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Biomarkers of Alzheimer's Disease: what to know in primary care

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I. I have no financial disclosures

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Objectives

1. Understand the challenges posed by the updated “2024 Revised Criteria for Diagnosis and Staging of Alzheimer’s Disease: Alzheimer’s Association Workgroup”
2. Describe the role and utility of specific biomarkers available for aiding in the diagnosis of Alzheimer’s Disease (AD)
3. Recognize the co-evolution of biomarkers and anti-amyloid treatment for AD
4. Understand the current FDA-approved anti-amyloid treatments for AD

A dementia diagnosis:

1. Impairment in ≥1 cognitive domain
2. Functional loss
3. Progression over time

DSM-5: Major Neurocognitive Disorder

DSM-5 criteria for major neurocognitive disorder due to Alzheimer disease

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*:
Learning and memory.
Language.
Executive function.
Complex attention.
Perceptual-motor.
Social cognition.
B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively in the context of a delirium.
D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia).
E. There is insidious onset and gradual progression of impairment in at least two cognitive domains.
F. Either of the following:
Evidence of a causative Alzheimer disease genetic mutation from family history or genetic testing.
All three of the following are present:
1) Clear evidence of decline in memory and learning and at least one other cognitive domain.
2) Steadily progressive, gradual decline in cognition, without extended plateaus.
3) No evidence of mixed etiology (ie, absence of other neurodegenerative disorders or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

DSM: diagnostic and statistical manual.
* Evidence of decline is based on: Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

2024 Revised criteria for diagnosis and staging of Alzheimer's Disease: Alzheimer's Association Workgroup

BOX 1: Fundamental principles

It is necessary to separate syndrome (clinically identified impairment) from biology (etiology).

Alzheimer's disease (AD) is defined by its biology with the following implications.

AD is defined by its unique neuropathologic findings; therefore, detection of AD neuropathologic change by biomarkers is equivalent to diagnosing the disease.

AD exists on a continuum. The disease is first evident in vivo with the appearance of disease-specific Core biomarkers while people are asymptomatic. Pathophysiologic mechanisms involved with processing and clearance of protein fragments may be involved very early in the disease process, but these are not yet well understood.

Symptoms are a result of the disease process and are not necessary to diagnose AD.

Unimpaired individuals with abnormal biomarker test results are at risk for symptoms due to AD. They are not at risk for a disease they already have.

Clinical syndromes commonly seen with AD may also be caused by disorders other than AD, and therefore clinical presentation alone is not diagnostic of AD.

The same AD biology may result in different phenotypic presentations.

TABLE 1 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[a]	Tau PET
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 MRI or CT, WMH
S α-synuclein	αSyn-SAA[a]	

Jack CR, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimer's Dement. 2024;20:5143–5169


Experts in the field do *not* agree on these revised criteria!

AGS response to the 2024 revised criteria and staging of Alzheimer's Disease

- Insufficient research on **asymptomatic persons** with abnormal biomarkers
  - Premature to expand guidelines from research to clinical care
  - Impact of clinical diagnosis of Alzheimer's Disease when there are no symptoms
- Data used in revised criteria is **not representative** of the many people living with Alzheimer's Disease
  - Age, gender, racial and ethnic representation needs to be generalizable
- Requests workgroup members **disclose any conflicts of interest**; there are members with considerable ties to related pharmaceutical companies

Workup of cognitive impairment

- History of cognitive changes, behaviors, exploring other etiologies to cognitive changes
- Functional status ADLs/IADLs
- Social history education level, occupation, substance use, social support
- Cognitive screen MoCA or SLUMS, +/- formal neuropsychology testing
- Mood disorder screen PHQ9 or GDS, GAD7
- Neurologic exam for focal deficits, gait and balance, parkinsonism
- Labs: CBC, CMP, TSH reflex, B12 +/- RPR, HIV (if risk factors) +/-APOE e4 (if considering anti-amyloid tx)
- Structural imaging – CT WO brain, MRI WO brain
- Biomarkers: next slides

Biomarker

(BY-oh-MAR-ker)

A biological molecule found in blood, body fluids, or tissue that is a sign of a normal or abnormal process, or of a condition or disease.

Examples:

A1C

PSA

TSH

troponin

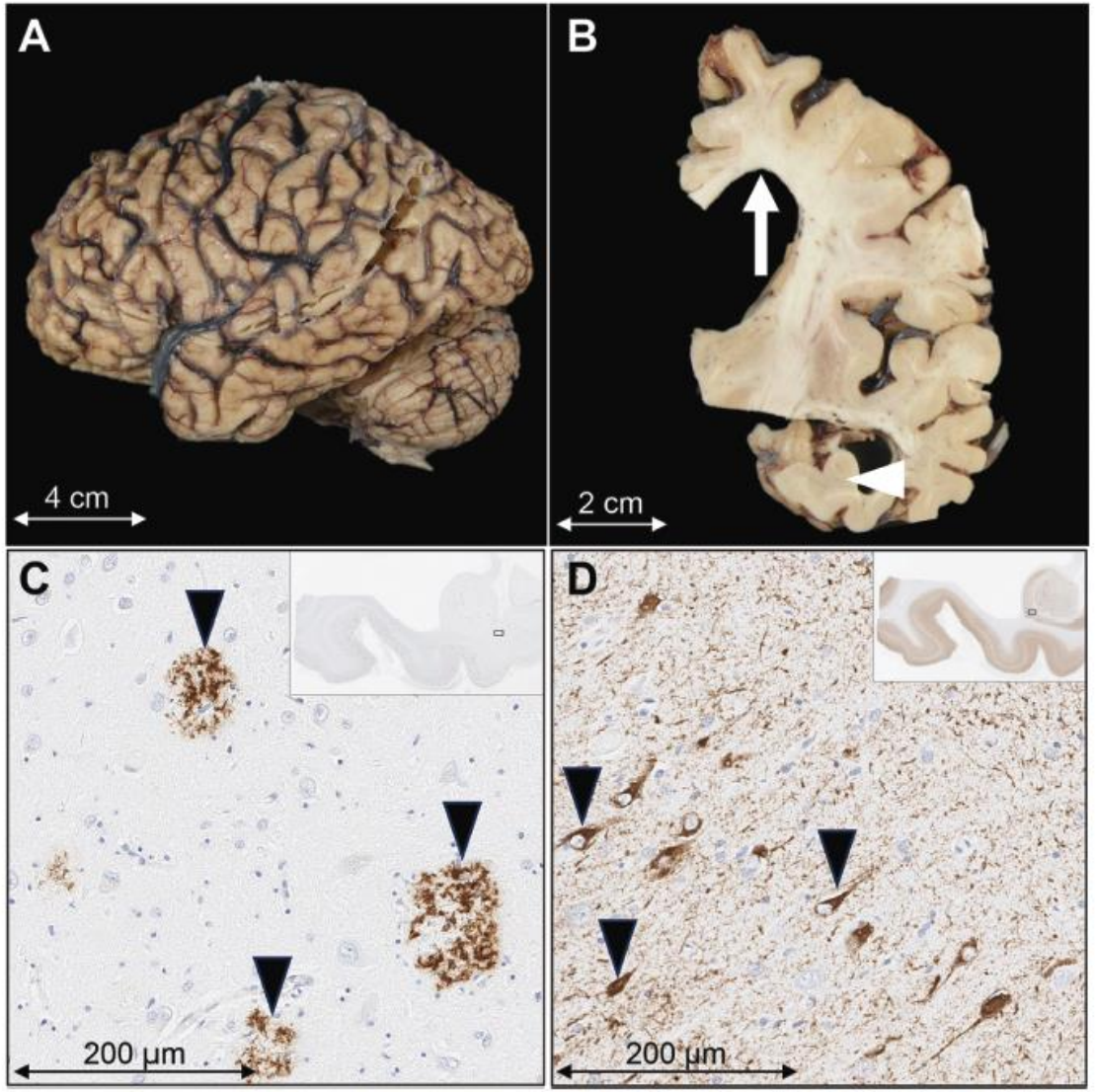

FIGURE 1-2
Typical Alzheimer disease neuropathologic change at autopsy. Macroscopic changes associated with Alzheimer disease include generalized atrophy (*A*) with thinning of the cortical ribbon, widening of sulci, expansion of the lateral ventricles (*B, white arrow*), and prominent hippocampal volume loss (*B, white arrowhead*). Key microscopic changes include abnormal accumulation of amyloid-β (Aβ)–containing cerebral plaques (*C, black arrowheads*) and tau-containing neurofibrillary tangles (*D, black arrowheads*). Immunohistochemistry performed on hippocampal sections (*C, D, insets*) with antibodies directed against Aβ42 (clone 6F/3D) and phosphorylated tau (AT8 phospho tau).

