cognitive impairment but do not have diabetes.

Trends in clinical AD research

- Biomarkers for screening, diagnosis, prognosis, and theragnosis
  - PET neuroimaging – glucose, Abeta/amyloid, tau/tangles
  - CSF proteins – Abeta, tau, p-tau, tau, NFL, GFAP
  - Blood biomarkers – Abeta, p-tau, tau, NFL
- Shift toward treatment earlier in earlier disease state
  - Prevention trials of normal at-risk individuals (preclinical AD)
  - MCI (prodromal AD) trials
  - Web-based screening and recruitment
- Increased NIH funding for dementia research
- Emphasis on diversity in recruitment and retention

Emphasis on Under-Represented Groups (URGs)

- The bulk of clinical research on dementia in the US, has been on Caucasian populations (~90-95%)
- According to UsAgainstAlzheimers Black Americans are twice as likely as non-Hispanic whites to develop AD, LatinX are 1.5 times as likely
- URGs in the US: Black or African-American, Hispanic/Latinx, Indigenous and Native American, Asian, Native Hawaiians and other Pacific Islanders

Prevention Trials

A4 study

Anti-Amyloid treatment in asymptomatic Alzheimer's disease. Sponsored by the NIA and Eli Lilly. Initial enrollment in 2014. Fully enrolled. Anti-amyloid monoclonal antibody, solanezumab, every 4 wks. Preliminary data is anticipated 1st quarter of 2023

AHEAD study

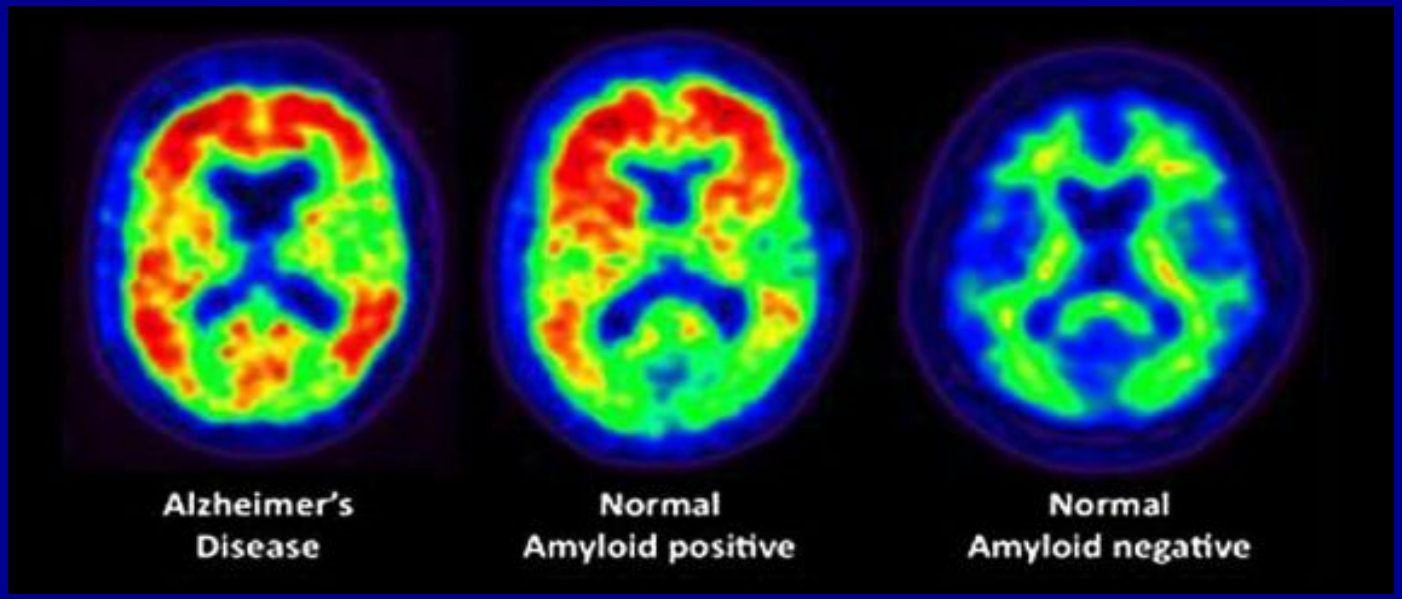
Enrolling cognitively normal individuals with risk factors for developing AD. Sponsored by Eisai. Evaluating the efficacy and safety of treatment with BAN2401 (Lecanemab) over 4 years in volunteers with preclinical Alzheimer's disease.

