The Intersectionality of IDD Dementia Care; Connecting Research to Direct Patient Care in the Community

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ntg
National Task Group on Intellectual Disabilities and Dementia Practices

CP State

AADMD
AMERICAN ACADEMY OF DEVELOPMENTAL MEDICINE & DENTISTRY

No Conflicts or Disclosures

Photos Courtesy of Rick Guidotti Positive Exposure

Aging and Intellectual and Developmental Disabilities

- In 2002, an estimated 641,000 adults with ID were older than 60.
- In 2002 about 75%of all older adults with ID were in the 40-60 year old age range.
- The number of adults with ID age 60 years and older is projected to nearly double from 641,860 in 2000 to 1.2 million by 2030 due to increasing life expectancy and the aging of the baby boomer generation.

With Age Comes Concerns for Decline

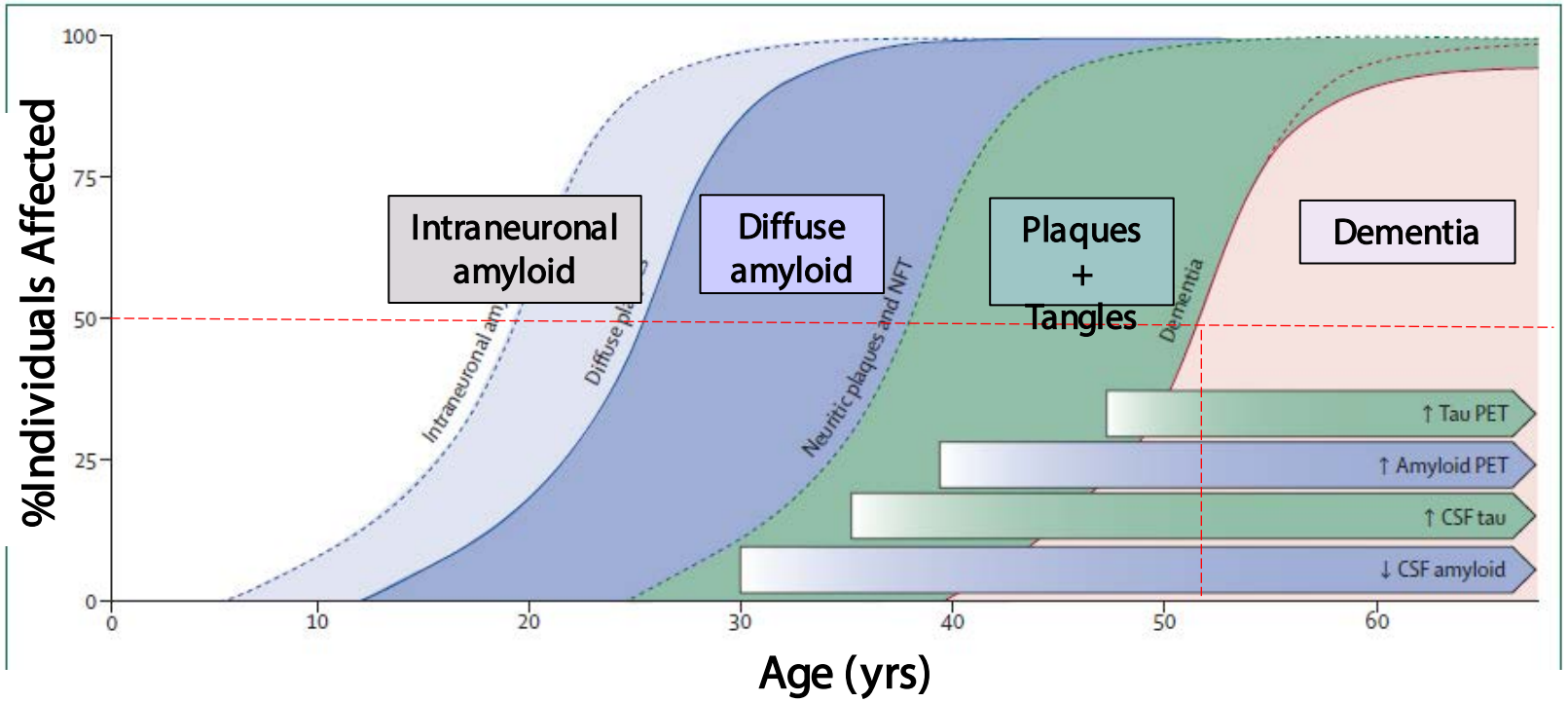
- Functional decline and dementia including Alzheimer's disease (AD)
- Early onset AD in those with Down syndrome; 60% by age 60
- Diagnostic overshadowing and lack of access to quality assessment and diagnostic care
- All too often a disconnection, living in "silos"
- Research will change on how DS AD is supported

AD/Aging DS Research Is Leading the Way

- Advances in AD Biomarkers
  - Preclinical/presymptomatic AD Diagnosis
- Appreciation of mitigating factors; risk reduction
- Antiamyloid and antitau therapeutics

Diagnosis of symptomatic AD in DS
Average age of onset ~54 yrs

Progression of DS- AD across lifespan



- Amyloid pathology by 30s
- Amyloid and tau pathology by 40s
- Symptomatic in 50s

adapted from Fortea et al, 2021, Alzheimer's disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol* 20: 930–42

AD/Aging DS Research Challenges and Roadblocks

- Getting individuals into studies
- Funding
- Messaging to families and support organizations
- Caregiver/Personal Concerns
- Timing of when to treat; presymptomatic
- Risks, side effects and benefits of therapies
- What about non-DS IDD aging/dementia??

Catching Up

- Advances in AD-DS research is moving fast; the future is NOW
- Will be able to provide an early diagnosis, preclinical
- Treatment options will be available
- Preparing for what lies ahead
- Mitigating age related decline/dementia
- Individuals, caregivers, supports and the general healthcare system is lagging further behind research

Person and Family Concerns

- Overcoming barriers; living life to the fullest
- Being aware of the future of getting AD; Being an information seeker or avoider
- Ensuring supports are in place now and in the future
- Concerns for an aging parent/sibling
- If found out prior to symptoms, then what????

Advocacy Organization Perspective

- Often will mirror that of person/family
- Difficult to have full/honest mention of AD
- No deep plans in place to discuss AD early
- If do talk about it before symptoms, what is the message??
- Most non-IDD/DS AD/Dementia organizations do not have a plan in place to discuss AD prior to symptoms

Healthcare Provider Perspective

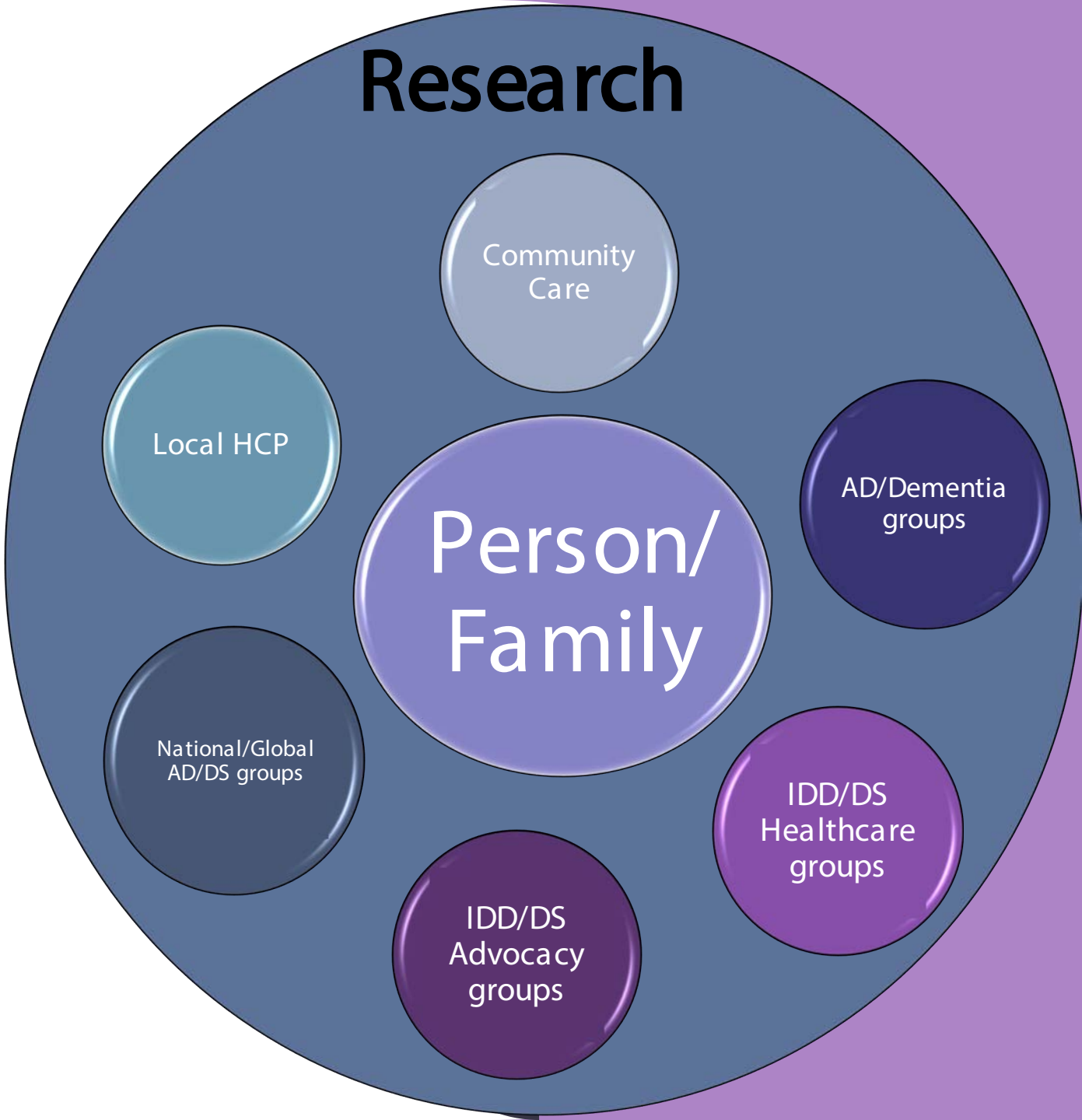
- Most do not have experience and appreciation of what normal aging looks like
- Many will not appreciate some of the complex personal and social issues that may arise
- Most may have heard that people with DS can get early onset AD or only think all decline is AD
- Many may not appreciate aspects of health and wellness and successful aging
- Academic/University Care often not a "home" for this population; GUIDE Program
- Diagnostic Overshadowing
- Most will not be aware of research opportunities

- Having an appreciation of comorbidity care
  - Seizures
  - Behaviors
  - Sleep apnea
  - Vision/hearing
  - Palliative/hospice
  - Supporting the caregiver

Providing information about AD; Before it Occurs

- When should this conversation start?
- When should people be tested?
  - Assessments, biomarkers
- Planning for an uncertain future
- Wellness and health promotion
- Research opportunities

- Getting updates in research out to all parties
- Advocating for more research
- Delivering a sensitive message and actionables
- Living with DS in anticipation of DS, living well with DS AD
- Preparing for the news before symptoms occur
- Organizations seeking out the info and passing it on
- Coordination of the news and fallout
- Advancing education and training to the healthcare community and supports
- **Must consider non-DS AD/Dementia**



Thank you!

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MEDICINE &
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Alzheimer's Disease, Revised Diagnostic and Staging Criteria and updates in Management.

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ALBANY MEDICAL CENTER

KNOWN FOR OUR EXPERTISE. CHOSEN FOR OUR CARE.

Disclosures

NIH, NIA

New York Department of Health

Goldberg Foundation

Eisai, Cassava ,Spear bio

Avanir, Otsuka, Biogen

Roche, Neurmedix,

Merck, BioVie,

EIP Pharma Inc,

Cognition Therapeutics

Learning Objectives

- **Understand the revised criteria for diagnosis and staging of Alzheimer's Disease (including Down Syndrome patients)**
- **Learn the Pathophysiology of the Alzheimer's Disease**
- **Learn the Standard of Care Recommendations for Management**
- **Learn the Disease Modifying Treatments for Alzheimer's Disease**

Revised criteria for diagnosis and staging of Alzheimer’s disease: Alzheimer’s Association Workgroup. Jack et al Alzheimer’s Disease and Dementia 2024

- The biologically based diagnosis of Alzheimer's disease (AD) is meant to assist rather than supplant the clinical evaluation of individuals with cognitive impairment.
- The revised criteria are in large part, a response to rapid advances in fluid-based biomarkers, especially blood, and the approval of drugs specifically targeting amyloid beta (Aβ) pathology for individuals with early symptomatic AD—specifically mild cognitive impairment and mild dementia.
- Both advances are of high relevance to clinical use in the immediate and near future.

Historical Data…

- On a Peculiar Disease of the Cerebral Cortex;
- A. Alzheimer (1907)

- A woman, 51 years old, showed jealousy towards her husband… Soon, rapidly increasing loss of memory could be noticed… At times she would think that someone wanted to kill her …
- She was totally disoriented to time and place …
- Periodically, she was totally delirious,…and seemed to have auditory hallucinations.…
- When reading, she went from one line into another, reading the letters or reading with senseless emphasis …
- When talking she frequently used perplexing phrases and some paraphasic expressions (milk-pourer instead of cup) …
- She seemed no longer to understand the use of some objects …
- The generalized dementia progressed … After 4 1/2 years of the disease, death occurred.

Historical Data

- **In 1948, Jervis described three patients with DS who had dementia, brain atrophy, plaques, and tangles.**
- **In 1952, Verhaart and Jelgersma published a case study of a 56-year-old woman with DS who met the diagnostic criteria for AD.**
- **In 1988, Mann observed that people with DS over 40 had high numbers of senile plaques and neurofibrillary tangles, similar to AD in the general population.**

Epidemiology

- **Down syndrome is the most frequent genetic cause of intellectual disability due to presence of all or part of a third copy of chromosome 21, which occurs approximately in 1:8000 births.**
- **In Europe and US, current estimate indicate a population prevalence of 5.6 and 6.7 per 10000 individuals respectively.**
- **200000 people in US and more than 400000 people in Europe.**

De Graaf G et al. Estimation of the number of people with Down Syndrome in the US. Genet. Med. 2017:19(4):439-447.doi:10.1038/gim.2016.127

Alzheimer's Disease and Down Syndrome

- **AD dementia: leading cause of death in adults with DS over age 35 years**
- **Individuals with DS have a 95% lifetime risk for developing AD dementia**
- **Disease-modifying therapeutics urgently needed due to genetically-determined AD**
- **Longitudinal AD biomarker data demonstrates accelerated disease progression**
- **The revised diagnosis and AD staging criteria (Jack et al, 2024) now includes DS as Stage 0 in the AD continuum**

Association of Alzheimer's Disease with Life Expectancy in People with Down Syndrome