Day, G. Diagnosing Alzheimer's Disease. Continuum. 2024. 30(6)1584-1613

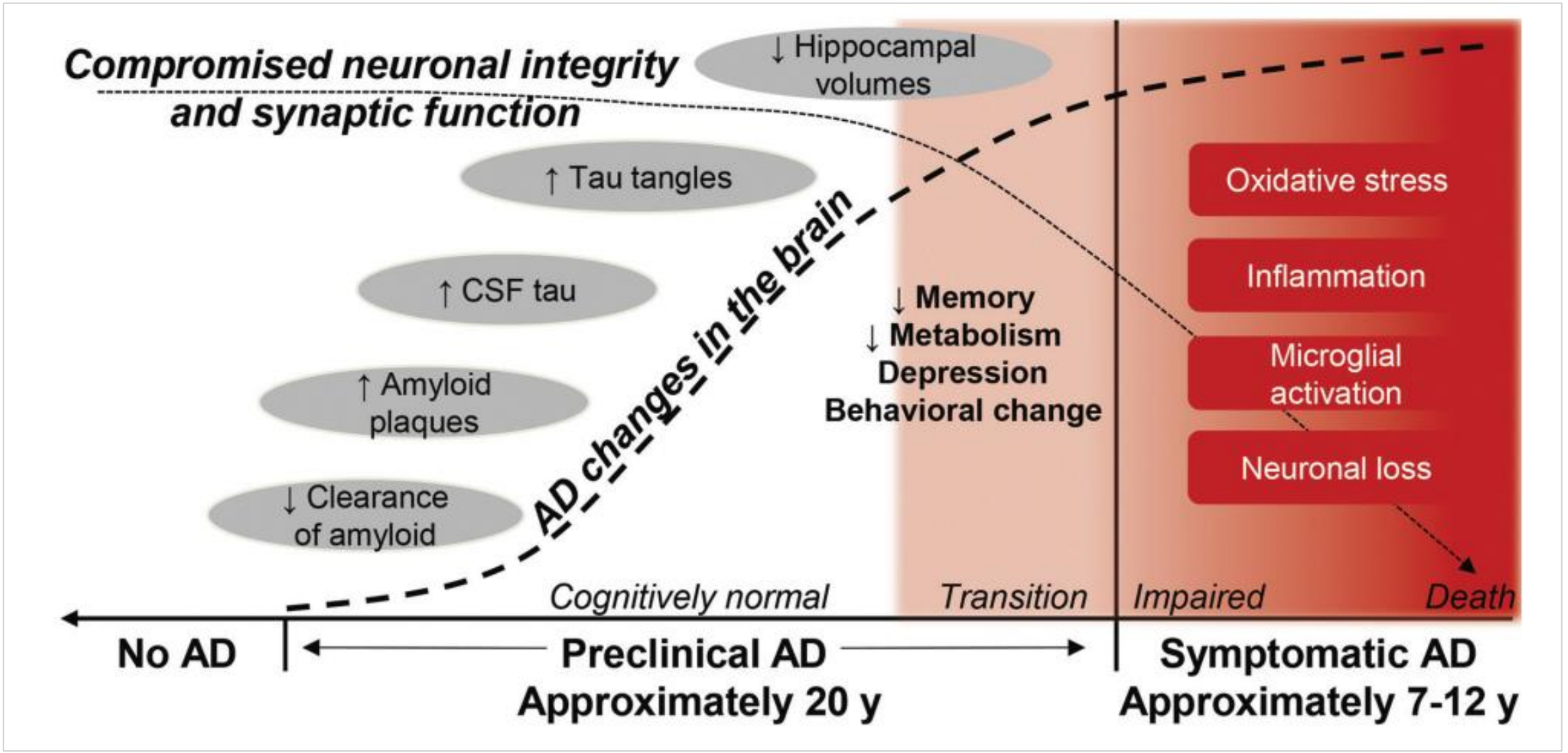

Figure 1-1 The Lifespan of Alzheimer Disease

Day, G. Diagnosing Alzheimer's Disease. Continuum. 2024. 30(6)1584-1613

Alzheimer's Disease: Fluid Biomarkers

- **CSF biomarkers**
  - Aβ42/40 ratio
  - p-tau181/Aβ42
  - t-tau181/Aβ42
- **Blood-based biomarkers**
  - p-Tau217 (equivalent to FDA approved CSF biomarkers and amyloid-PET, Sn/Sp >90%)
  - Aβ42/40 ratio
  - p-Tau217 with Aβ42/40 ratio
  - Others: p-Tau181, p-Tau 231, NfL
- **Salivary biomarkers** – *in studies*

Alzheimer's Disease: Blood-Based Biomarkers

When to use?

- Early in disease (MCI or mild dementia) to help differentiate or support a hypothesis
- Not yet being used to evaluate disease progression or to monitor treatment response
- Not for screening of asymptomatic persons

Logistics:

- Check collection requirements
- Not covered by insurance ($200-1,500)

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Phospho-Tau 217, Plasma

Interpretive Data

Interpretive information: The Phospho-Tau 217, Plasma test is intended for use in patients aged 60 years and older who present with cognitive impairment and who are being evaluated for Alzheimer's disease and other causes of cognitive decline. The test is reported as a qualitative result (positive, negative, or indeterminate). Assay results correlate highly with the presence or absence of amyloid deposition as measured by amyloid PET scan. In a clinical validation set of 524 participants aged 60 years and over who presented with cognitive impairment, a positive result had a sensitivity of 90%, a negative result had a specificity of 90%, and 17% of results were indeterminate.

Limitations: Plasma phospho-Tau 217 must be interpreted in conjunction with other patient clinical information. It is not intended to be used as a screening test or stand-alone diagnostic test and is not intended for therapeutic monitoring. Results obtained with different assay methods or kits cannot be used interchangeably.

pTau 217 Result	Value	Interpretation
Negative	<0.13 U/mL	A test result reported as negative is consistent with absence of amyloid deposition in brain as detected by amyloid PET scan. A negative result reduces the likelihood that a patients cognitive impairment is due to Alzheimer's disease.
Indeterminate	>=0.13 to <0.20 U/mL	A test result reported as indeterminate indicates that amyloid plaques may or may not be present. Additional diagnostic testing, such as other laboratory testing or amyloid PET scan, should be considered based on clinical presentation. If symptomatology persists or evolves, repeat testing may be helpful.
Positive	>=0.20 U/mL	A test result reported as positive is consistent with the presence of amyloid deposition in brain as measured by amyloid PET scan. A positive result by itself does not establish a diagnosis of Alzheimer's disease or other cognitive disorder.

Blood-Based Biomarkers: Patient Scenarios

- Differentiating neurodegenerative disease from mood disorders, attention disorders
- Differentiing different dementia types when it is not clear
- Identifying neurodegenerative disease when there is fixed cognitive impairment at baseline
- Patient wants objective marker to support diagnosis
- Patient interested in anti-amyloid treatment

Racial & Ethnic Differences

Characterizing Plasma Biomarkers of Alzheimer's in a Diverse Community-Based Cohort: A Cross-Sectional Study of the HAB-HD Cohort

James R. Hall[1], Melissa Petersen[1,2], Leigh Johnson[1] and Sid E. O'Bryant[1] on behalf of the Health and Aging Brain Study (HABS-HD) Study Team*

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[2] Department of Family Medicine, University of North Texas Health Science Center, Fort Worth, TX, United States

Background: Due to their low cost, less invasive nature, and ready availability, plasma biomarkers of Alzheimer's disease have been proposed as one-time screening tools for clinical trials and research. The impact of ethnoracial factors on these biomarkers has received little attention. The current cross-sectional study investigated the levels of $A\beta_{40}$, $A\beta_{42}$, total tau (t tau), and neurofilament light (NfL) across diagnoses for each of the three major ethnoracial groups in the United States in a community-based cohort of older adults.

Methods: A total of 1,862 participants (852 Mexican Americans (MAs); 775 non-Hispanic Whites (NHWs), and 235 African Americans (AAs)) drawn from The Health & Aging Brain Study—Health Disparities (HABS-HD) study were included. Diagnoses were assigned using an algorithm (decision tree) verified by consensus review. Plasma samples were assayed using Simoa technology. Levels of each biomarker were compared for the three ethnoracial groups across cognitive diagnoses using ANOVA covarying sex and age.

Results: Significant differences were found across the groups at each level of cognitive impairment. Cognitively unimpaired (CU) AA had significantly lower levels of each of the biomarkers than cognitively unimpaired MA or NHW and NHW had higher levels of $A\beta_{40}$, and NfL than the other two groups. MA had higher t tau than AA or NHW. Mild cognitive impairment (MCI) group NHW had the highest levels on all the biomarkers and AA had the lowest. NHW and MA have higher levels of $A\beta_{40}$, $A\beta_{42}$, and t tau there was no difference between the groups for $A\beta_{42}$. NHW had significantly higher levels of $A\beta_{40}$, t tau, and NfL than AA. AA had a higher $A\beta_{42}/A\beta_{40}$ ratio than either NHW or MA for CU MCI.