- elevated amyloid (A45 Trial) infusion every 2-4 wks
- intermediate amyloid (A3 Trial). Infusion every 4 wks

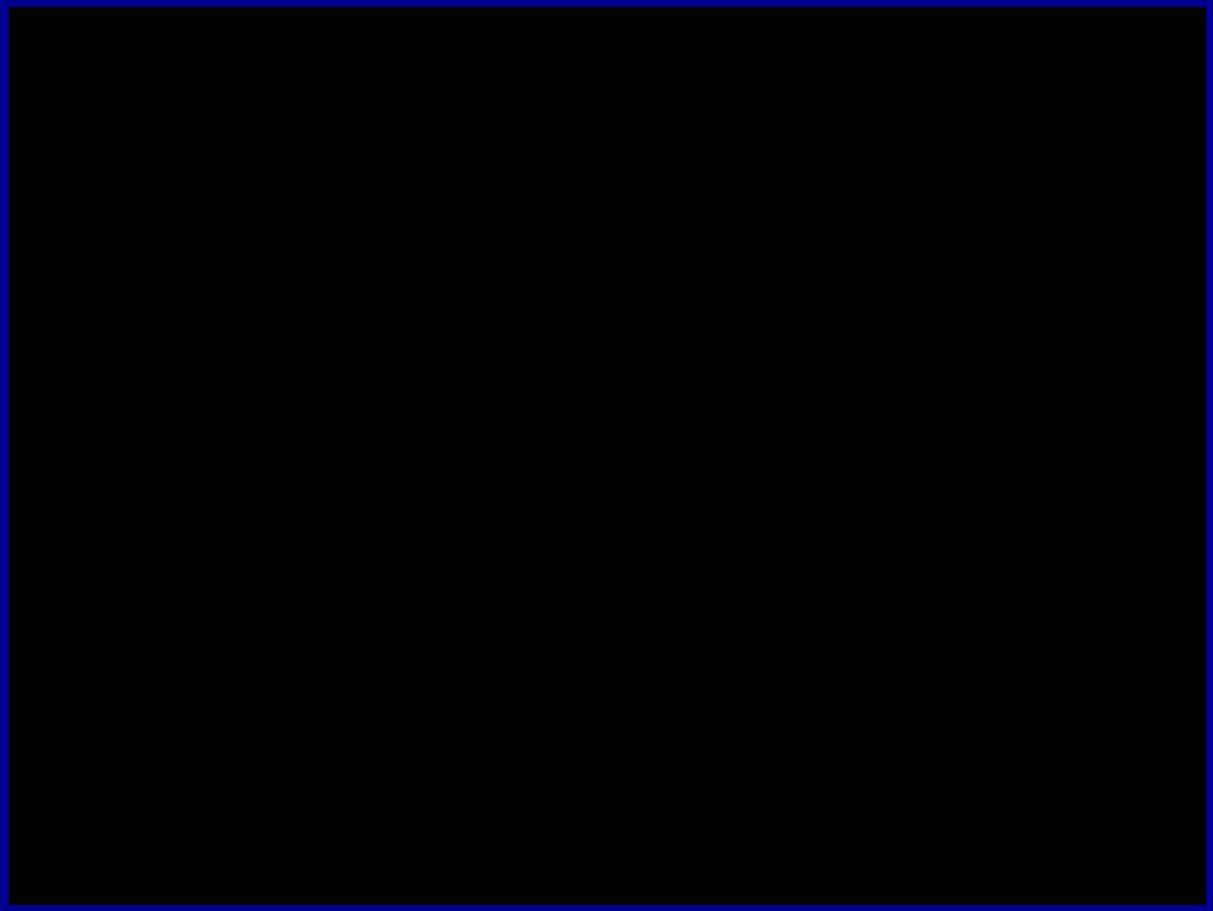
AHEAD study

Overarching Aim: To get AHEAD of AD

- Prevent onset of AD in individuals at risk (by the use of Lecanemab) over 4-years.
- To include 20% of volunteers from historically excluded and underrepresented groups