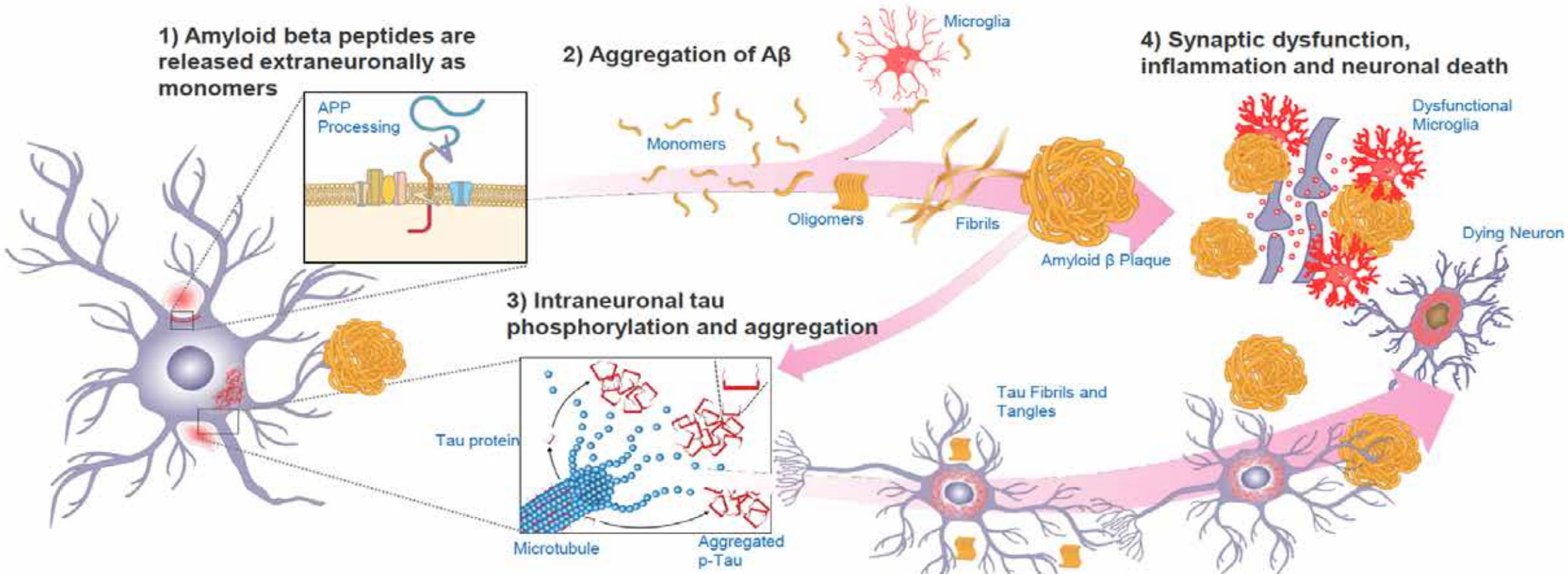
- **Down syndrome is a complex condition with multiple associated comorbidities that vary throughout the life span.**
- **Improvements in Health Care, most notably surgery from congenital heart defects, have remarkably increased life expectancy, from approximately 5 years in the 1950's to roughly 60 years in the 2020.**
- **Closing the life expectancy gap for individual with Down syndrome compared with the general population will require effective prevention or management of Alzheimer’s Disease.**
- JAMA network Open. 2022;5(5):e2212910.doi:10.1001

Alzheimer's Disease in People with Down Syndrome. Genetic basis of Strong Association

- **People with Down Syndrome are born with an extra copy of chromosome 21, which carries the APP gene.**
- **This gene produces a specific protein called amyloid precursor protein (APP).**
- **Too much APP leads to a buildup of protein clumps called beta amyloid plaques in the brain.**
- **By the age of 40, almost all people with Down syndrome have these plaques, along with other protein deposits, called tau tangles, which cause problems how brain cells function and increase the risk of developing AD.**
- **Biomarker changes follow a predictable course that is strikingly similar to that found in autosomal dominant Alzheimer's Disease.**
- **Not all people with these brain plaques will develop symptoms of AD.**

NIH: Alzheimer's Disease in People with Down Syndrome, JAMA network Open. 2022;5(5):e2212910.doi:10.1001

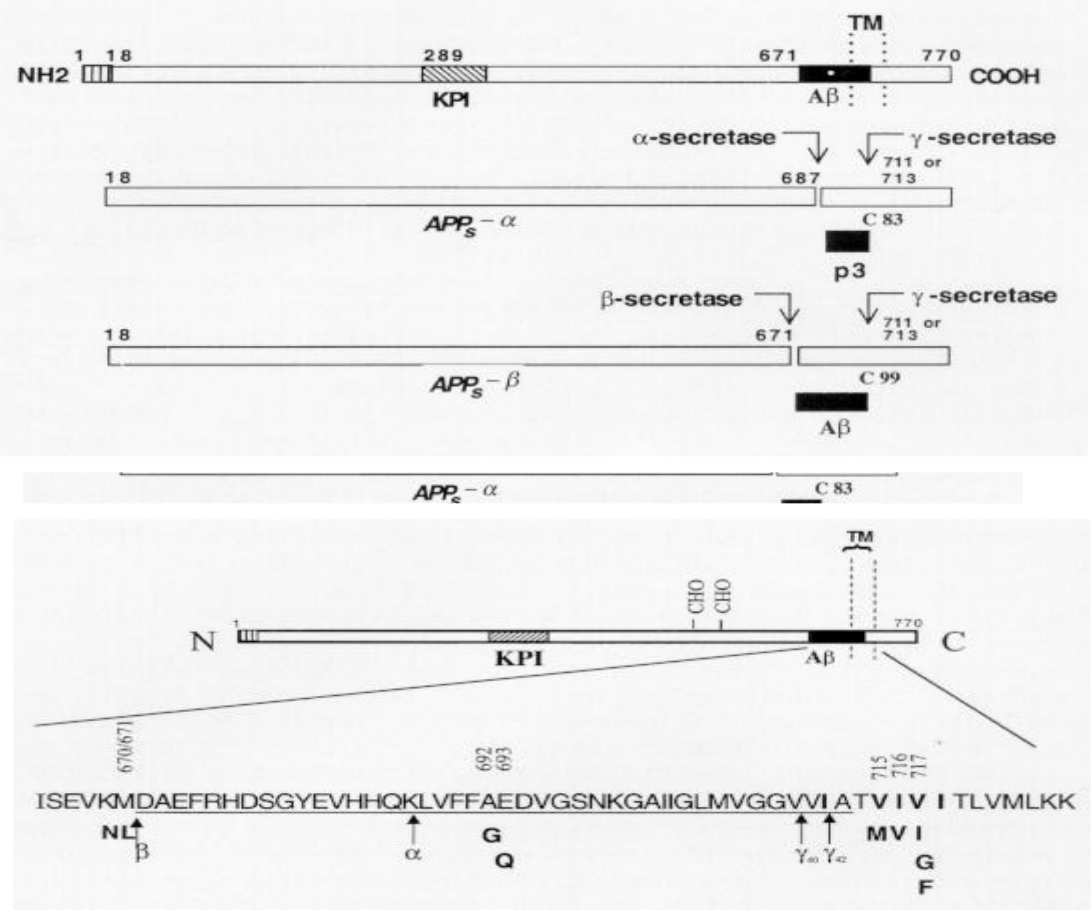
The Two Pathological Hallmarks of Alzheimer's Disease in the Brain Are Aβ Plaques and Neurofibrillary Tangles



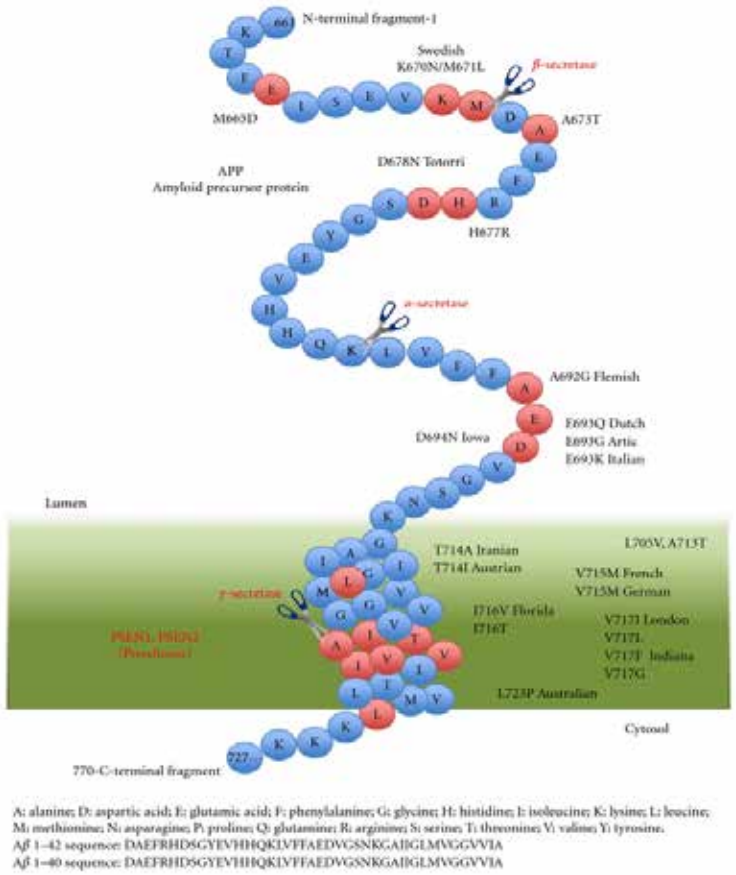
Aβ=amyloid beta; APP=amyloid precursor protein.
Based on Pospich S, Raunser S. *Science*. 2017;358(6359):45-46.

https://www.fda.gov/media/143506/download

Molecular Basis of AD



Amyloid precursor protein (APP) cleavage and mutation.



Association of Alzheimer’s Disease with life Expectancy in People with Down Syndrome

- **Down syndrome has been conceptualized as genetically determined Alzheimer's Disease, just like the autosomal dominant forms.**
- **The implications of this conceptualization on the predictability of symptoms onset in Down syndrome and the limit Alzheimer's Disease imposes on life expectancy, have not been fully explored.**
- JAMA network Open. 2022;5(5):e2212910.doi:10.1001

Aging and Genetic Factors Underlying Alzheimer's Disease

- **Increasing age has the largest impact on risk**

- **ApoE4 gene is the strongest known genetic risk factor for**
- **late-onset Alzheimer's disease**

- **Autosomal dominant mutations with young age at onset account for 1% of Alzheimer's disease cases. Familial AD typically results from mutations in the genes encoding amyloid precursor protein (*APP*), presenilin 1 or presenilin 2.**

- **In both familial and sporadic Alzheimer's disease, changes in amyloid production and/or clearance are important factors.**
- https://www.fda.gov/media/143506/download

Clinical features

- Orientation
- Abstract thinking
- Short term memory
- Long term memory
- Language
- Speech
- Praxis
- Perceptual problems
- Apathy
- Bradykinesia
- Behavior
- Gait

The Neuropsychiatric inventory as a checklist for behavioral issues

- Delusions
- Hallucinations
- Agitation/Aggression
- Depression
- Anxiety
- Elation
- Apathy
- Disinhibition
- Irritability
- Aberrant motor behaviors
- Sleep disturbances
- Eating disturbances

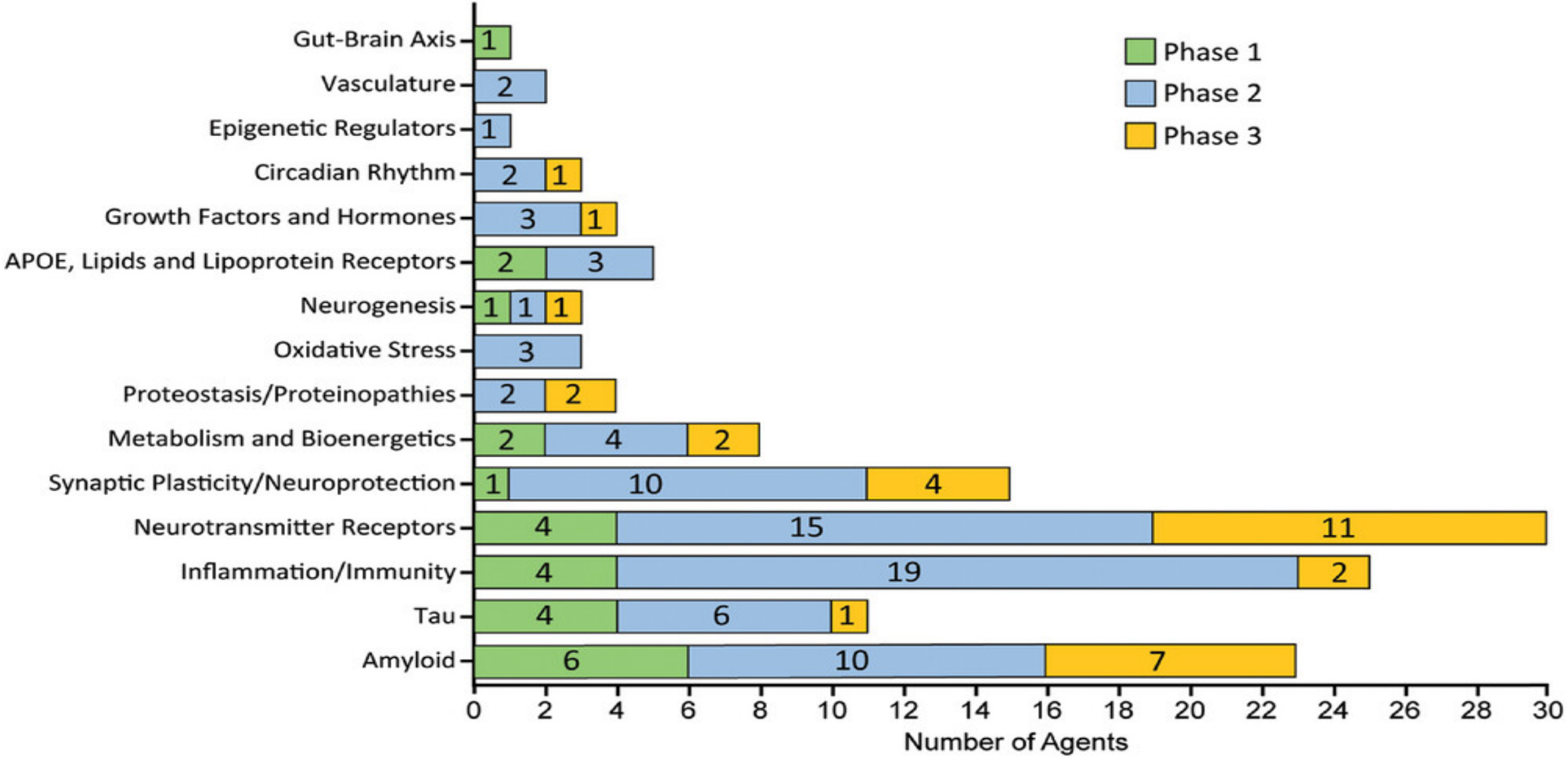
CummingsJl, et al. Neurology 1994;44(12):2308-2314

Alzheimer’s Disease risk factors

- Substantial body of evidence indicates that **immune/inflammatory mechanisms** are important in AD pathogenesis.
- Biomarkers of inflammatory/immune process are divided into two subcategories:
  - Reactivity of astrocytes: marker with potential clinical use is the **Glial fibrillary acidic protein (GFAP)** measured in plasma or CSF, associated with Early amyloid PET higher risk of incident dementia and fast rates of cognitive decline.
  - Reactivity of microglia: Soluble **TREM2** can be measured in CSF.

Jack et al Alzheimer’s Disease and Dementia 2024

Alzheimer-related processes as categorized by the Common Alzheimer's Disease Research Ontology (CADRO) for agents in each phase of the Alzheimer's drug development pipeline (© J Cummings; M de la Flor, PhD, Illustrator).2024



Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Jack et al Alzheimer's Disease and Dementia 2024

- We define Alzheimer's disease (AD) to be **a biological process** that begins with the appearance of AD neuropathologic change (ADNPC) while people are asymptomatic. Progression of the neuropathologic burden leads to the later appearance and progression of clinical symptoms.

- Early-changing Core 1 biomarkers (**amyloid positron emission tomography [PET],approved cerebrospinal fluid biomarkers, and accurate plasma biomarkers [especially phosphorylated tau 217**) map onto either the amyloid beta or AD tau pathway; however, these reflect the presence of ADNPC more generally (i.e., bothneuritic plaques and tangles).

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Jack et al Alzheimer's Disease and Dementia 2024

- **An abnormal Core 1 biomarker result is sufficient to establish a diagnosis of AD and to inform clinical decision making throughout the disease continuum.**·
- Later-changing Core 2 biomarkers (biofluid and tau PET) can provide prognostic information, and when abnormal, will increase confidence that AD is contributing to symptoms.·
- An integrated biological and clinical staging scheme is described that accommodates the fact that common copathologies, cognitive reserve, and resistance may modify relationships between clinical and biological AD stages

AD Blood-Based Biomarkers: Context of Use Recommendations

- Less invasive, better accessibility and potentially less expensive than CSF biomarkers or amyloid PET.
- **Recommended for Secondary Care**:
  - Providers with experience and expertise in Dementia
  - Help established amyloid pathology as the likely cause of cognitive impairment in asymptomatic individuals.
- Primary Care:
  - Additional data is needed
  - May be useful for triaging for patients 55 or older
  - Identify individuals who are unlikely to have amyloid pathology (rule out).