Conclusions: The use of plasma biomarkers of cognitive decline is promising given their advantages over other biomarkers such as CSF and imaging but as the current research shows, ethnoracial differences must be considered to enhance accuracy and

- **Lack of representation in dementia research**, both in biomarkers and treatment
- This 2022 study showed significant differences in blood-based biomarkers levels across Mexican American, Non-Hispanic White, and African Americans
- We may need normative values for different groups

Hall JR et al. Characterizing Plasma Biomarkers of Alzheimer's in a Diverse Community-Based Cohort: A Cross-Sectional Study of the HAB-HD Cohort. *Front Neurol*. 2022;13:871947

Alzheimer's Disease: Imaging Biomarkers

1. Amyloid-PET
2. Tau-PET
3. MRI w/ NeuroQuant analysis
4. FDG-PET

MRI vs CT ?

Structural imaging is the first step before other imaging biomarkers

MRI WO brain

- More detail
  - Better discrimination of gray-white matter
  - High sensitivity for cerebrovascular pathology and tumors
  - Detects microhemorrhages and superficial siderosis
- More expensive
- Takes longer (45-60 minutes)

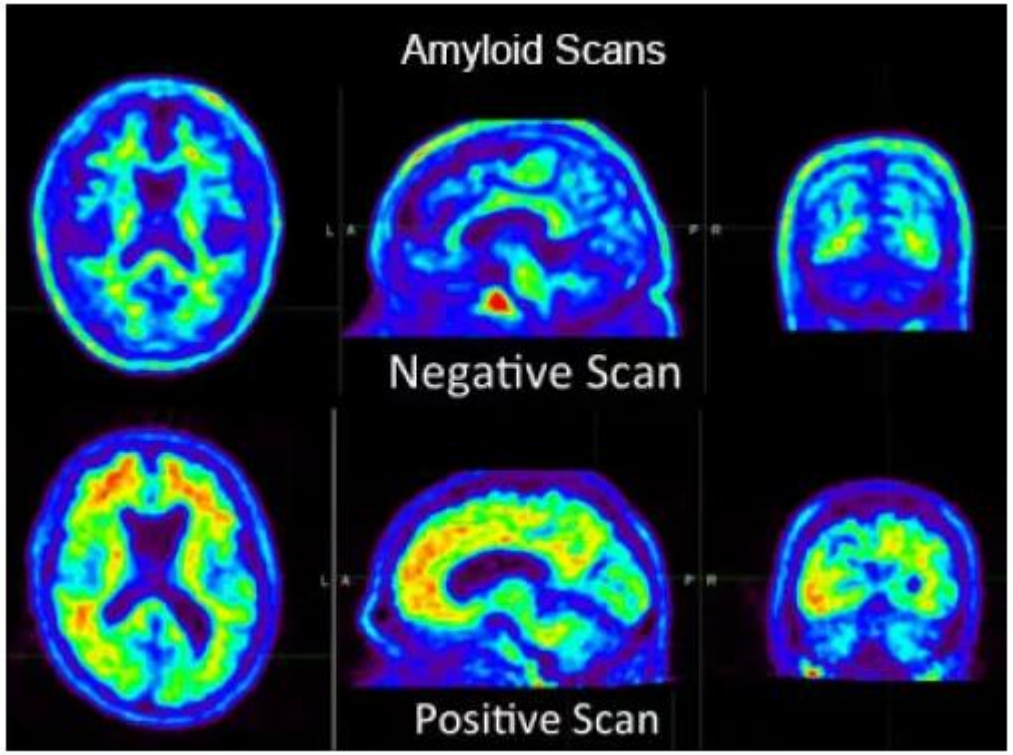
- **CT WO brain**
  - Less detail
  - Less expensive
  - Very quick (5-10 minutes)

*Check records (ER visits) for prior imaging during course of cognitive impairment

Why do structural imaging?
To rule out tumors, vascular lesions, normal pressure hydrocephalus (NPH)

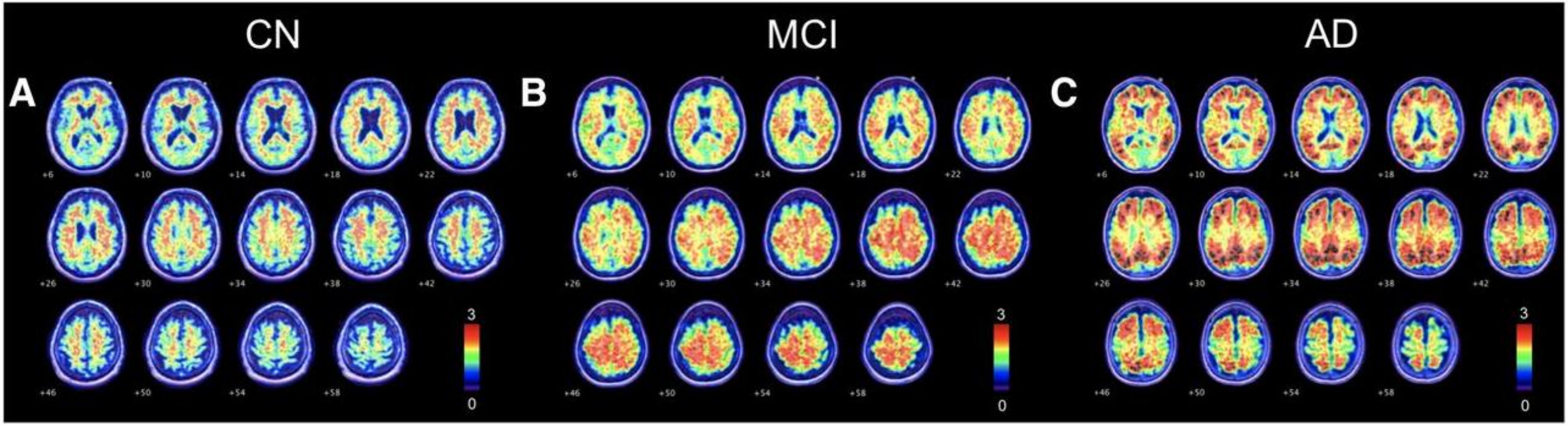
Imaging biomarkers: Amyloid-PET

- **Amyloid PET**
  - Core biomarker for AD
  - Uses amyloid tracers to detect amyloid plaques
  - High sensitivity/specificity (>90%) for amyloid pathology
  - Poor ability to detect AD stage, however, is used to measure anti-amyloid therapy effects
  - Now covered by Medicare B ($3K)



https://radiology.ucsf.edu/patient-care/services/amyloid-pet-scan-alzheimers-assessment

normal **MCI due to AD** **Dementia due to AD**



Evolution of amyloid PET positivity across AD spectrum. (A) Positive ^{11}C-PiB scan of cognitively normal (CN) participant, in which significant binding is observed in precuneus, posterior cingulate cortex, and medial prefrontal areas. (B) Positive ^{11}C-PiB scan of MCI patient, in which significant and moderate binding is observed throughout cortex. (C) Positive ^{11}C-PiB scan of AD patient, in which significant and severe binding is observed throughout cortex.

Amyloid-PET+ but asymptomatic?

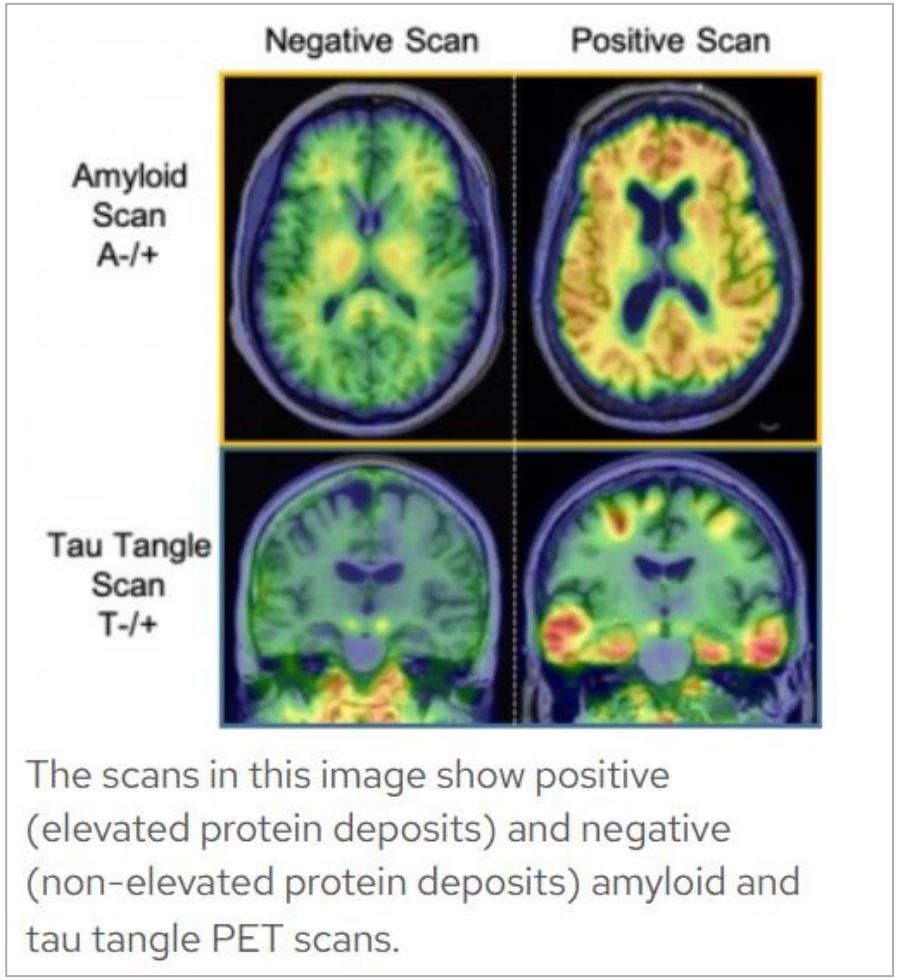
Positive amyloid-PET scans are found in 10-44% of adults 50–90 year-olds who have no cognitive impairment!