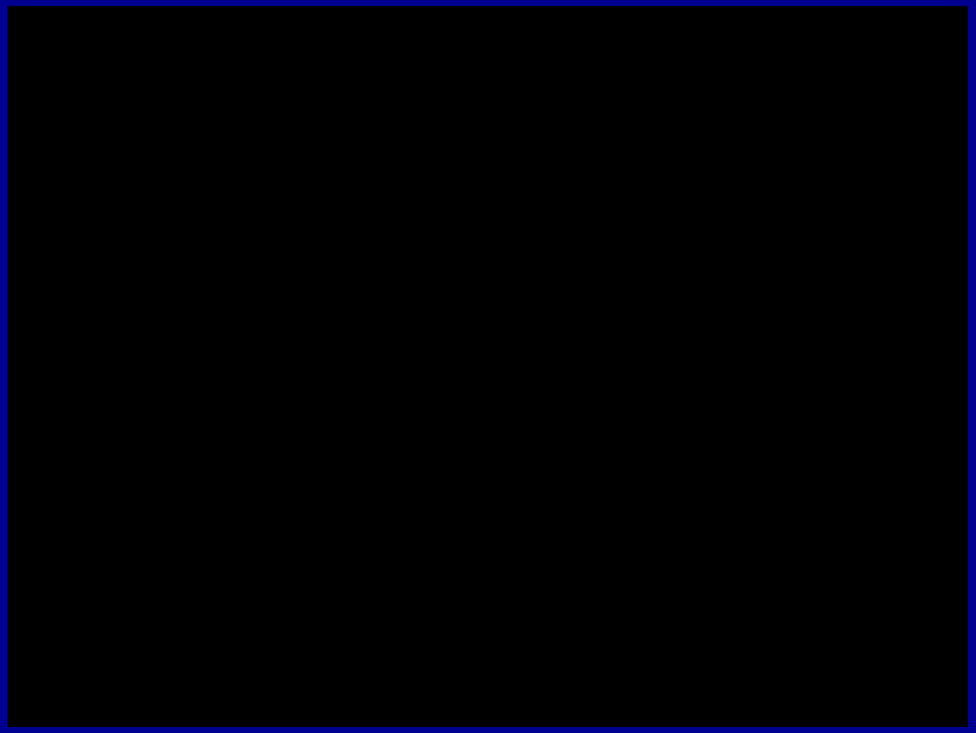
AHEAD video



Now screening CN healthy volunteers for 4-year study

- Age 55-64 must have additional risk factor
  - APOE 4 carrier
  - first degree family member
  - elevated Amyloid
- Medical information is disclosed (APOE and PET)
- Complimentary transportation (LYFT)
- Study reimbursement (50$ per visit)
- Continuity of excellent research care

ADNI video



- Nontreatment longitudinal trial started in 2004
- Aim: to track progression of disease using biomarkers + clinical measures, to assess brain structure/function
- ADNI 4 is recruiting CN, MCI and AD (mild/moderate)
- Annual/bi-annual visits for cognitive tests, labs, spinal tap, brain MRI and PET scans

ADNI Inclusion Criteria

- Prioritizing individuals from URGs to achieve diversity
- No other neurologic disorder (seizures, stroke, etc.)
- Medically stable (5-year cancer-free)
- Have a study partner (usually spouse or adult child)
- MRI-compatible (no pacemakers)
- Native English-language speaker
- No anti-coagulants (if LP is mandatory)

Alzheimer Prevention Trials Webstudy
age 50+

- aptwebstudy.org, funded by NIA/NIH
- Tracks cognitive performance every 3 months
- Information on brain health and AD prevention
- Private and secure
- No cost
- Possible referral to local research sites if performance declines over time

Other Registries

- ResearchMatch* nonprofit program funded by NIH to connect volunteers with researchers

- Alzheimer's Prevention Registry* age 18 + , register to be notified of study opportunities

- BrainHealth Registry* age 18+, register and take on-line brain tests. Aims to discover treatments for AD, Parkinson's, PTSD, depression and other brain disorders.

- NIA-ADEAR* education and information about trials

Resources

clinicaltrials.gov easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions.

healthybrains.org provides brain health info, tools, and resources to help reduce risk for brain disease. Aims to advance knowledge and research on brain health.

endalznow.org/Genematch uses genetic testing (through free cheek swab kits) to match volunteers with research opportunities. Must be cognitively normal age 55-90.

Contact Us!

https://memory.georgetown.edu

Clinic appointments or Research information

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Thank You for Attending!