Categorization of fluid analyte and imaging biomarkers

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	**Aβ 42**	**Amyloid PET**
T 1: (phosphorylated and secreted AD tau)	**p-tau217, p-tau181,p-tau231**	
Core 2		
T 2 (AD tau proteinopathy)	**MTBR-tau243, other phosphorylated tau forms e.g., p-tau205), non-phosphorylated mid-region tau fragments**	**Tau PET**

Jack et al Alzheimer's Disease and Dementia 2024

Categorization of fluid analyte and imaging biomarkers.

Biomarkers of non-specific processes involved in AD pathophysiology

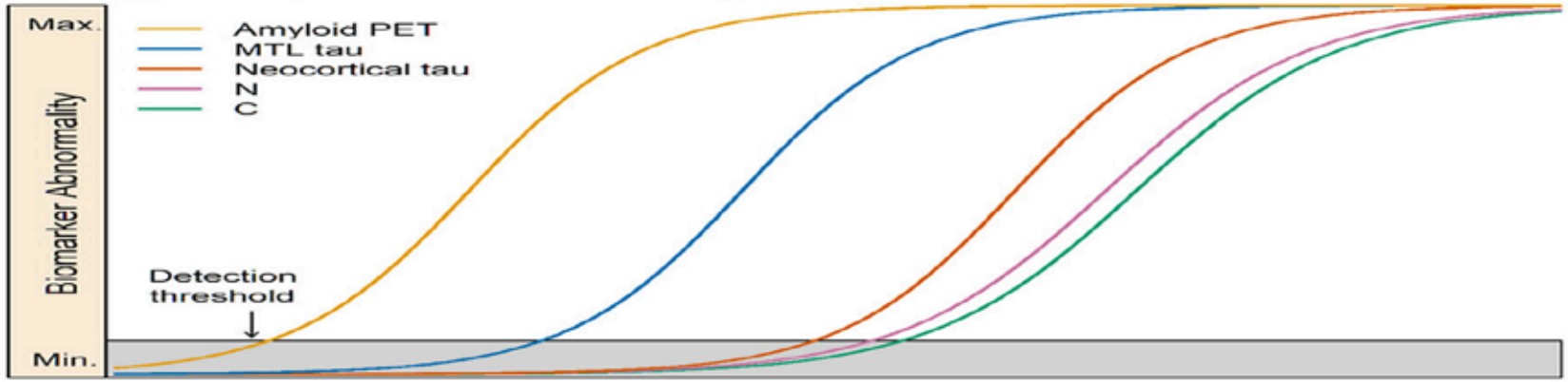
N(injury, dysfunction or degeneration of neuropil)	**NfL**	**Anatomic MRI,FDG PET**
I (inflammation) Astrocytic activation	**GFAP**	

Biomarkers of non-AD copathology

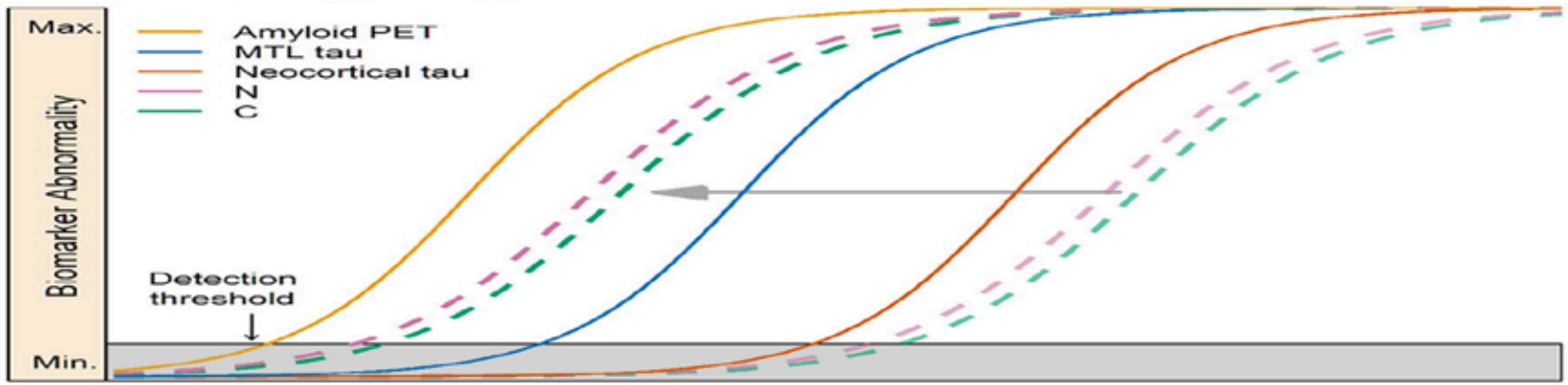
V vascular brain injury	**Infarction on MRIor CT, WMH**
S α-synuclein	**αSyn-SAA a**

Jack et al Alzheimer's Disease and Dementia 2024

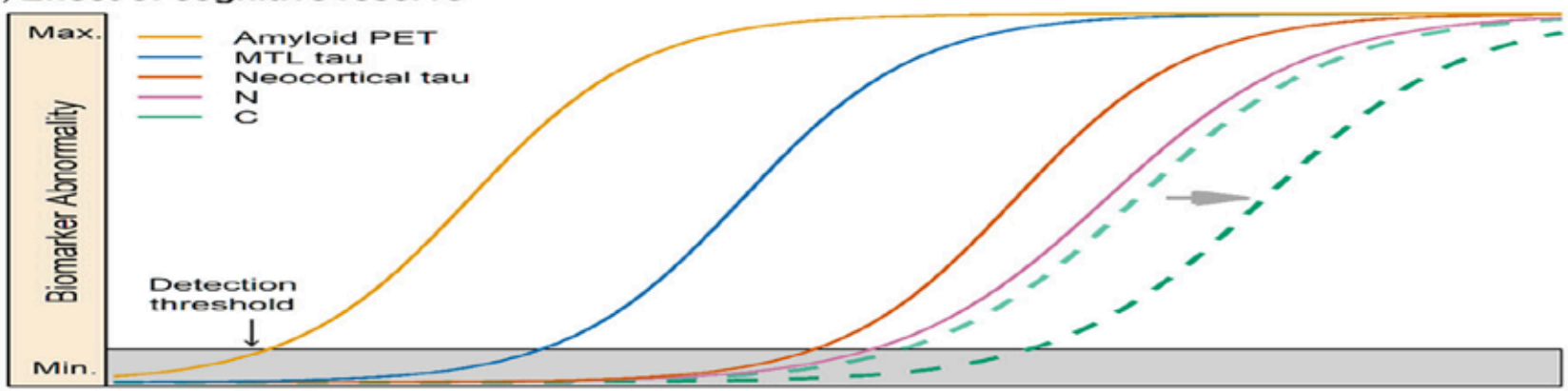
(A) **Archetypical sequence of biomarker changes**

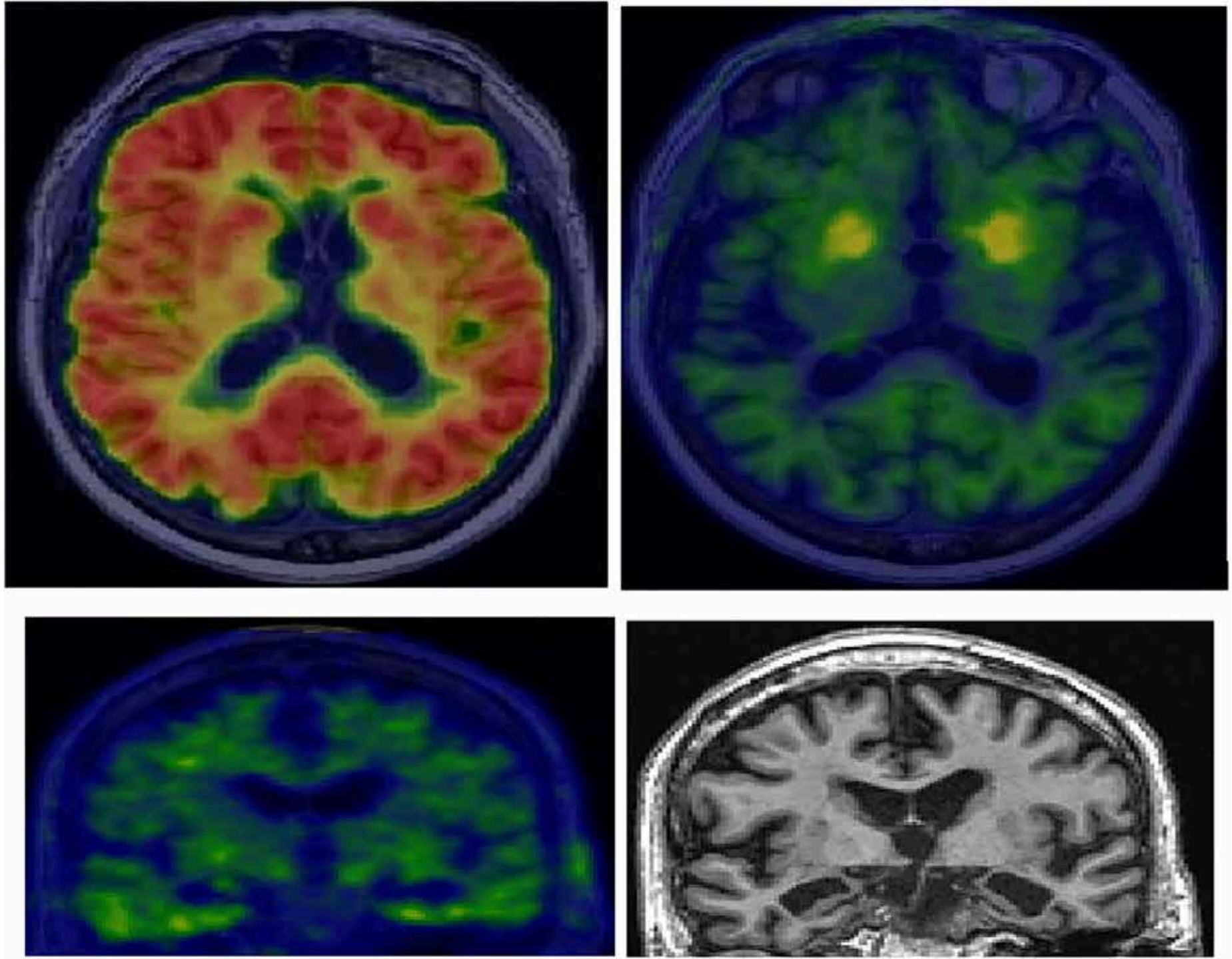


(B) **Effect of coexisting pathologies**



(C) **Effect of cognitive reserve**





Clinical staging for individuals on the Alzheimer's disease continuum.

0	**Stage 0 Asymptomatic, deterministic gene**[a]
	No evidence of clinical change. Biomarkers in **normal range.**
1	**Stage 1 Asymptomatic, biomarker evidence only**
	Performance within expected range on objective cognitive tests.
	No evidence of recent cognitive decline or new symptoms.
2	**Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function (*SCI*)**
	Normal performance within expected range on objective cognitive tests.
	Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years, and has been persistent for at least 6 months.
	May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range.
	May be documented through subjective report of cognitive decline.
	May be documented with recent-onset change in mood, anxiety, motivation not explained by life events.
	Remains fully independent with no or minimal functional impact on activities of daily living (ADLs)

Clinical staging for individuals on the Alzheimer's disease

3	**Stage 3 Cognitive impairment with early functional impact *(MCI*)**
	Performance in the impaired/abnormal range on objective cognitive tests.
	Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments.
	Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete—either self-reported or corroborated by an observer).
4	**Stage 4 Dementia with mild functional impairment(*Dementia at the mild stage of severity*)**
	Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.
5	**Stage 5 Dementia with moderate functional impairment(*Dementia at the moderate stage of severity*)**
	Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.
6	**Stage 6 Dementia with severe functional impairment(*Dementia at the severe stage*)**
	Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

Individuals with Down syndrome may not be fully independent even in stage 0 because of underlying intellectual disability. In these individuals, decline in functional independence from baseline may be a more appropriate indicator of stage.

Dementia

- **Development of multiple cognitive deficits manifested by**
  - **Memory impairment**
  - **One of the following cognitive disturbances**
    - **Aphasia**
    - **Apraxia**
    - **Agnosia**
    - **Disturbance in executive function**

- **The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning**
- **The deficits do not occur exclusively during the course of a delirium.**
- DSM-V criteria for dementia
- **Is diagnosed when there are cognitive or behavioral symptoms that:**
- **Interfere with the ability to function at work or at usual activities and**
- **Represent a decline from previous levels of functioning and performing and**
- **Are not explained by delirium or major psychiatric disorder.**

The diagnosis of dementia due to Alzheimer's disease. G M McKhann et al. Alzheimer's & Dementia (2011) 1 May;7(3):263-9. doi: 10.1016

Core Clinical Criteria Dementia

- **Cognitive impairment is detected and diagnosed through a combination of**
  - **(1) history-taking from the patient and a knowledgeable informant and**
  - **(2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing.**
- **Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.**

The diagnosis of dementia due to Alzheimer's disease. G M McKhann et al. Alzheimer's & Dementia (2011) 1 May;7(3):263-9. doi: 10.1016

Core Clinical Criteria Dementia

- **The cognitive or behavioral impairment involves a minimum of two of the following domains:**
- **Impaired ability to acquire and remember new information-symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.**

- The diagnosis of dementia due to Alzheimer's disease. G M McKhann et al. Alzheimer's & Dementia (2011) 1 May;7(3):263-9. doi: 10.1016

Core Clinical Criteria Dementia

- **Impaired reasoning and handling of complex tasks, poor judgement-symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequencial activities.**

- **Impaired visuospatial abilities-symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements or orient clothing to the body.**

The diagnosis of dementia due to Alzheimer's disease. G M McKhann et al. Alzheimer's & Dementia (2011) 1 May;7(3):263-9. doi: 10.1016

Core Clinical Criteria Dementia

- **Impaired language functions (speaking, reading, writing)-symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling and writing errors.**
- **Changes in personality, behavior, or comportment-symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiate, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive, or obsessive behaviors, socially unacceptable behaviors.**

The diagnosis of dementia due to Alzheimer's disease. G M McKhann et al. Alzheimer's & Dementia (2011) 1 May;7(3):263-9. doi: 10.1016