Amyloid imaging is <u>insufficient</u> to predict time to clinical conversation in prodromal or asymptomatic stages.

Chételat G et al. Amyloid-PET and ^{18}F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. *Lancet Neurol*. 2020;19(11):951-962

Imaging biomarkers: Tau-PET

- **Tau-PET**
  - Core biomarker for AD
  - Uses tau tracers, tau neurofibrillary tangles occurs later in AD
  - Tau buildup correlates with cognitive decline and disease stage (more so than amyloid)
  - Emerging use, primarily in research
  - Not covered by Medicare



The scans in this image show positive (elevated protein deposits) and negative (non-elevated protein deposits) amyloid and tau tangle PET scans.

Image from: https://adrc.wisc.edu/

Imaging biomarkers: MRI with NeuroQuant

- **MRI with NeuroQuant analysis**
  - Non-specific biomarker for AD
  - NeuroQuant software looks at volumes of key brain structures involved in AD, notably the hippocampi, and compares them to normative values
  - Calculates a Hippocampal Occupancy Score (HOC) a ratio of hippocampal to ventricle volumes, **a low HOC is associated with AD**
  - Volume changes show up later in AD course
  - Covered by Medicare

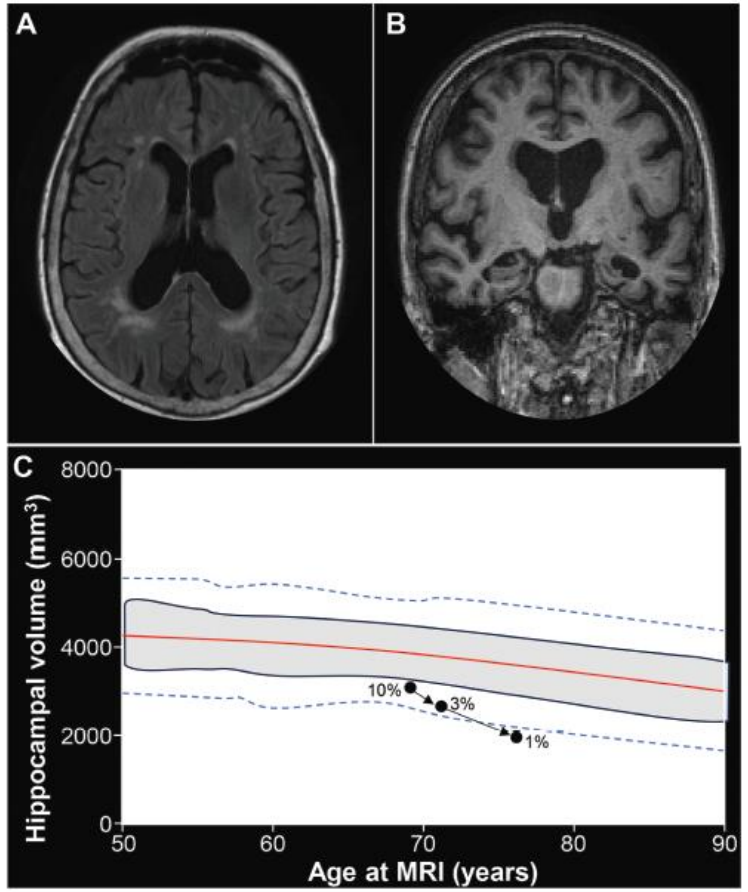
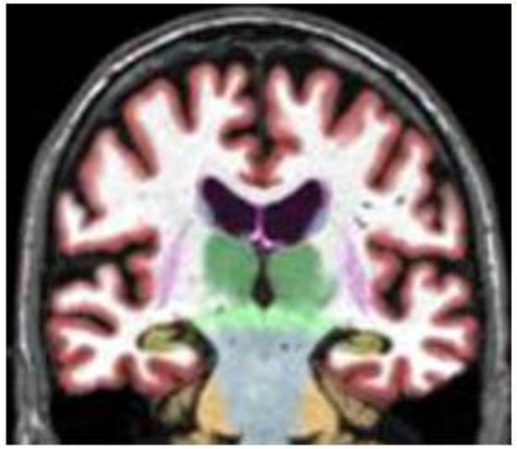
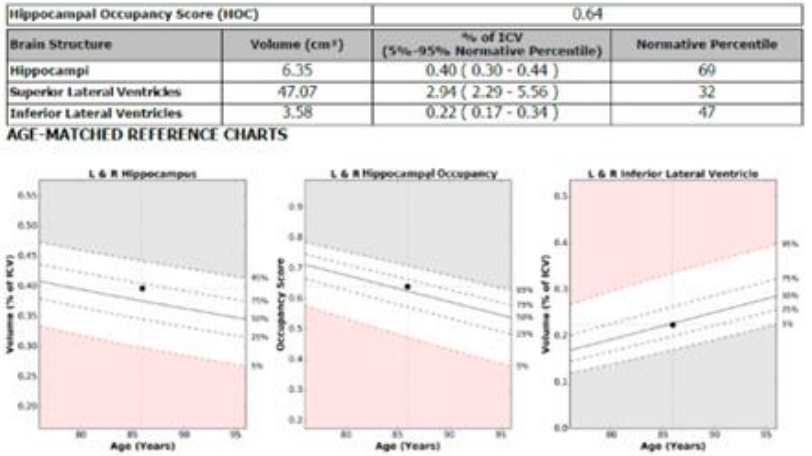
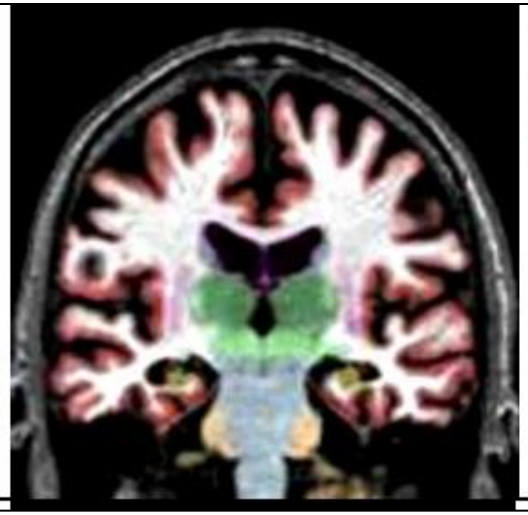
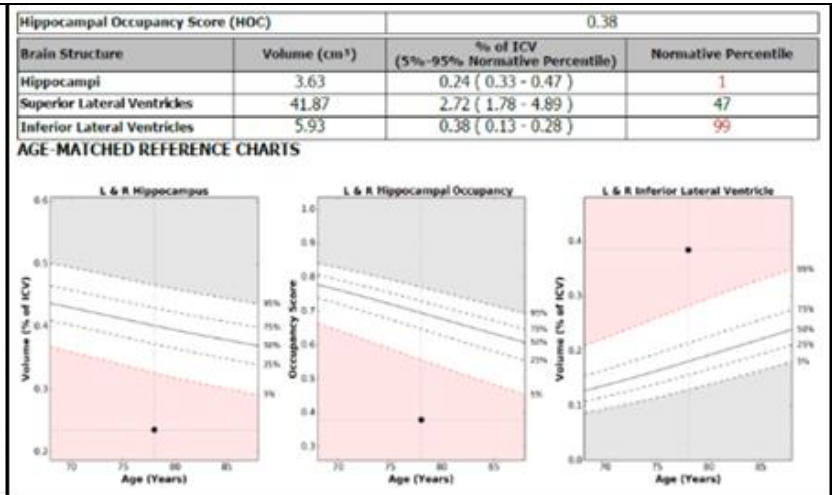


FIGURE 1-4
Imaging studies of the patient in CASE 1-1. Axial fluid-attenuated inversion recovery (FLAIR) MRI at the level of the caudates confirms diffuse global atrophy (*A*), with more pronounced involvement of the hippocampi seen on coronal magnetization-prepared rapid gradient echo (MP-RAGE) (*B*). Serial imaging confirms progressive decreases in hippocampal volumes (*C, black dots*) with increasing age. Commercial software was used to quantify volume loss, referencing volumes in age-matched cognitively normal individuals (*red line*, mean volumes; *gray-shaded areas*, ±1 SD; *dashed blue lines*, ±2 SD).

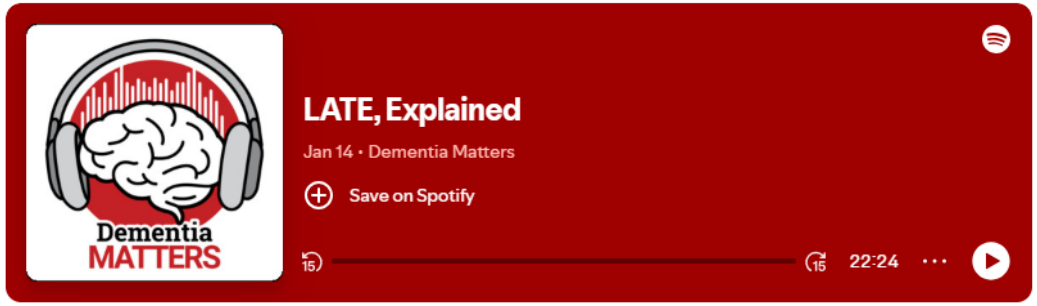
Sample Segmented MRI	Example vMRI findings	Hippocampi	Hippocampal Occupancy	Lateral Ventricles	Interpretation
		Normal volume (Not atrophied)	Normal HOC	Superior and Inferior: Normal volume (Not enlarged)	<u>Normal Scan</u>: Does not support neurodegeneration
		Low volume	Low HOC	Superior: Normal Inferior: High volume	<u>Low hippocampal volume and suggestive of **LOCAL** ex-vacuo dilatation:</u> Supports MTL-focused neurodegenerative etiology

https://medfordradiology.com/wp-content/uploads/2018/11/NeuroQuant_Understanding_Age_Related_Atrophy_Findings.pdf

Limbic-predominant Age-related TDP-43 Encephalopathy (LATE)

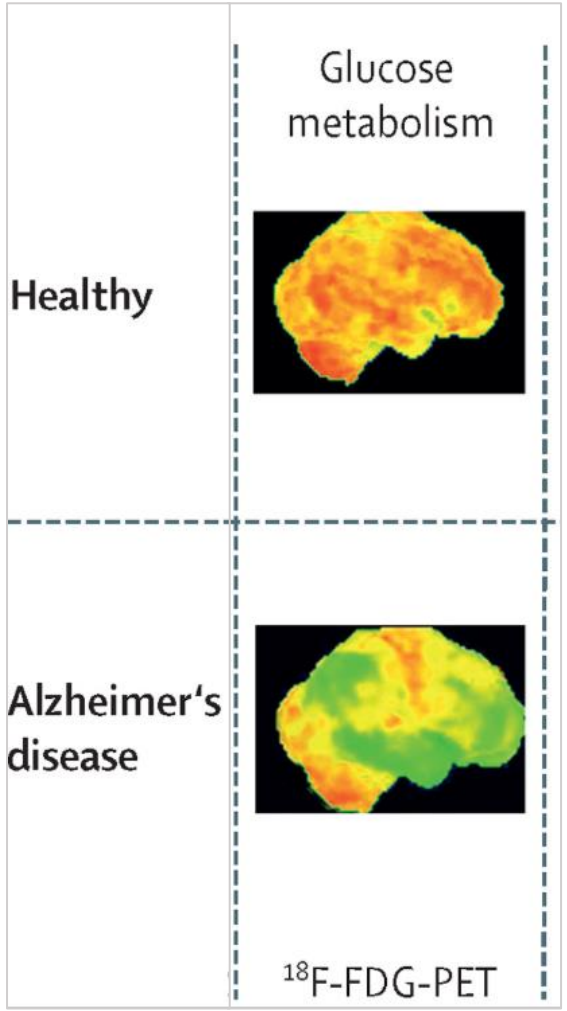
- Recently identified, AD-mimic
- Highly prevalent in late life (80+)
- Slowly progressive, amnestic syndrome (isolated memory problems)
- **Biomarkers:**
  - No specific biomarker
  - Severe hippocampal atrophy
  - Negative amyloid biomarkers *unless co-pathology with AD

Podcast: https://dementiamatters.adrc.wisc.edu/



Imaging biomarkers: FDG-PET

- **FDG-PET**
  - Non-specific biomarker for AD
  - Radionucleotide-tagged glucose, creates patterns of hypometabolism in the brain for which there are typical presentations
  - Used to differentiate AD from frontotemporal dementia (FTD)
  - Characteristic patterns of hypometabolism will show up earlier on FDG-PET than MRI in mild AD
  - Covered by Medicare



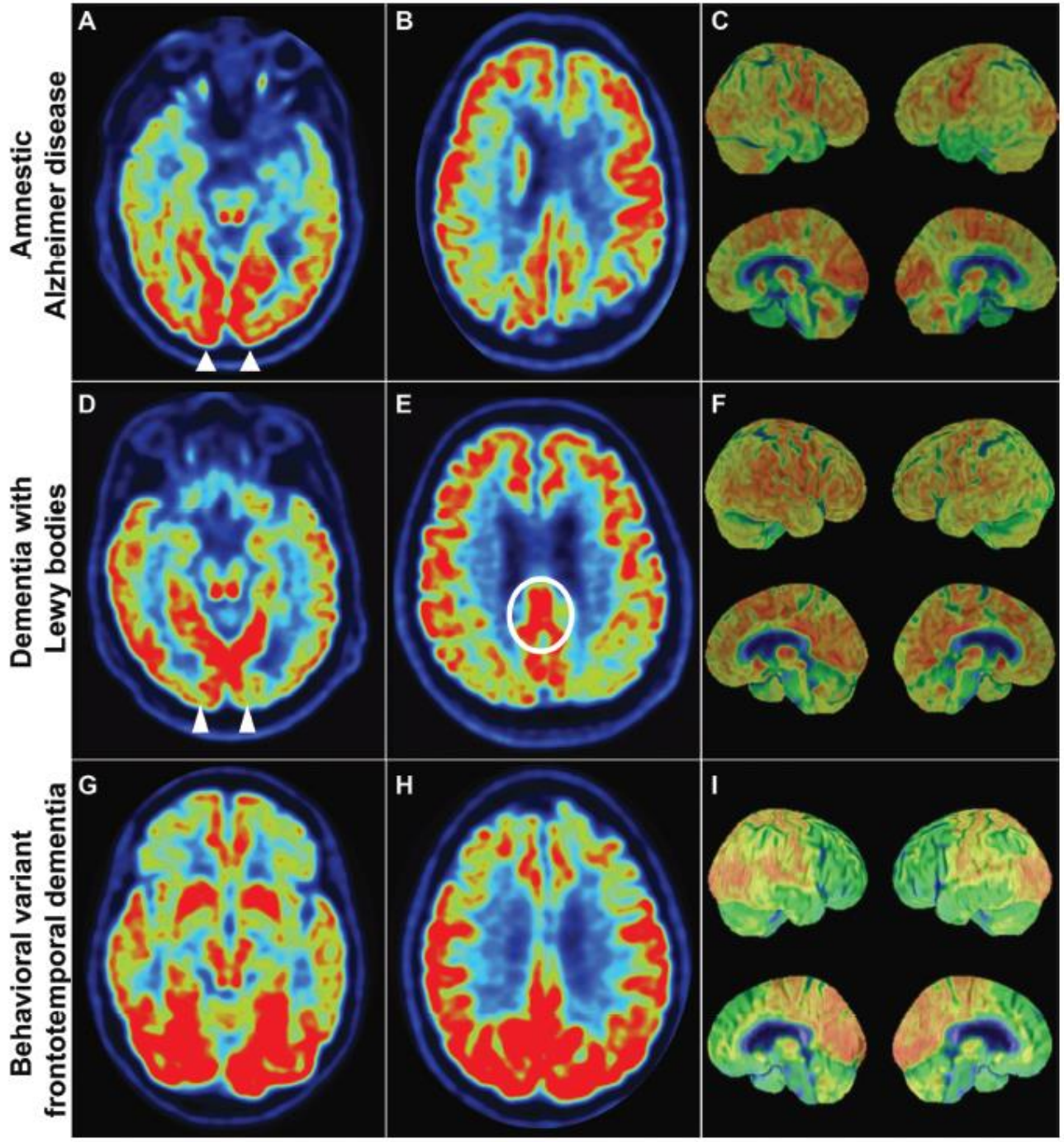


FIGURE 1-7

Expected fludeoxyglucose positron emission tomography (FDG-PET) findings in patients with typical neurodegenerative disease. Patterns of metabolism on FDG-PET are shown in patients with amnestic-predominant (typical) Alzheimer disease (*A-C*), dementia with Lewy bodies (*D-F*), and behavioral variant frontotemporal dementia (*G-I*). Alzheimer disease is classically associated with bitemporal and biparietal hypometabolism. Relative preservation of occipital metabolism distinguishes patients with typical AD from those with dementia with Lewy bodies (*A*, *D*, *white triangles*), who may also have relative sparing of metabolism within the posterior cingulate (cingulate island sign[111]; *E*, *white circle*). In contrast to Alzheimer disease and dementia with Lewy bodies, FDG-PET in behavioral variant frontotemporal dementia typically shows prominent frontal and temporal hypometabolism with relative preservation of posterior structures. FDG-PET axial images are shown at the level of the midbrain (*A*, *D*, *G*) and caudate heads (*B*, *E*, *H*). *Panels C*, *F*, and *I* depict whole-brain metabolism; warmer colors indicate greater metabolism.