Core Clinical Criteria Dementia

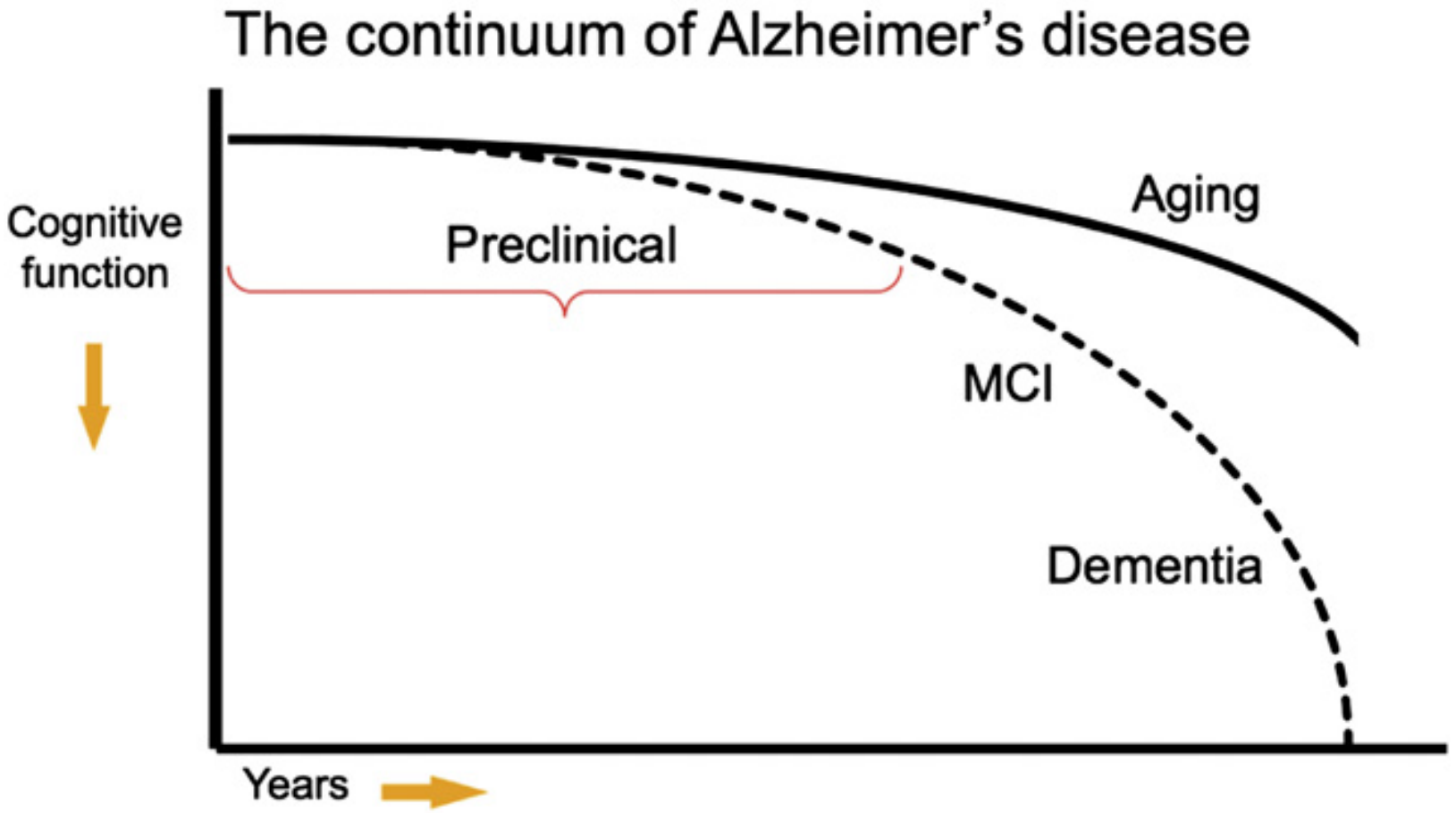
- **Probable AD dementia**
- **Possible AD dementia**
- **Probable or possible AD dementia with evidence of the AD pathophysiological process.**

- The diagnosis of dementia due to Alzheimer's disease. G M McKhann et al. Alzheimer's & Dementia (2011) 1 May;7(3):263-9. doi: 10.1016

Core Clinical Criteria Dementia

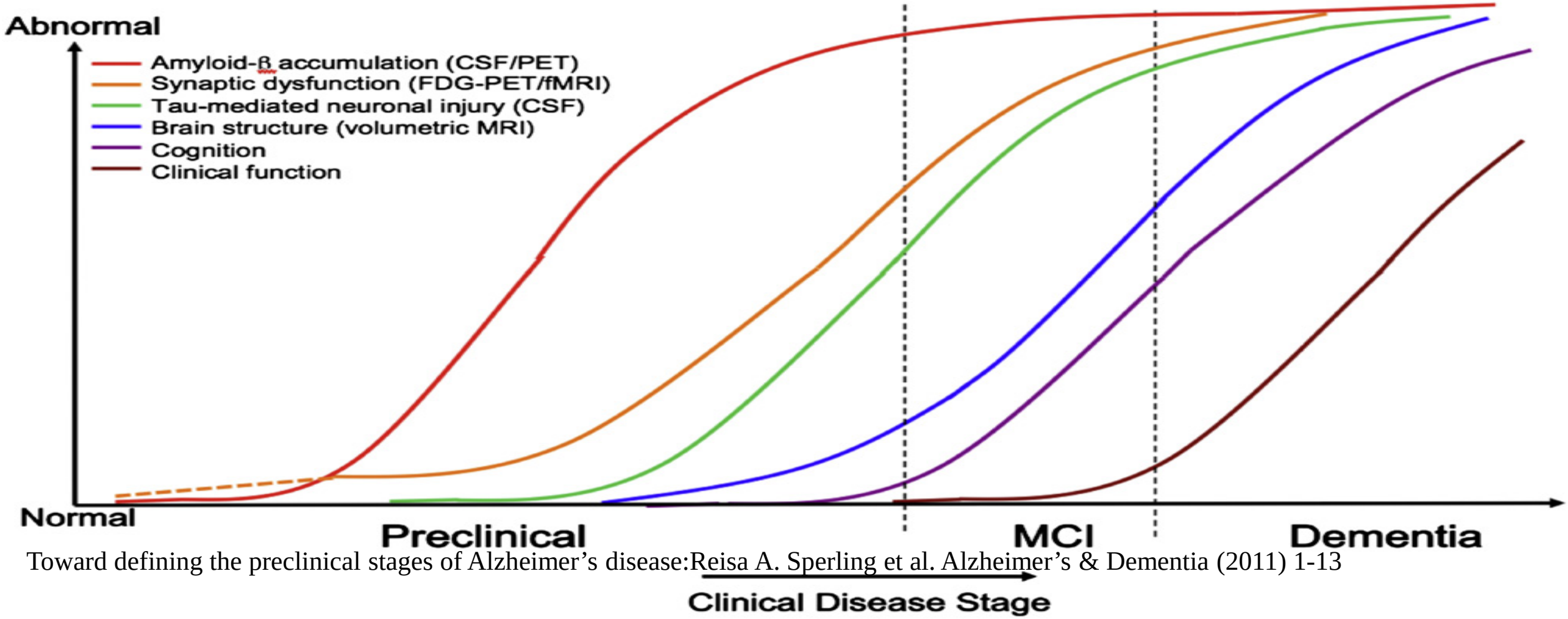
- **Probable AD is diagnosed when:**
- **Dementia**
- **Insidious onset**
- **Clear –cut history of worsening of cognition by report or observation and**
- **The initial and most prominent cognitive deficits are evident by history and examination in one of the following:**
  - **Amnestic presentations**
  - **Non Amnestic presentations (Language, Visuospatial presentation, executive dysfunction).**

The diagnosis of dementia due to Alzheimer's disease. G M McKhann et al. Alzheimer's & Dementia (2011) 1 May;7(3):263-9. doi: 10.1016



Toward defining the preclinical stages of Alzheimer's disease: Reisa A. Sperling et al. Alzheimer's & Dementia (2011) 1-13

Hypothetical model of dynamic biomarkers of the AD



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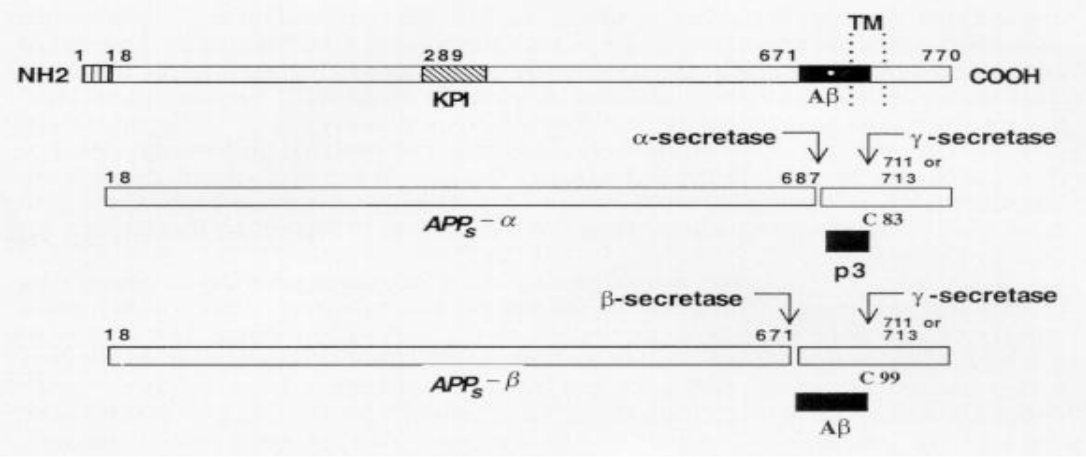
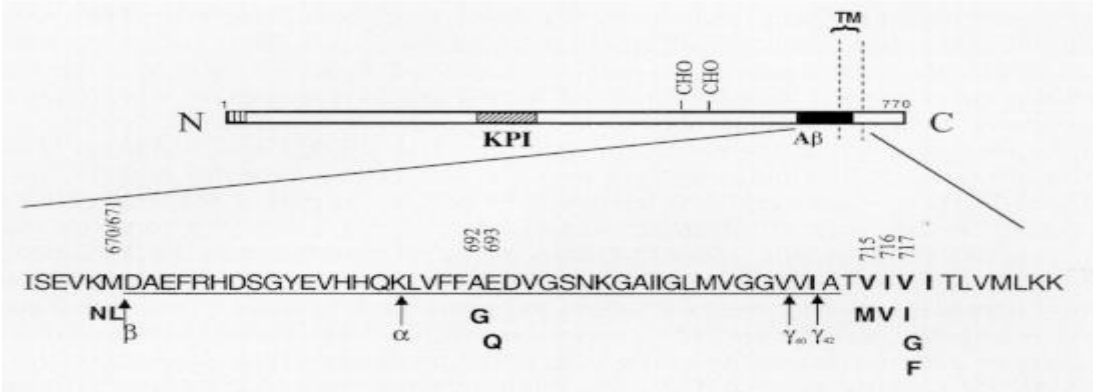
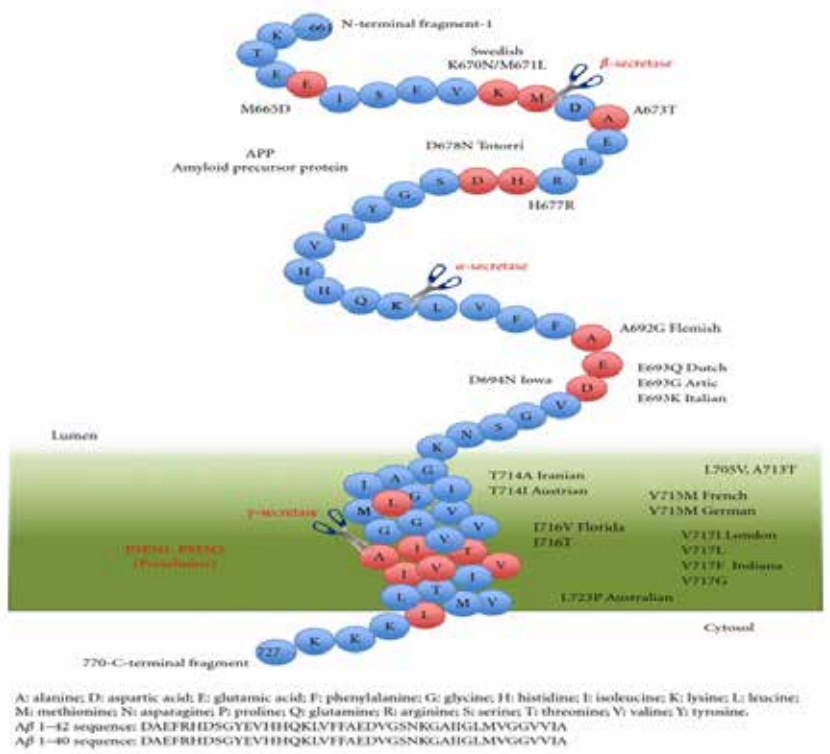
Molecular Basis of AD