Chételat G, Arbizu J, Barthel H, et al. Amyloid-PET and ^{18}F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. *Lancet Neurol*. 2020;19(11):951-962

Alzheimer's Disease: Imaging Biomarkers

- **Amyloid-PET**
  - Core biomarker for Alzheimer's Disease (AD)
  - Detect amyloid plaques, which occur earlier in disease
  - Covered by Medicare
- **Tau-PET**
  - Core biomarker for AD
  - Detects tau tangles, which occur later in disease
  - Emerging use, mostly in research
  - *Not* covered by Medicare
- **MRI with NeuroQuant analysis**
  - Non-specific biomarker for AD
  - Volume analysis of key structures in the brain impacted by AD
  - Covered by Medicare
- **FDG-PET**
  - Non-specific biomarker for AD
  - To differentiate frontotemporal dementia from AD, further evaluate the patterning of brain disease
  - Covered by Medicare

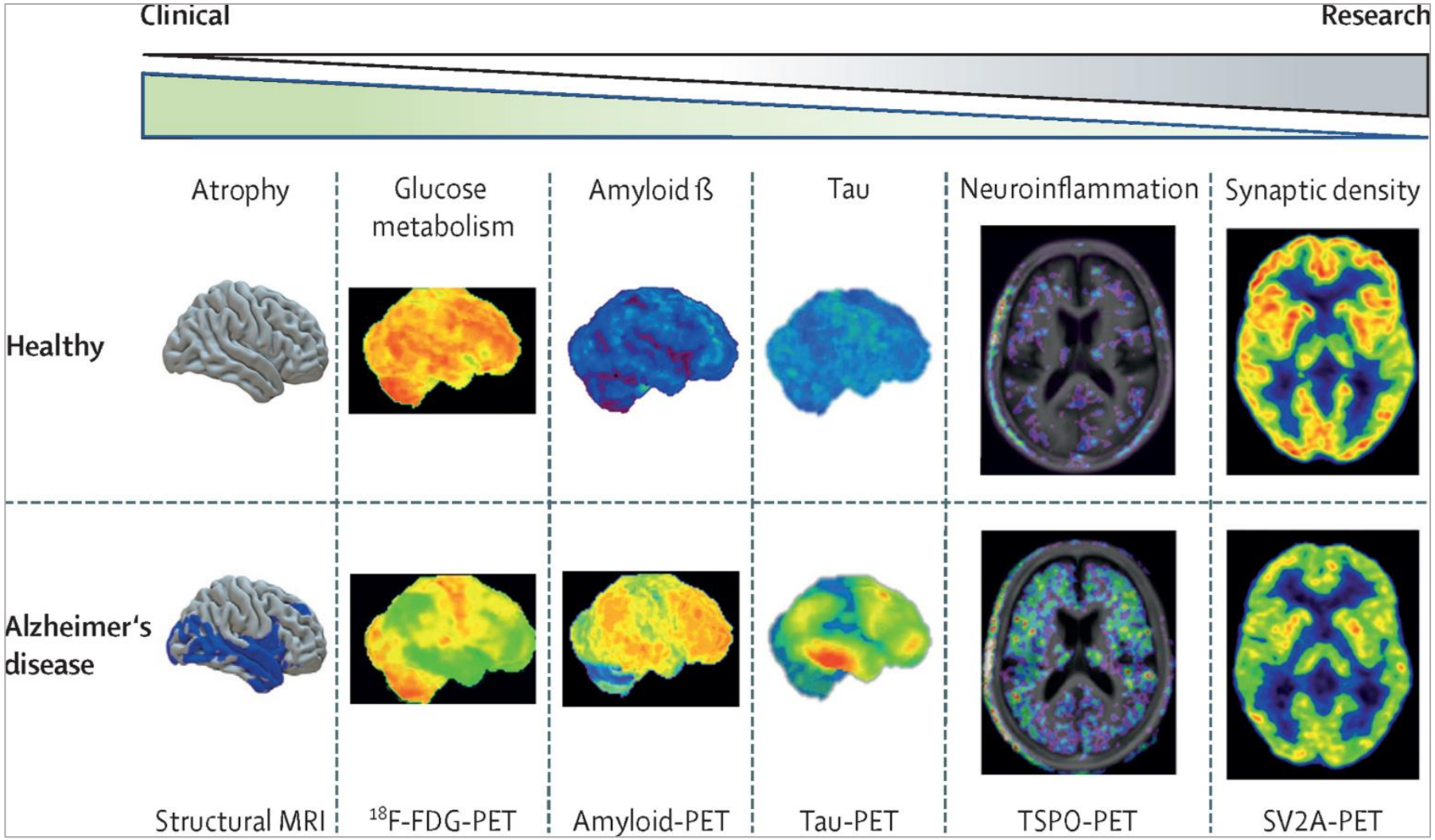


Figure 1. Neuroimaging obtained with structural MRI or PET using different radiotracers
The top row shows images from healthy controls and the bottom row from individuals with late-onset Alzheimer's disease. The different neuroimaging techniques are illustrated from the most relevant in clinical setting (left) to the most relevant for research (right). Structural MRI-based Z-score deviations of grey-matter volume in patients compared with controls, displayed in blue on the right hemisphere of a template image. ^{18}F-FDG-PET glucose metabolism are displayed as a 3D-surface projection of the right hemisphere with normal metabolism shown in yellow or red and reduced metabolism in green or blue. Amyloid-PET with ^{11}C-PiB images are displayed as a 3D-surface projection of the right hemisphere, with high amyloid burden indicated in yellow or red and no or low amyloid deposition in green or blue. Tau-PET with ^{18}F-AV-1451 images are displayed as a 3D-surface projection of the right hemisphere, with high tau-tracer retention shown in yellow or red and no or low tau-tracer retention in green or blue. TSPO-PET with ^{11}C-PK11195 images are displayed as axial slices (caudal aspect, frontal to the top) with yellow or red showing elevated TSPO expression reflecting neuroinflammation. SV2A-PET of synaptic density with ^{11}C-UCB-J images are displayed as axial slices (caudal aspect, frontal to the top) with yellow or red showing normal synaptic density and green reflecting reduced synaptic density. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. TSPO=translocator protein. SV2A=synaptic vesicle glycoprotein 2A. Images courtesy of Alexander Drzezga, University of Cologne, Germany; David Brooks, Aarhus University, Denmark; and Ming-Kai Chen, Yale School of Medicine, USA.

Chételat G et al. Amyloid-PET and ^{18}F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. *Lancet Neurol*. 2020;19(11):951-962

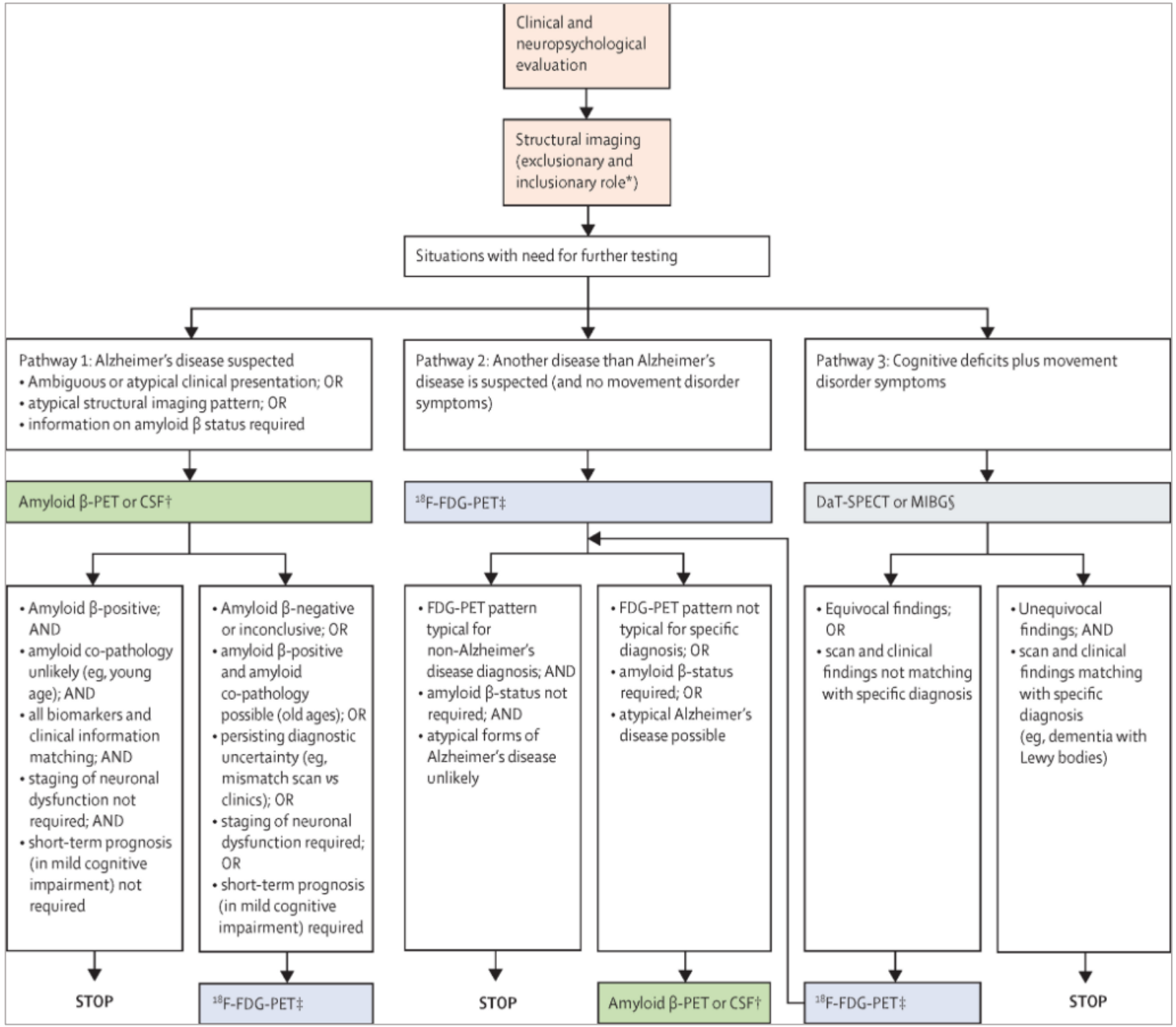


Figure 2. Proposal for a diagnostic algorithm for early and differential diagnoses of dementia

This algorithm is a theoretical proposal and further validation of the order of tests is needed (see text for details). ^{18}F-FDG=18F-fluorodeoxyglucose. mIBG=^{123}I-meta-iodobenzylguanidine. *Exclusion of neoplastic, vascular, and inflammatory changes supporting non-neurodegenerative causes and evaluation of topography of atrophy might inform on the neurodegenerative disease (but ^{18}F-FDG-PET might be more sensitive and accurate). † Whatever is established or available and preferred; Amyloid β-PET should always be used if CSF is contraindicated or inconclusive. ‡Age and *APOE* status (when available) might influence the use of ^{18}F-FDG-PET, even before amyloid-PET, especially in individuals with available but inconclusive CSF results. Analyses of ^{18}F-FDG-PET images should also take into account comorbidities (ie, uncontrollable diabetes, brain trauma, chronic ischaemia), as well as some medications (eg, psychotropic drugs or corticosteroids) that might affect the images, as they can alter cerebral metabolism. §^{18}F-FDG-PET can be done before DaT-SPECT or mIBG, particularly if the cortical involvement of neurodegeneration is the diagnostic focus.

Chételat G et al. Amyloid-PET and ^{18}F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. *Lancet Neurol*. 2020;19(11):951-962

Medicare coverage: cost considerations

When a diagnostic or treatment is “covered” by Medicare B, it does not mean the cost is zero to the patient, rather they have a 20% copay.

Examples:

- ***Amyloid PET scan = $3,000 -> patient pays 20% ($600)***
- ***Lecanemab infusions = $26,500/yr -> patient pays 20% ($5,300)***

The value of an accurate diagnosis

- Early diagnosis allows for patient involvement in care planning, engage in lifestyle and behavioral changes to promote autonomy, and foresight to mitigate risks associated with more complex daily activities (driving, medications, finances etc.)
- Reduction in unnecessary tests, consultations, therapeutic trials
- Many patients and care partners want information

Take caution!

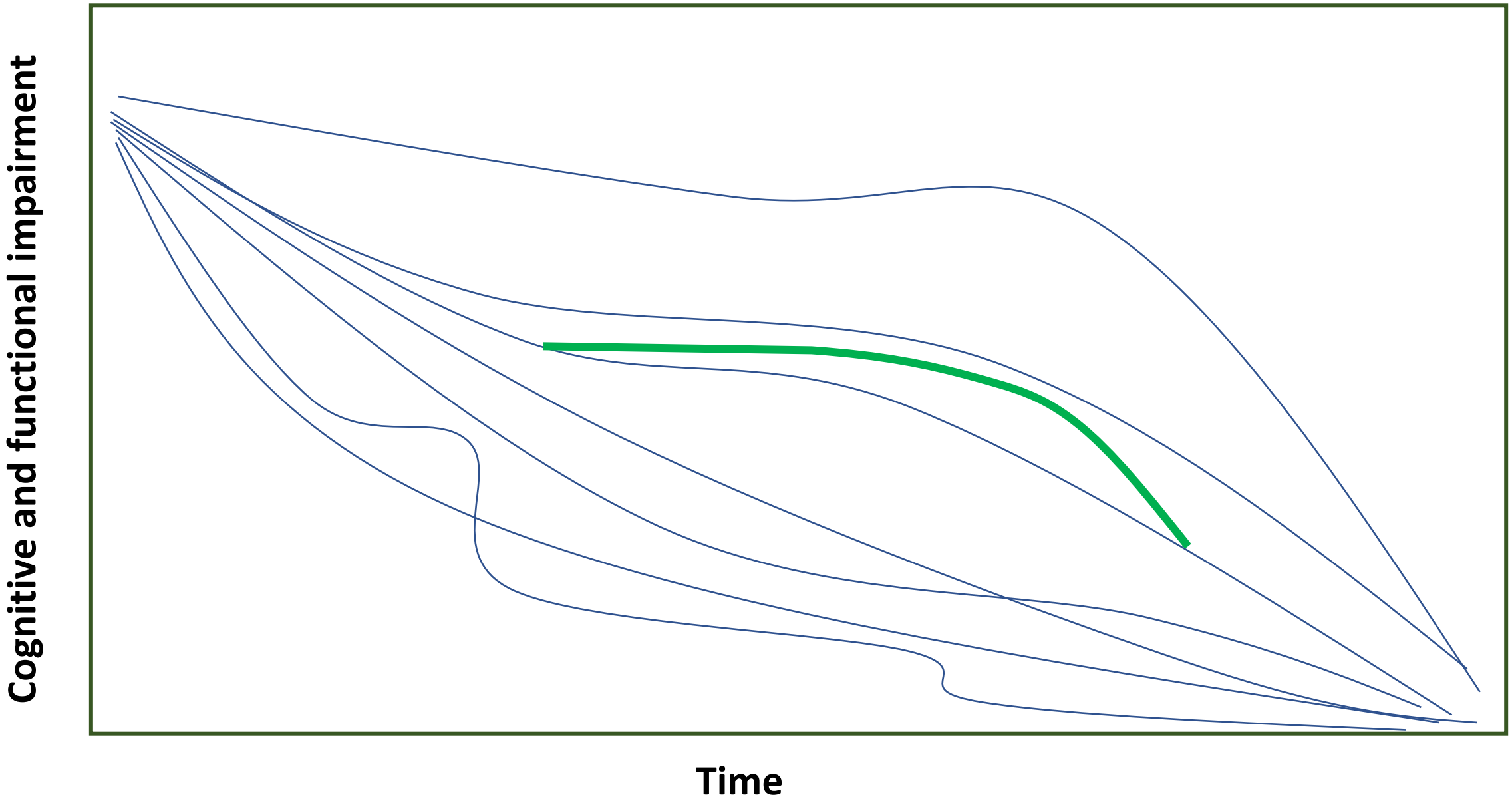
While it is very enticing to have a quick diagnostic marker….

A diagnosis of Alzheimer’s Disease should always be interpreted within clinical context and should never be made on a single abnormal test!