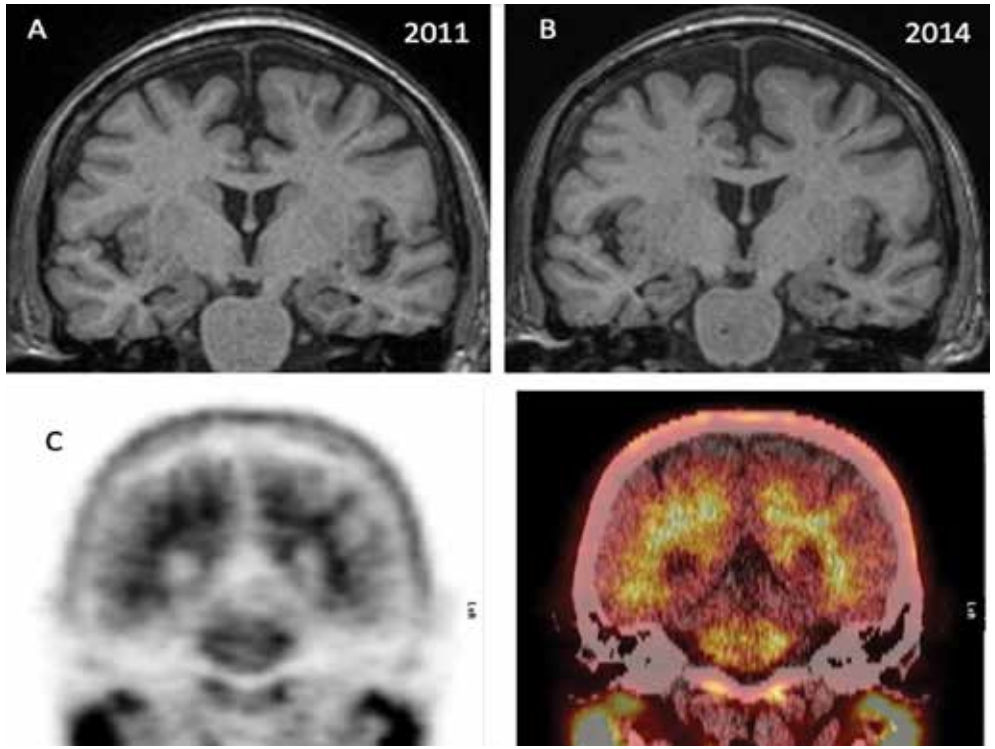


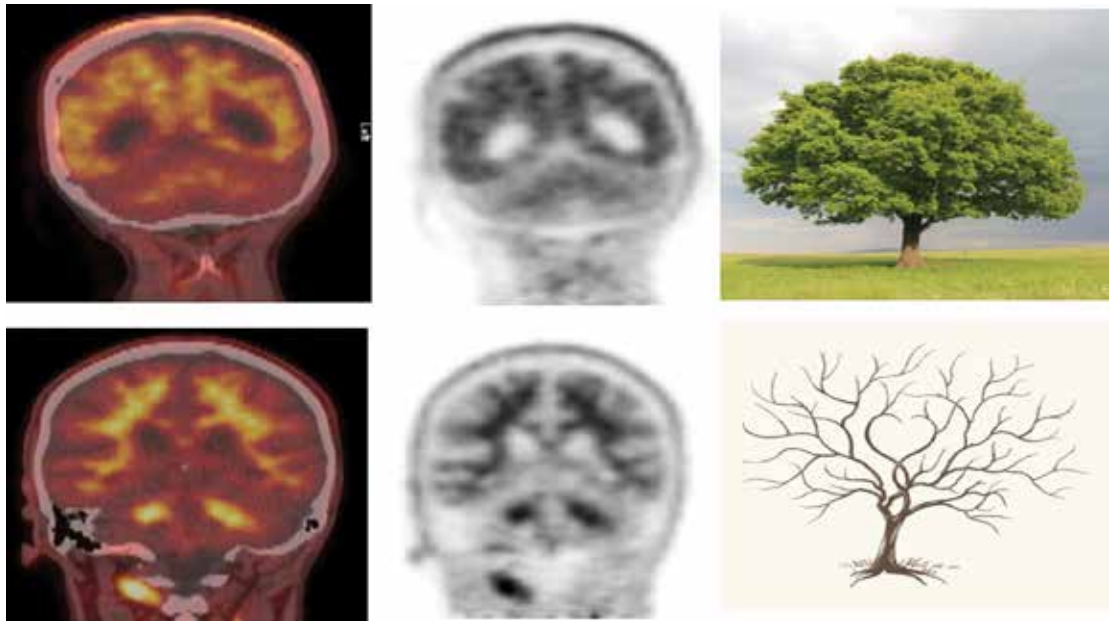


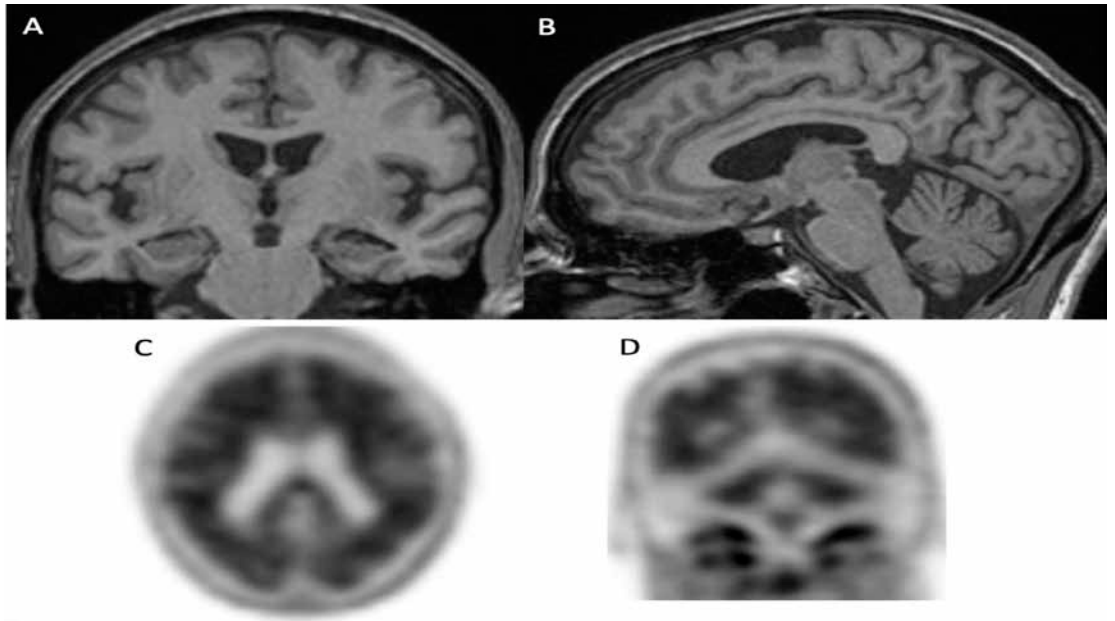
Amyloid precursor protein (APP) cleavage and mutation.



F Modarresi ea tal. Int Journal of Alzheimer's disease, 2011.
https://doi.org/10.4061/2011/929042



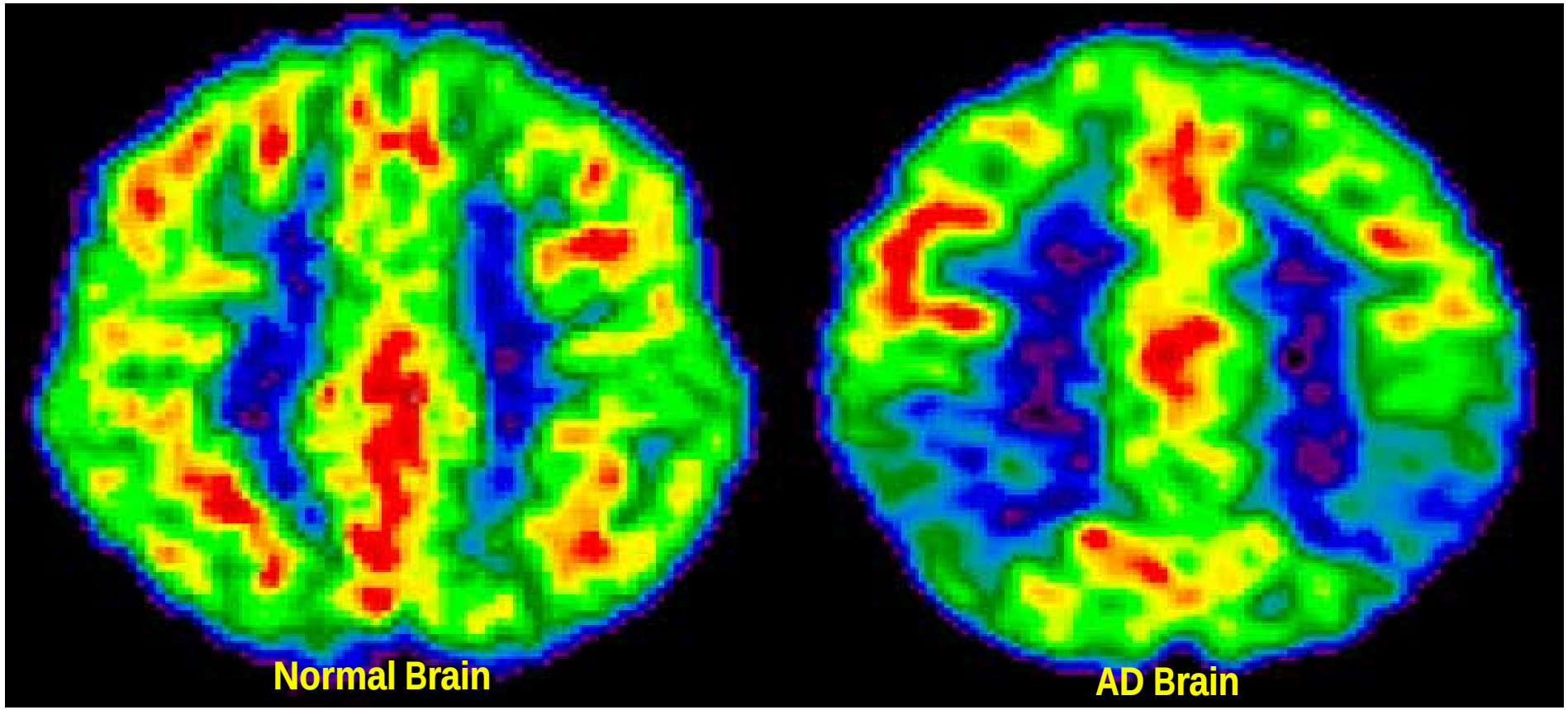




Amyloid PET imaging in clinical practice. Kolanko et al**:**Pract Neurol. 2020 Dec;20(6):451-462.

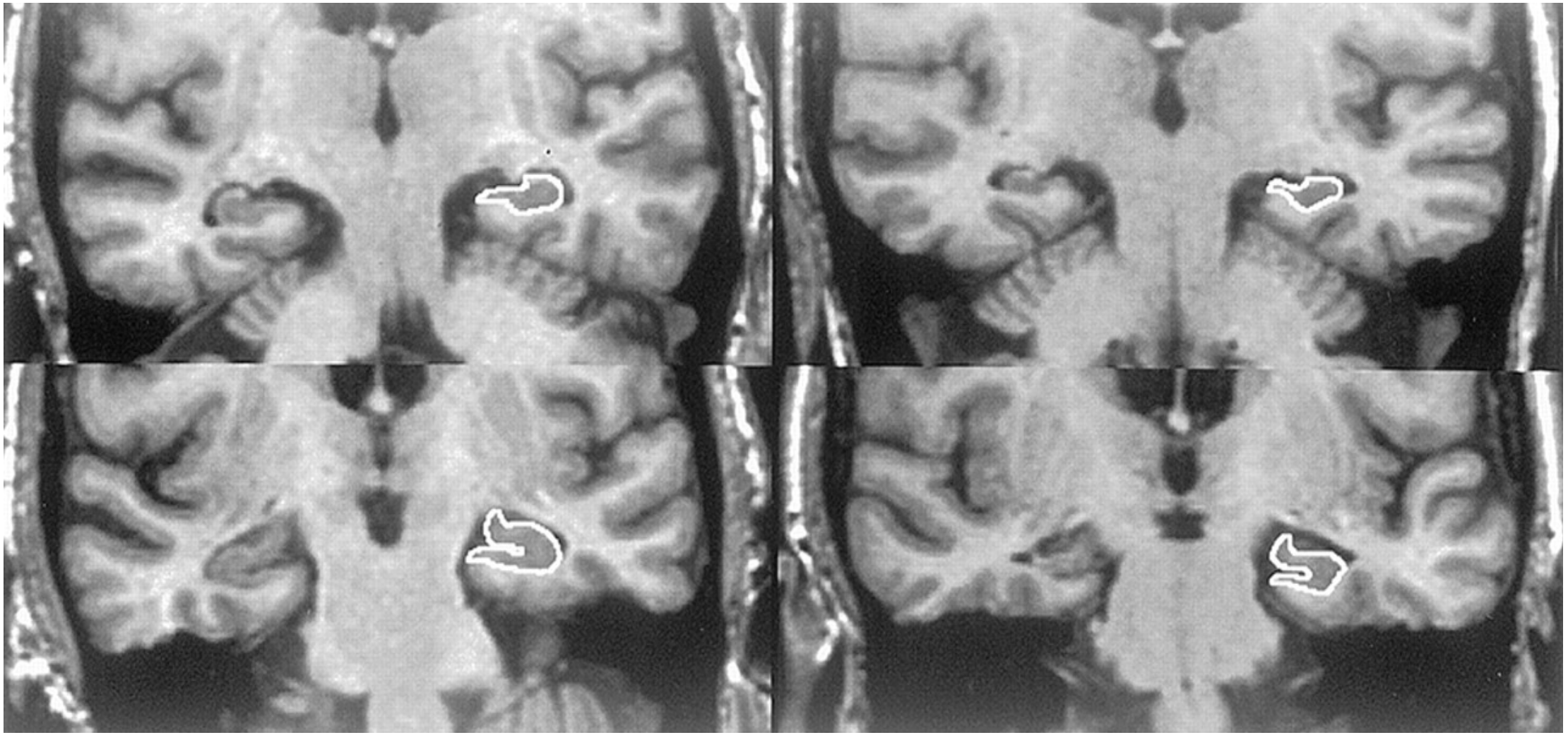
doi: 10.1136/practneurol-2019-002468.

FDG PET Neuroimaging



PET shows hypometabolism in bilateral parietal, temporal, and posterior cingulate cortex in AD subjects and in those who are asymptomatic but at increased risk for AD (those with Apo E • 4)

Neuroanatomic boundaries



Jack, C. R. et al. Neurology 1999;52:1397

Classification of Dementia Syndromes

Degenerative disorders	**Alzheimer disease, a Lewy body dementia spectrum, a frontotemporal dementia, Huntington disease, tauopathies, amyotrophic lateral sclerosis (ALS), and prion disorders**
Vascular dementias	Multi-infarct, diffuse white matter disease (Binswanger's)
Toxic conditions	Alcoholism, drug/medication intoxication, other toxic disorders
Metabolic disorders	Vitamin deficiencies (B12, B1, folate, niacin), endocrine disorders (thyroid, adrenal, para- thyroid), uremia, hepatic encephalopathy, and cardiopulmonary failure
Infectious dementias	HIV, syphilis, progressive multifocal leuko- encephalopathy (PML), and other chronic infections
Traumatic conditions	Chronic traumatic encephalopathy and others
Hydrocephalic syndromes	Normal pressure hydrocephalus
Psychiatric conditions	Depression, conversion disorder, and others
Autoimmune/ inflammatory conditions	Multiple sclerosis, vasculitis, sarcoidosis, and more
Cancer or related mass effects	

Clinical Approach to Dementia. Soumya Bouchachi and Maria Kataki. Practical Neurology. June 2021

The 3 Ds in the differential diagnosis

- **Dementia**
- **Delirium**
  - **Acute confusional state**
  - **Attention, concentration deficits,**
  - **fluctuations,**
  - **psychomotor and or autonomic overactivity,**
  - **fragmented speech, hallucinations**
- **Depression**

VITAMINS
Mnemonic for Differential Categories of RPDs

- **Vascular**
- **Infectious**
- **Toxic-Metabolic**
- **Autoimmune**
- **Metastases**
- **Iatrogenic**
- **Neoplastic/Neurodegenerative**
- **Systemic**

M Geschwind AAN syllabus 07

Practice Recommendations

– **Structural neuroimaging** (Guideline).

– **Depression** (Guideline).

– **B12 deficiency** (Guideline).

– **Hypothyroidism** (Guideline).

Knopman et al. Neurology Volume 56 • Number 9 • May 8, 2001

FDA approved medications for Alzheimer's disease

Drug Name	Brand Name	Approved for	FDA approval
Donepezil	**Aricept/Adlarity patch**	**All stages**	**1996/2022**
Galantamine	**Razadyne**	**Mild To moderate**	**2001**
Rivastigmine	**Exelon capsules/patch**	**All stages**	**2000/2007**
Memantine	**Namenda**	**Moderate to severe**	**2003**
Donepezil and Memantine	**Namzaric**	**Moderate to severe**	**2014**
Lecanemab	**Leqembi**	**MCI and Mild Dementia due to AD**	**accelerated approval by FDA 1/6/2023** **Full regulatoraty approval 7/6/23**
Donanemab	**Kisunla**	**MCI and Mild Dementia due to AD**	7/2/24

Disease Modifying treatments for Alzheimer's Disease

- **Over the past decade, considerable advances occurred in testing the amyloid cascade hypothesis in Alzheimer's Disease clinical trials.**
- **Numerous amyloid-targeting therapy trials failed to show appreciable slowing of clinical disease progression.**
- **Aducanumab,lecanemab and Donanemab recently showed promising amyloid plaque clearance, potentially benefiting patients.**
- **Aducanumab was granted accelerated approval by FDA 6/7/21, has not been available for prescription as of 11/2024.**
- **Lecanemab was granted accelerated approval by FDA 1/6/2023 and full regulatory approval 7/6/2023 amid concerns about its safety, cost and accessibility.**
- **Donanemab was granted approval 7/2/24**

J Sims et al. JAMA, August 8 2023 Volume 330, number 6

Albany Medical Center Offers Groundbreaking Alzheimer's Treatment

- August 19, 2024
  by Sue Ford Rajchel

- **Albany Medical Center is the first hospital in the region** to offer a therapy that has been shown to delay the progression of Alzheimer's disease. Lecanemab, manufactured by Eisai and Biogen, was approved by the U.S. Food and Drug Administration in July of 2023 after it was shown to delay cognitive and functional decline by approximately five months in an 18-month double-blind, placebo-controlled trial.
- **The first infusion was administered to a patient at The Alzheimer's Center at Albany Medical Center, a New York State designated Center of Excellence for Alzheimer's Disease (CEAD) on July 22**.
- "This is a new era of disease-modifying treatments for Alzheimer's disease, altering the biology of the disease," said Maria Kataki, MD, PhD, Medical Director of The Alzheimer's Center at Albany Medical Center. "As the first hospital to offer this therapy, we are thrilled to revolutionize the treatment of Alzheimer's disease in our region and to offer new hope to our patients and their families."

Albany Medical Center Offers Groundbreaking Alzheimer's Treatment

- Lecanemab is a monoclonal antibody treatment that works by targeting and binding to the amyloid plaque that forms in the brains of Alzheimer's patients, thereby slowing the cognitive and functional decline caused by these plaques.
- Patients eligible for lecanemab include those with a diagnosis of mild cognitive impairment or mild dementia due to Alzheimer's disease with evidence of amyloid plaques in the brain. Patients undergo a comprehensive neurological evaluation to determine eligibility. Infusions take place every two weeks and patients must be carefully monitored for potential adverse reactions.
- According to Dr. Kataki, the infrastructure required to administer the treatment requires a team of specialists from multiple disciplines and departments, including experts from radiology, apheresis, pharmacy, laboratory services, and numerous members of the Department of Neurology. In addition, the CEAD has worked closely with community neurologists and the Center of Excellence for Alzheimer's Disease at Glens Falls Hospital to educate physicians.
- "Each of us has worked diligently to serve our patients the best way we can. I am grateful for the response and support of this multidisciplinary team that has been eager to learn and implement this new practice for dementia care," said Dr. Kataki.

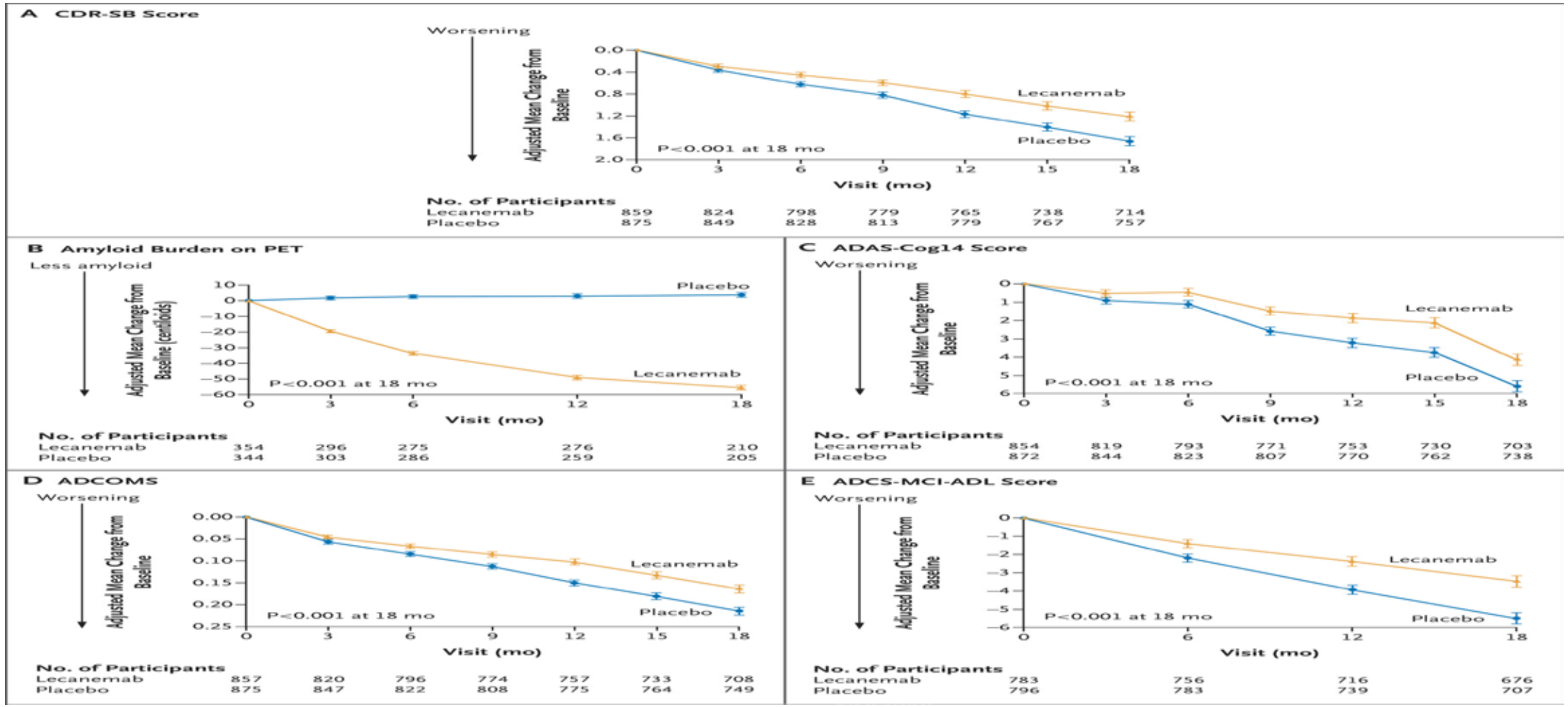
Lecanemab in Early Alzheimer's Disease

Christopher H. van Dyck, M.D., et al January 5, 2023N Engl J Med 2023; 388:9-21 DOI: 10.1056/NEJMoa2212948

- The accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate pathologic processes in Alzheimer's disease***. Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils***, is being tested in persons with early Alzheimer's disease.
- A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean ***CDR-SB score*** at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at ***18 months was 1.21 with lecanemab*** and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001).
- In a substudy involving 698 participants, there were ***greater reductions in brain amyloid burden with lecanemab than with placebo*** (difference, −59.1 centiloids; 95% CI, −62.6 to −55.6).
- Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ***ADAS-cog14 score***, −1.44 (95% CI, −2.27 to −0.61; P<0.001); for the ***ADCOMS,*** −0.050 (95% CI, −0.074 to −0.027; P<0.001); and for the ***ADCS-MCI-ADL score***, 2.0 (95% CI, 1.2 to 2.8; P<0.001).
- Lecanemab resulted in ***infusion-related reactions in 26.4%*** of the participants and ***amyloid-related imaging abnormalities with edema or effusions in 12.6%, ARIA with cerebral microhemorrhages, cerebral macrohemorrhages or superficial siderosis 17.3%.***
- **CONCLUSIONS**
- **Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events. Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease. (Funded by Eisai and Biogen; Clarity AD ClinicalTrials.gov number, NCT03887455. opens in new tab.)**

Lecanemab in Early Alzheimer's Disease

Christopher H. van Dyck, M.D., et al January 5, 2023N Engl J Med 2023; 388:9-21 DOI: 10.1056/NEJMoa2212948



Lecanemab inclusion criteria

- Progressive memory loss noticeable by informant for at least one year.
- Diagnosis of MCI due to AD or Mild Dementia due to AD established by comprehensive Neurological evaluation.
- MMSE or equivalent of >21/30, SAGE >10, MOCA >17
- Proof of Amyloid status established by amyloid Brain PET , P-217 plasma test or CSF biomarkers for AD.
- Recent MRI brain including DWI, SWI, FLAIR, T1 images without evidence of strokes, TBI, ICH, Tumors, NPH, ARIAE/H.
- APOE genotype not homozygotes for E4/4

Lecanemab Exclusion criteria

Memory problems of duration of less than six months duration, not noticeable by informant for at least a year.

No formal diagnosis of MCI or Mild Dementia Stage due to AD established by Neurologist.

No proof of amyloid status (Amyloid Brain PET, P-217 plasma test or CSF biomarkers for AD).

APOE4 genotype (homozygote or heterozygote)

Pacemaker, metal brain aneurysm clip, or other metal object, or other reason that will not allow the patient to have an MRI scan.

Anticoagulation medication

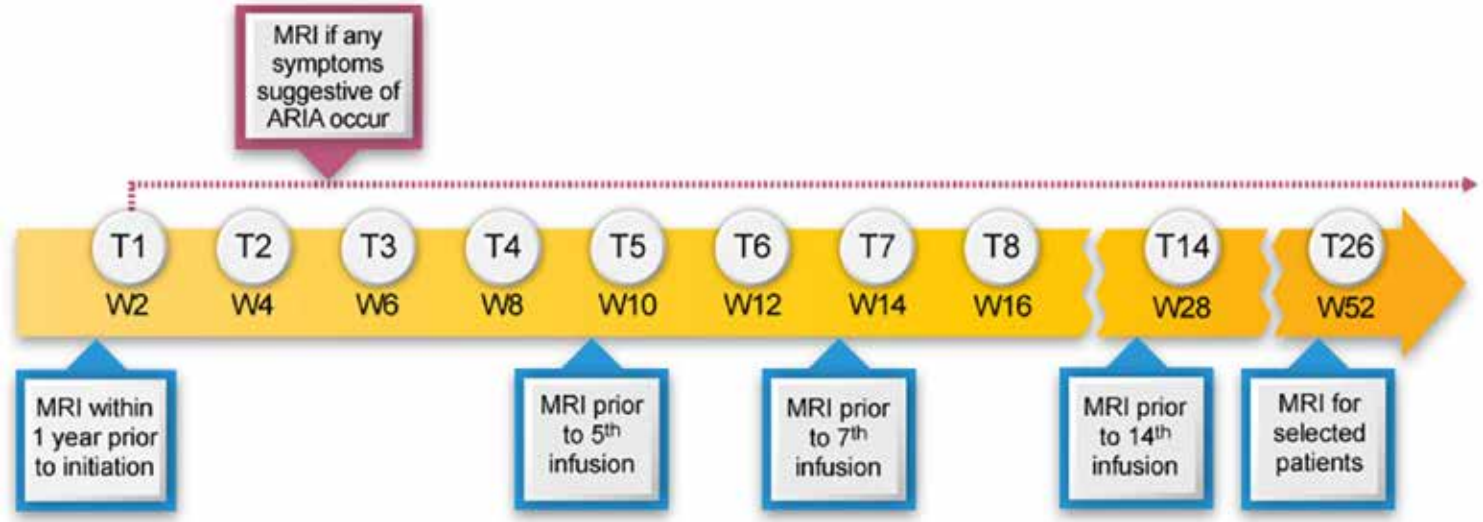
International normalized ration (INR)>1.5, platelet count<50000, or untreated bleeding disorder.
Stroke in a major vascular territory,, >2 lacunar infarcts, history of TIA or seizures within 12 months of screening, brain bleeding, diffuse white matter disease, other major intracranial pathology, history of amyloid related angiitis, (ABRA), history of cerebral amyloid angiopathy inflammation (CAARI), Immunologic disease, head trauma, or severe depression, chronic systemic condition, Epilepsy, cancer requiring chemotherapy, chronic treatment with immunosuppressants, immunoglobulins or monoclonal antibodies or other derivatives.

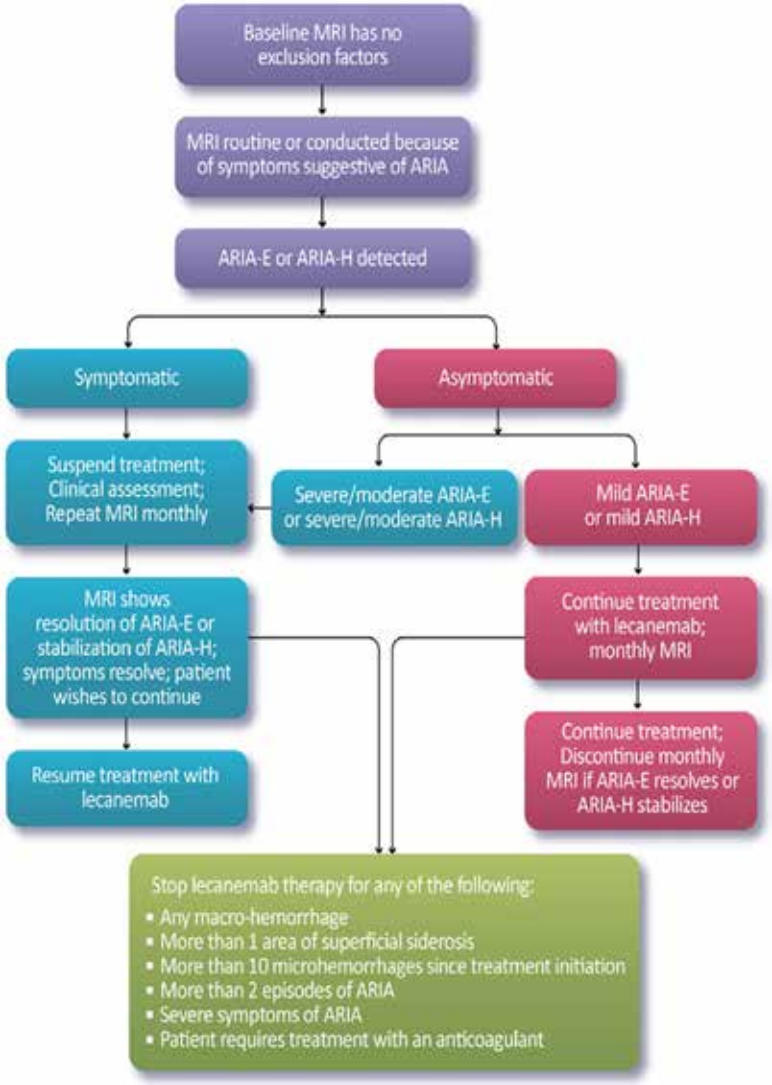
History of ARIA, moderate or severe

Douglas Scharre, Soumya Bouchachi, Joseph Castle, *Maria Kataki*, Renee Kovesci, Arun Ramamurthy, Jessica Truelove. OSUWMC Clinical Practice Guideline: Anti-amyloid Monoclonal Antibody Prescribing in Patients with Alzheimer's Disease. 7/2023

Lecanemab: Appropriate Use Recommendations

J. Cummings,et al, and Alzheimer's Disease and Related Disorders Therapeutics Work GroupJ Prev Alzheimers Dis. 2023; 10(3): 362–377.
doi: 10.14283/jpad.2023.30





Lecanemab Planning Blueprint for Safe and Effective Management of Complex Therapies

Rita Shane et al. Neurology: Clinical Practice 2024;14:e200361. doi:10.1212/CPJ.0000000000200361

- Lecanemab is associated with modest reduction in functional decline in patients with mild dementia or mild cognitive impairment.
- In Clarity-AD 26.6% of patients experienced amyloid-related imaging abnormalities (ARIAs) overall.
- The complexity of treatment and risks of adverse events necessitate a multidisciplinary collaborative approach.
- Processes to support patient selection, access, and safety are important given the monitoring requirements and total cost of care.
- The comprehensive multidisciplinary planning process has provided a blueprint for management of lecanemab and forms the foundation for supporting patient's safety and ensuring access to future novel therapies.

July 17, 2023
Donanemab in Early Symptomatic Alzheimer DiseaseThe TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD[1]; Jennifer A. Zimmer, MD[1]; Cynthia D. Evans, PhD[1]; et al

- **Multicenter** (277 medical research centers/hospitals **in 8 countries**), randomized, double-blind, placebo-controlled, 18-month phase 3 trial that enrolled 1736 participants with early symptomatic Alzheimer disease (mild cognitive impairment/mild dementia) with amyloid and low/medium or high tau pathology based on positron emission tomography imaging from June 2020 to November 2021 (last patient visit for primary outcome in April 2023).
  Interventions Participants were randomized in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 72 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met.
  Main Outcomes and Measures The primary outcome was change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0-144; lower scores indicate greater impairment). There were 24 gated outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) score (range, 0-18; higher scores indicate greater impairment). Statistical testing allocated α of .04 to testing low/medium tau population outcomes, with the remainder (.01) for combined population outcomes.

  Trial Registration ClinicalTrials.gov Identifier: NCT04437511

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

John R. Sims, et al JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239 Published online July 17, 2023

- **Results** Among 1736 randomized participants (mean age, 73.0 years; 996 [57.4%] women; 1182 [68.1%] with low/medium tau pathology and 552 [31.8%] with high tau pathology), 1320 (76%) completed the trial. **Of the 24 gated outcomes, 23 were statistically significant**.
- The least-squares mean (LSM) change in iADRS score at 76 weeks was −6.02 (95% CI, −7.01 to −5.03) in the donanemab group and −9.27 (95% CI, −10.23 to −8.31) in the placebo group (difference, 3.25 [95% CI, 1.88-4.62]; $P < .001$) in the low/medium tau population and −10.2 (95% CI, −11.22 to −9.16) with donanemab and −13.1 (95% CI, −14.10 to −12.13) with placebo (difference, 2.92 [95% CI, 1.51-4.33]; $P < .001$) in the combined population. LSM change in CDR-SB score at 76 weeks was 1.20 (95% CI, 1.00-1.41) with donanemab and 1.88 (95% CI, 1.68-2.08) with placebo (difference, −0.67 [95% CI, −0.95 to −0.40]; $P < .001$) in the low/medium tau population and 1.72 (95% CI, 1.53-1.91) with donanemab and 2.42 (95% CI, 2.24-2.60) with placebo (difference, −0.7 [95% CI, −0.95 to −0.45]; $P < .001$) in the combined population.
- Amyloid-related imaging abnormalities of edema or effusion occurred in 205 participants (24.0%; 52 symptomatic) in the donanemab group and 18 (2.1%; 0 symptomatic during study) in the placebo group and infusion-related reactions occurred in 74 participants (8.7%) with donanemab and 4 (0.5%) with placebo. Three deaths in the donanemab group and 1 in the placebo group were considered treatment related.

Conclusions and Relevance **Among participants with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab significantly slowed clinical progression at 76 weeks in those with low/medium tau and in the combined low/medium and high tau pathology population.**

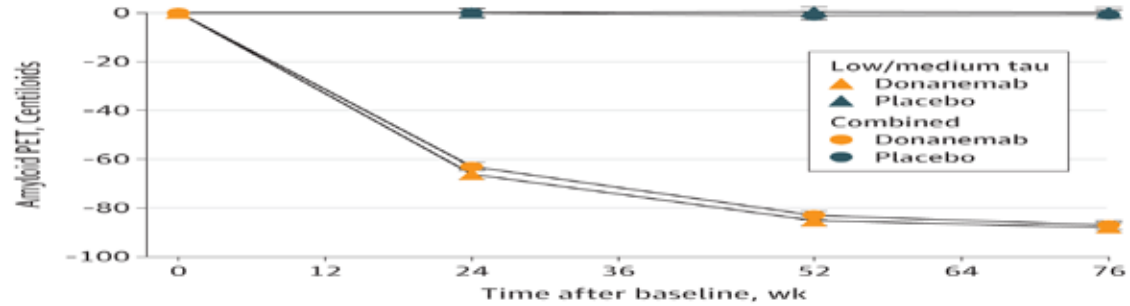
Trial Registration ClinicalTrials.gov Identifier: NCT04437511

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

John R. Sims, et al JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239 Published online July 17, 2023

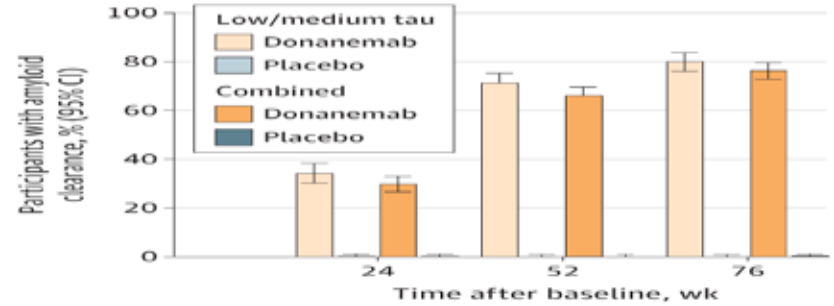
- Donanemab treatment resulted in clinically meaningful benefit (considered to be >20% slowing of clinical progression 39-41) on the iADRS and CDR-SB scales for both the low/ medium tau and combined populations, regardless of statistical model.
- Additional support for clinical relevance is the 38.6% risk reduction of disease progression as measured on the CDR-G score and the **4.4 to 7.5 months saved over the 18- month study** (low/medium tau population).
- Furthermore, an estimated 47% of participants receiving donanemab had no change in the CDR-SB at 1 year (no disease progression), compared with 29% of participants receiving placebo.

A Adjusted mean change (95% CI) in amyloid PET



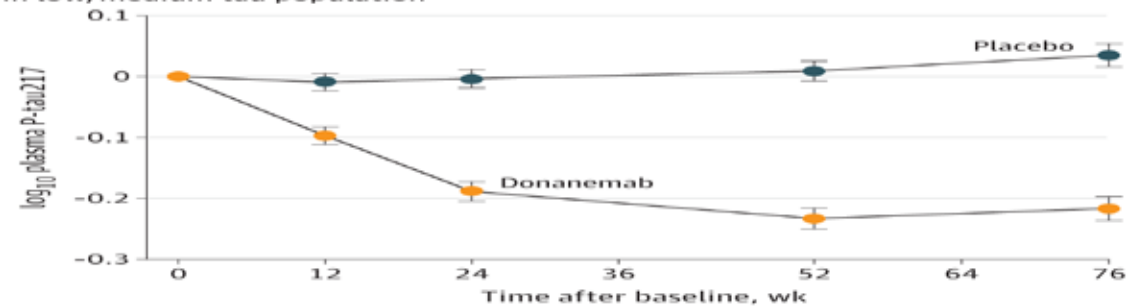
No. of participants					76-wk value, Centiloids	Difference from baseline %
Low/medium tau						
Donanemab	525	521	463	433	-88.0	-85.5
Placebo	556	552	498	470	0.2	0.2
Combined						
Donanemab	765	760	670	614	-87.0	-83.7
Placebo	812	805	729	690	-0.7	-0.7

B Participants with amyloid clearance (<24.1 Centiloids)



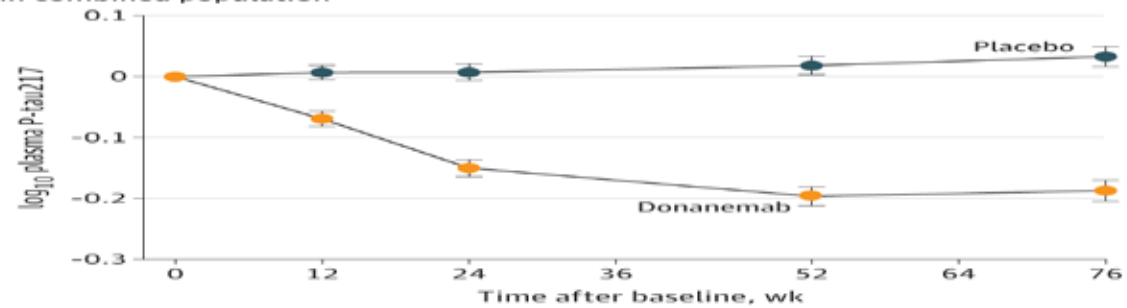
No. of participants			
Low/medium tau			
Donanemab	521	463	433
Placebo	553	498	470
Combined			
Donanemab	761	670	614
Placebo	805	730	690

C Adjusted mean change (95% CI) of $\log_{10}$ plasma P-tau217 in low/medium tau population



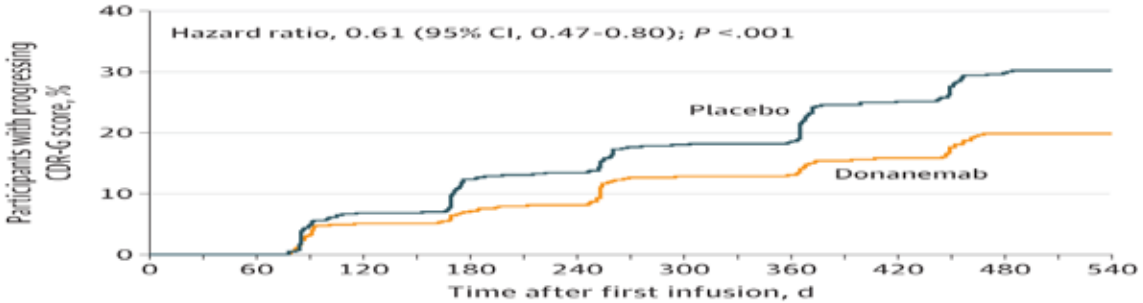
No. of participants					
Placebo	537	517	511	449	429
Donanemab	522	493	464	410	395

D Adjusted mean change (95% CI) of $\log_{10}$ plasma P-tau217 in combined population



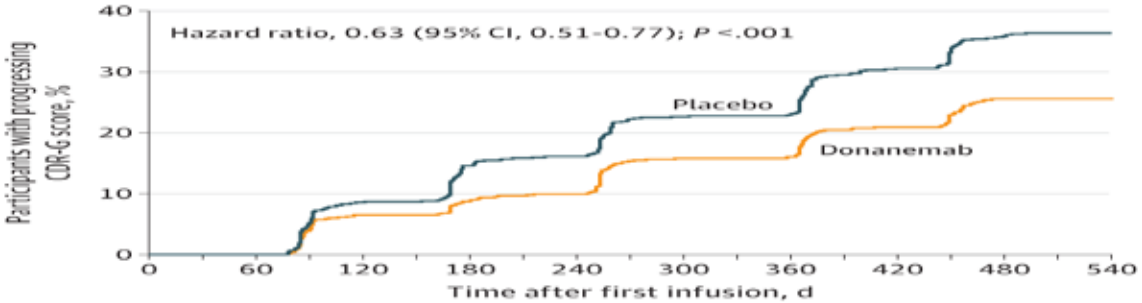
No. of participants					
Placebo	786	758	734	658	620
Donanemab	758	717	686	602	568

E CDR-G score in low/medium tau population



Treatment	No. of participants at risk 60 d	120 d	180 d	240 d	360 d	480 d
Placebo	570	529	489	474	425	345
Donanemab	552	514	492	470	412	335

F CDR-G score in combined population



Treatment	No. of participants at risk 60 d	120 d	180 d	240 d	360 d	480 d
Placebo	840	764	700	671	587	462
Donanemab	801	737	696	696	575	474

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

John R. Sims, MD[1]; Jennifer A. Zimmer, MD[1]; Cynthia D. Evans, PhD[1]; et al

- Treatment with donanemab was associated with ***significant safety risks.***
- Three deaths were determined to be drug related among participants who developed ***serious amyloid-related imaging abnormalities or brain bleeding and swelling.***
- Donanemab ***decreased whole-brain volume and increased ventricular volume.***
- In the treatment group, ***amyloid-related imaging abnormalities were seen in about 37%*** vs 15% in the placebo group and were seen in ***40.6% of APOE ε4 homozygotes***.
- ***Microhemorrhage occurred in 26.8%*** in the donanemab group vs 12.5% in the placebo group.

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

John R. Sims, et al JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239 Published online July 17, 2023

- Key Points Question Does donanemab, a monoclonal antibody designed to clear brain amyloid plaque, provide clinical benefit in early symptomatic Alzheimer disease?
- Findings In this randomized clinical trial that included 1736 participants with early symptomatic Alzheimer disease and amyloid and tau pathology, the least-squares mean change in the integrated Alzheimer Disease Rating Scale score (range, 0-144; lower score indicates greater impairment) at 76 weeks was −6.02 in the donanemab group and −9.27 in the placebo group for the low/medium tau population and −10.19 in the donanemab group and −13.11 in the placebo group in the combined study population, both of which were significant differences.
- **Meaning Among participants with early symptomatic Alzheimer disease and amyloid and tau pathology, donanemab treatment significantly slowed clinical progression at 76 weeks.**

Donanemab inclusion criteria

- **Progressive memory loss noticeable by informant for at least one year.**
- **Diagnosis of MCI due to AD or Mild Dementia due to AD established by comprehensive Neurological evaluation.**
- **MMSE or equivalent of >20/30, < 28, SAGE >10, MOCA >17,**
- **Proof of Amyloid status established by amyloid Brain PET, P-217 plasm test or CSF biomarkers for AD.**
- **Inclusion criteria for tau pathology: Low/medium or high tau indicated by standardize uptake vlue ration >1.10 or positive read assessed by 18F-flortaucipir PET imaging.**
- **Recent MRI brain including DWI, SWI, FLAIR, T1 images without evidence of strokes, TBI, ICH, Tumors, NPH, ARIAE/H.**
- **APOE genotype not homozygotes for E4/4**
- **IV infusion every 4 weeks: Infusion 1,2 and 3: 700mg. Infusion 4 and beyong 1400mg.**
- **Obtain a recent baseline brain MRI prior to initiating treatment with KISUNLA. Obtain an MRI prior to the 2nd, 3rd, 4th and 7th infusions.**

Donanemab Exclusion Criteria

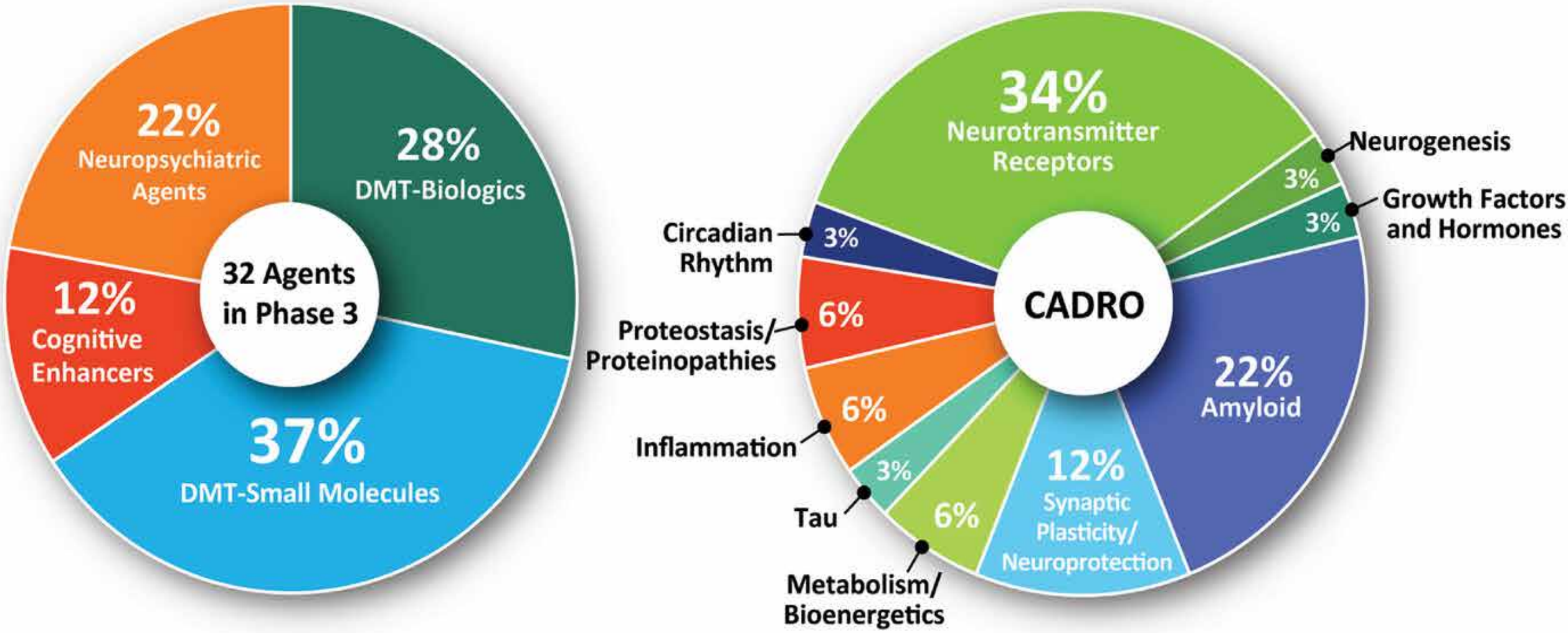
- Memory problems of duration of less than six months duration, not noticeable by informant for at least a year.
- No formal diagnosis of MCI or Mild Dementia Stage due to AD established by Neurologist.
- No proof of amyloid status (Amyloid Brain PET or CSF biomarkers for AD).
- Low Tau pathology.
- P-tau 181 pathology
- APOE4 genotype (homozygote or heterozygote)
- Pacemaker, metal brain aneurysm clip, or other metal object, or other reason that will not allow the patient to have an MRI scan.
- International normalized ration (INR)>1.5, platelet count<50000, or untreated bleeding disorder.
- If female, is the patient pregnant or breastfeeding.
- If female and of child-bearing potential, is the patient unwilling or unable to practice contraception.

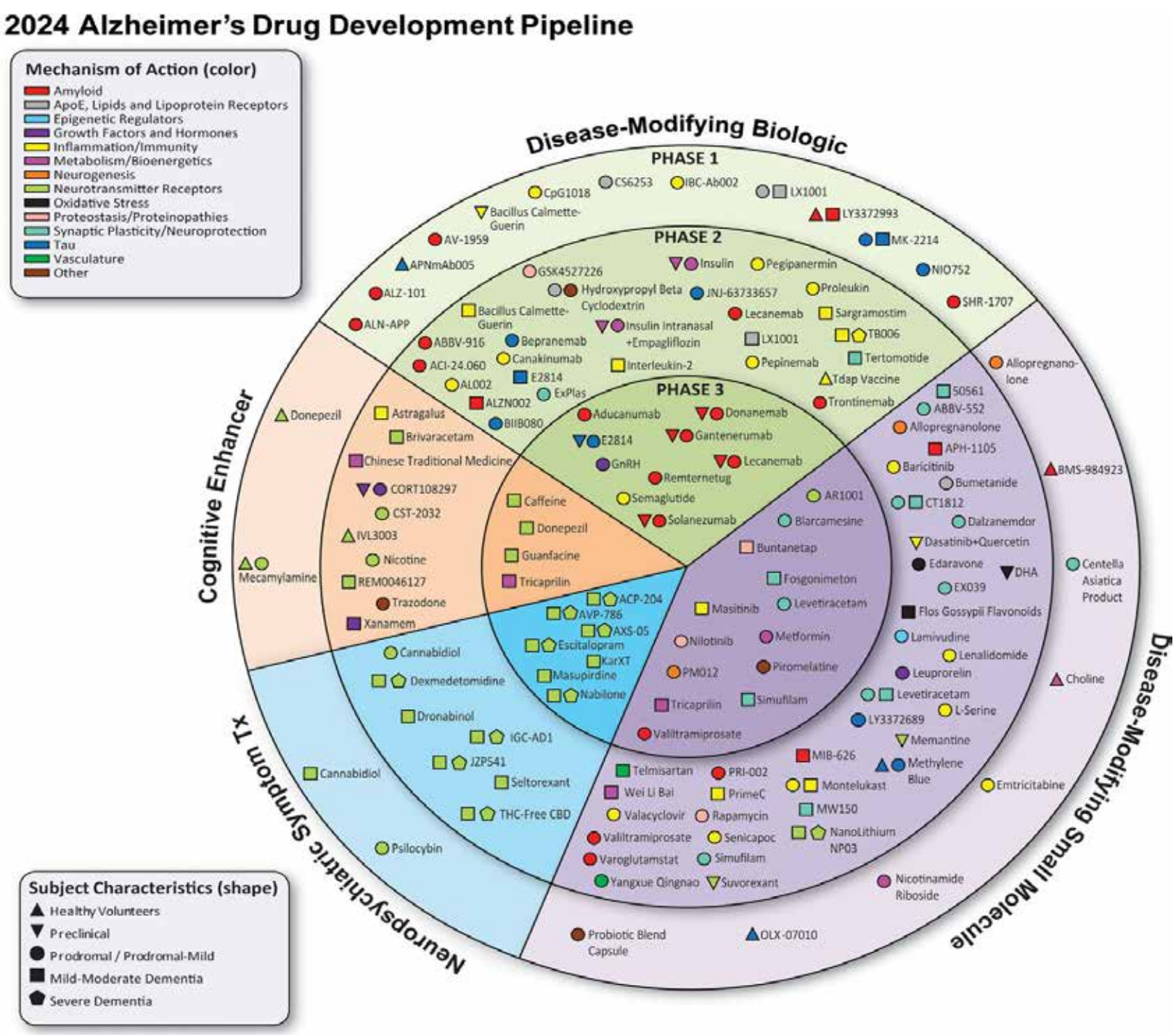
- Concurrent Illness
- Clinically important abnormality
- Significant neurological disease
- History of Cancer
- Age >85
- Elevated liver enzymes
- Caregiver circumstances
- Presence of ARIA:
- ARIA E
- >4 microhemorrhages, one area > 1cm, any superficial siderosis

Side effects

	LECANEMAB	DONANEMAB
ARIA-E (cerebral edema)	12.6% (32.6% APOE 4/4)	24% (40.6% APOE 4/4)
ARIA-H (cerebral microherrhages)	17.4% (39% APOE 4/4)	21%
Infusion reactions	24.6%	9%
Treatment with thormbolytics for stroke management	NO	NO
Anticoagulation	No	NO
MRI requirements	**Obtain MRI within a year prior to initiation of treatment. Obtain MRI brain prior to the 5th, 7th, 14th and 26th infusion.**	**Obtain a recent baseline brain MRI prior to initiating treatment with KISUNLA. Obtain an MRI prior to the 2nd, 3rd, 4th and 7thand 26th infusions.**

CUMMINGS ET AL.2024 FIGURE 3 Mechanisms of action of agents in Phase 3 Alzheimer clinical trials as classified using 4 categories of therapeutic purpose (left) or the Common Alzheimer's Disease Research Ontology (CADRO) approach (right)(figure © J Cummings; M de la Flor, PhD, Illustrator)





There are 48 Phase 3 trials assessing 32 drugs (Table 1; Figure 3). Sixty six percent of agents (N = 21) in Phase 3 are DMTs including nine biologics (43% of DMTs) and 12 small molecules (57%). There are four (12% of Phase 3 agents) cognitive enhancing agents and seven (22% of Phase 3 agents) neuropsychiatric agents in Phase 3. There are nine new trials assessing eight drugs since the Index Date of January 1, 2023

Clinical trial in patients with Down Syndrome

- ALADDIN – Amyloid Lowering for Alzheimer's in Down's with Donanemab INvestigation ▪ A Randomized, Double-Blind, Placebo-Controlled, Phase 4 Dose-Escalation Study Evaluating the Safety, Tolerability, and Efficacy of Donanemab in Adults with Down Syndrome ▪ Led by Michael Rafii, MD, PhD, Alzheimer's Therapeutic Research Institute, Keck School of Medicine USC

Conclusions

- Alzheimer's disease as a **biological entity**, defined by positive biomarkers for amyloid and tau.
- **An abnormal biomarker result is sufficient to establish a diagnosis of AD and to inform clinical decision making throughout the disease continuum.**

- **Most recent revised criteria are based on emergence of fluid biomarkers, approval of disease modifying therapies, interchageability of biomarkers.**
- The clinical use of **AD biomarkers** is presently intended for the evaluation of **symptomatic individuals**, not cognitively unimpaired individuals
- **Early initiation of pharmacological management** (standard of care recommendations) and disease modifying treatments should be offered upon establishment of diagnosis of symptomatic Alzheimer's Disease.

Questions

1.The clinical use of Alzheimer's Disease biomarkers is presently intended for the evaluation of symptomatic individuals, not cognitively unimpaired individuals

True (correct)

False

2. The biological diagnosis of Alzheimer's Disease is different than the clinical diagnosis of Dementia.

True (correct)

False

Alzheimer's disease as a biological entity defined by positive biomarkers for amyloid and tau.

Clinical diagnosis of Dementia is independent of biomarker status and require the involvement of at least two domains of cognition.

Combination therapies in clinical trials

- In the 2024 Alzheimer's disease drug development pipeline, there are 164 clinical trials assessing 127 drugs (Alzheimer's Dement. 2024;10:e12465)
- **Combination therapies** are present in the 2024 AD drug development pipeline:
- Tdap, a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine associated with a reduction in the occurrence of AD in epidemiologic studies.
- The Dominantly Inherited Alzheimer's Disease—Treatment Unit (DIAN-TU) will include assessment of the combination of lecanemab, an anti-amyloid agent, and E2814 and antitau agent.
- Several trials are assessing the combination of dasatinib and quercetin for its senolytic activity in AD.
- Combination of insulin and empagliflozin addresses metabolic and bioenergetic pathways.
- Combination of dronabinol (tetrahydrocannabinol) and palmitoylethanolamide (an endogenous cannabinoid with putative antiinflammatory properties) is being used to treat agitation in AD.
- Pharmacokinetic combinations are also evident in the pipeline. AVP786 is a putative anti-agitation agent consisting of dextromethorphan and quinidine.
- AXS-05 is being assessed as an anti-agitation agent consisting of dextromethorphan and bupropion.
- KarXT, consisting of a combination of this xanomeline and trospium, is an being tested as an antipsychotic agent.
- Trontinemab, a combination of gantenerumab and a transferrin-based brain-shuttle.
- Combination of aducanumab with focused ultrasound to increase the entry of aducanumab into the brain through the blood-brain barrier. Alzheimer's Dement. 2024;10:e12465

Self-Administered Gerocognitive Examination: Longitudinal cohort testing for the early detection of dementia conversion. AZRT-D-21-00371R2 Alzheimer's Research & Therapy 13, Article number: 192 (2021).
Douglas W Scharre, Shu ing Chang, Haikady N Nagaraja, Natalie C Wheeler, *Maria Kataki*

- A cohort study evaluating ***annual rates of change*** was performed on 665 consecutive patients from Ohio State University Memory Disorders Clinic. Patients with at least two visits 6 months apart evaluated with SAGE and MMSE and classified according to standard clinical criteria as subjective cognitive decline (SCD), mild cognitive impairment (MCI), or Alzheimer's disease (AD) dementia were included. ***The pattern of change in SAGE scores was compared to MMSE***. One way and repeated measures ANOVA and linear regression models were used.
- In summary, our longitudinal retrospective study revealed that for the ***MCI converters to dementia and for the AD dementia individuals, significant changes in SAGE scores occurred at least 6 months earlier than significant changes in MMSE scores.***
- The annual rate of decline in SAGE scores, just under two points per year, is similar for individuals who have MCI due to AD and for those with mild to moderate AD dementia while the MMSE declines more slowly for those with MCI due to AD. ***SAGE aids in the identification of MCI status and is sensitive to cognitive changes over time.***

- SAGE test website. https://wexnermedical.osu.edu/brain-spine-neuro/memory-disorders/sage.

Self Administered Gerocognitive Examination

How Well Are You Thinking?

Please complete this form in ink **without** the assistance of others.

Name_____ Date of Birth ____/____/____

How far did you get in school?_____ I am a Man_____ Woman_____

I am Asian_____ Black_____ Hispanic_____ White_____ Other_____

Have you had any problems with memory or thinking? Yes_____ Only Occasionally_____ No_____

Have you had any blood relatives that have had problems with memory or thinking? Yes_____ No_____

Do you have balance problems? Yes_____ No_____

If yes, do you know the cause? Yes (specify reason)_____ No_____

Have you ever had a major stroke? Yes_____ No_____ A minor or mini-stroke? Yes_____ No_____

Do you currently feel sad or depressed? Yes_____ Only Occasionally_____ No_____

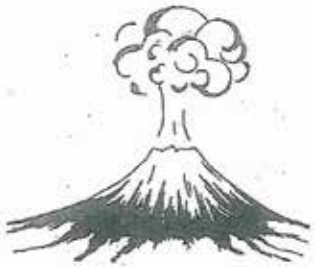
Have you had any change in your personality? Yes (specify changes)_____ No_____

Do you have more difficulties doing everyday activities due to thinking problems? Yes_____ No_____

1. What is today's date? (from memory – no cheating!) Month_____ Date_____ Year_____

2. Name the following pictures (don't worry about spelling):

_____



_____

Answer these questions:

3. How are a watch and a ruler similar? Write down how they are alike. They both are… what?

_____

4. How many nickels are in 60 cents? _____

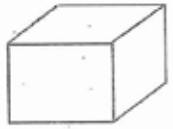
5. You are buying $13.45 of groceries. How much change would you receive back from a $20 bill?

_____

6. Memory Test (memorize these instructions). Do later only after completing this entire test:

At the bottom of the very last page: Write "I am done" on the blank line provided.

7. Copy this picture:



8. Drawing test

- Draw a large face of a clock and place in the numbers
- Position the hands for 5 minutes after 11 o'clock
- On your clock, label "L" for the long hand and "S" for the short hand

Self Administered Gerocognitive Examination

9. Write down the names of 12 different animals (don't worry about spelling):

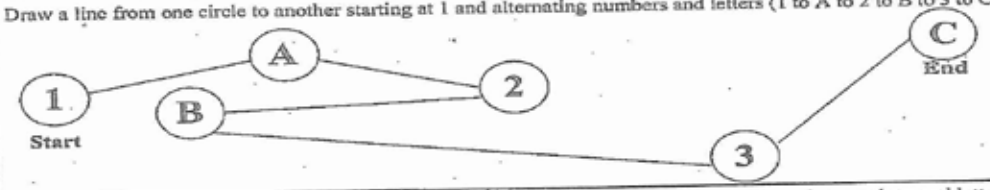
_____ _____ _____ _____

_____ _____ _____ _____

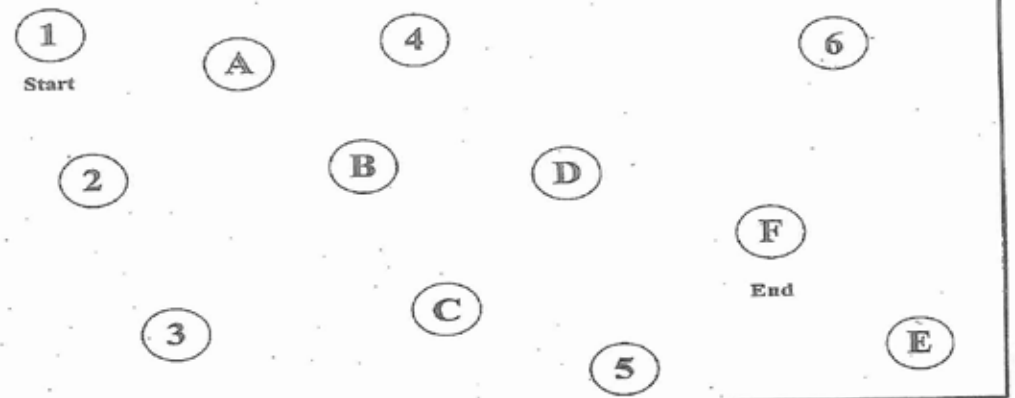
_____ _____ _____ _____

Review this example (this first one is done for you) then go to question 10 below:

Draw a line from one circle to another starting at 1 and alternating numbers and letters (1 to A to 2 to B to 3 to C).

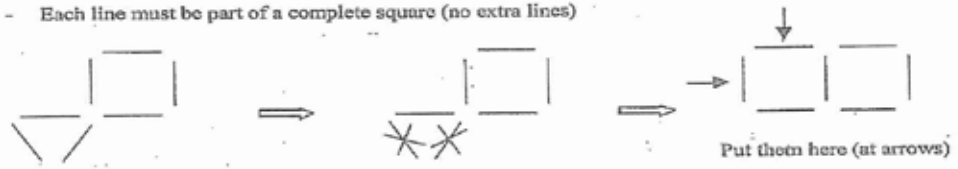


10. Do the following: Draw a line from one circle to another starting at 1 and alternating numbers and letters in order before ending at F (1 to A to 2 to B and so on).



Review this example (this first one is done for you) then answer question 11 below:

- Beginning with 1 triangle and 1 square
- Move 2 lines (marked with an X)
- To make 2 squares and no triangle
- Each line must be part of a complete square (no extra lines)



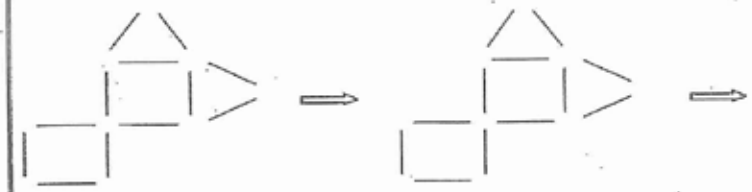
1 triangle, 1 square (Example)

Move these 2 lines (Example)

Put them here (at arrows) Makes 2 squares (answer) (Example)

11. Solve the following problem:

- Beginning with 2 squares and 2 triangles
- Move 4 lines (mark with an X)
- To make 4 squares and no triangles
- Each line must be part of a complete square (no extra lines)



2 squares, 2 triangles

Move 4 lines Mark with an X

Draw answer here 4 squares

12. Have you finished? _____

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- Four hundred twenty-four individuals (40 SCD, 94 MCI non-converters to dementia, 70 MCI converters to dementia (49 to AD dementia and 21 to non-AD dementia), 220 AD dementia) met inclusion criteria.
- SAGE and MMSE scores declined respectively at annual rates of 1.91 points/year ($p < 0.0001$) and 1.68 points/year ($p < 0.0001$) for MCI converters to AD dementia, and 1.82 points/year ($p < 0.0001$) and 2.38 points/year ($p < 0.0001$) for AD dementia subjects. SAGE and MMSE scores remained stable for SCD and MCI non-converters.
- **Statistically significant decline from baseline scores in SAGE occurred at least 6 months earlier than MMSE for MCI converters to AD dementia (14.4 vs. 20.4 months), MCI converters to non-AD dementia (14.4 vs. 32.9 months), and AD dementia individuals (8.3 vs. 14.4 months).**