Alzheimer's Disease: pharmacologic treatment

- **Deprescribe**
  - CNS-acting meds (anticholinergics, sleep meds, opiates, muscle relaxers, hypoglycemia inducing) *refer to 2023 AGS Beers Criteria
  - Simplify regimens and reduce pill burden
  - Ensure safe adherence

- **To consider**
  - Standard treatment: Acetylcholinesterase inhibitors & NMDA-R antagonists
  - Anti-amyloid therapy


Cognitive and functional impairment
Time

Alzheimer's Disease: Anti-amyloid therapy

Lecanemab (Leqembi) & Donanemab (Kisunla)

- FDA approved for MCI and mild dementia due to Alzheimer's Disease
- IV infusions every 2-4 weeks
- Serial MRI monitoring
- $$$ (26,000-32,000/yr, Medicare B covers +20% copay)
- Outcomes need to be clear: disease-oriented vs patient-oriented
- Adverse events:
  - Infusion reactions, headache, **Amyloid Related Imaging Abnormalities** (ARIA-E edema, or ARIA-H hemorrhage)
  - Risk of ARIA is highest in first 6 months and with ApoE ε4 homozygotes

Anti-amyloid: inclusion/exclusion criteria

Inclusion Criteria

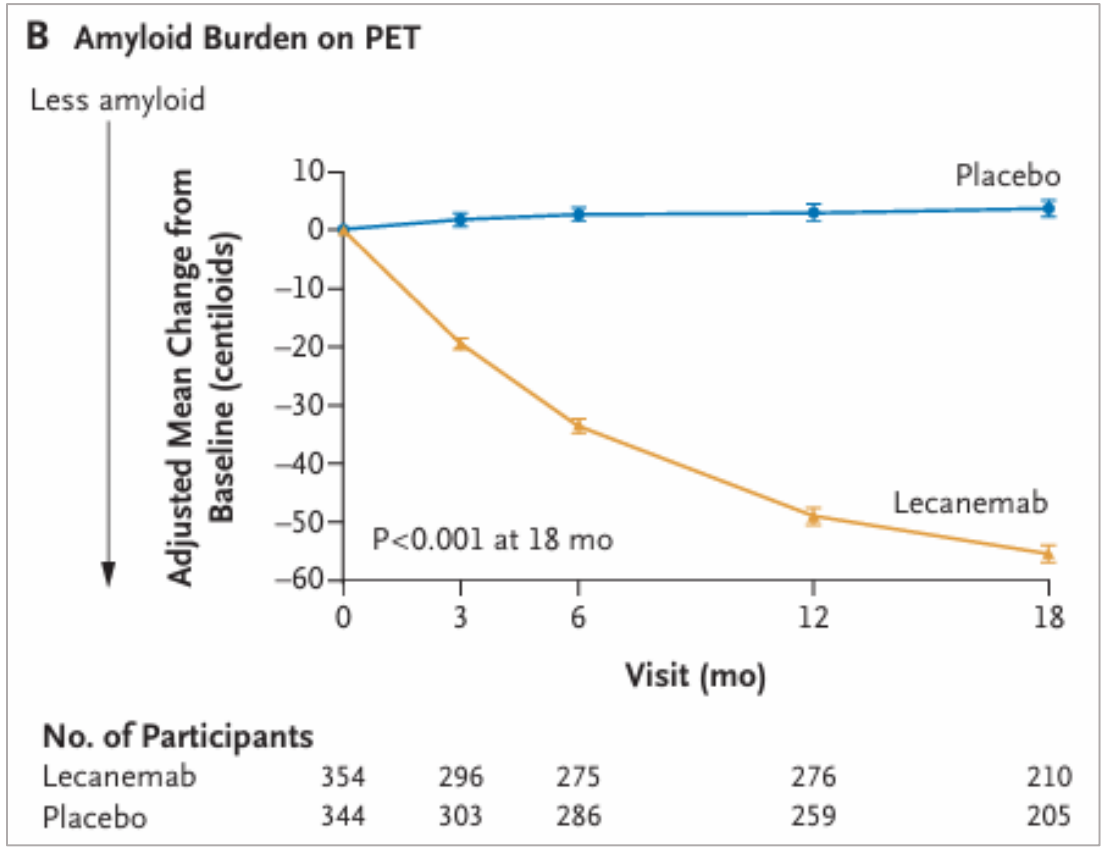
- MCI or mild dementia due to Alzheimer's Disease
- + biomarker (fluid and/or amyloid PET)
- Relatively healthy! Need to be able to tolerate numerous infusions and MRIs

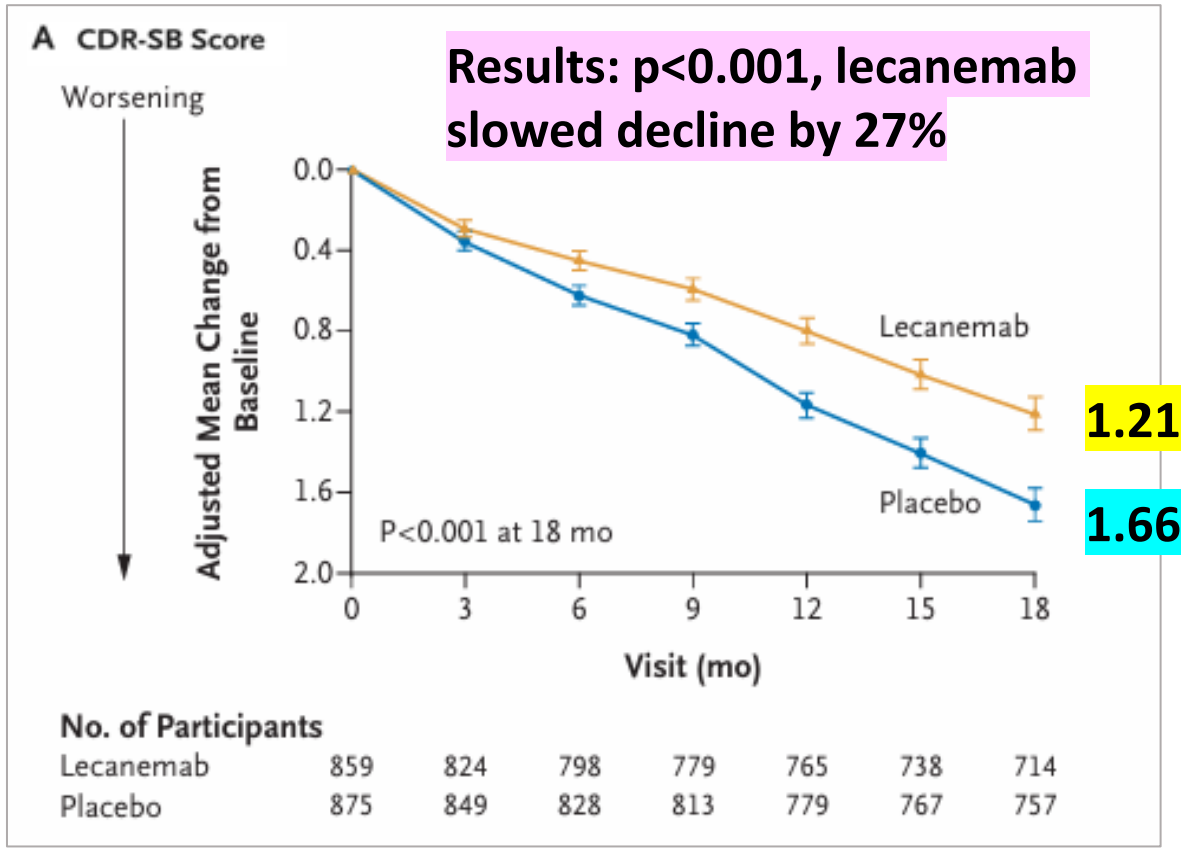
Exclusion Criteria

- CVA in past year, h/o large vessel ischemia, h/o brain hemorrhage, active malignancy, on immunomodulators, non-Alzheimer's Disease dementia
- Anticoagulation (antiplatelet OK)
- Homozygous APOE4 (relative contraindication)

Lecanemab: Clarity-AD

- 18-month, double-blind, placebo controlled, n=1795, +MCI/mild AD, avg age 72, 77% white





Results: p<0.001, lecanemab slowed decline by 27%

1.21

1.66

Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21

Rating scale for each domain[11]		0 None	0.5 Questionable	1 Mild	2 Moderate	3 Severe
Cognition	Memory	No memory loss, or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss, more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
	Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationship; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
	Judgement/ Problem-solving	Solves everyday problems, handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in these activities	Moderate difficulty in handling problems, similarities and differences; social judgment usually maintained	Severely impaired in handling problems, similarities and differences; social judgment usually impaired	Unable to make judgments or solve problems
Function	Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Life at home, hobbies and intellectual interests slightly impaired.	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside the home	
					Appears well enough to be taken to functions outside the family home	Appears too ill to be taken to functions outside the family home
	Home and hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests; poorly maintained	No significant function in the home
	Personal care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Table adapted from Morris, JC. Neurology. 1993;43(11):2412–4[11]

- CDR yields two scores: Global CDR score and CDR-SB scores (table)[10]
- The global CDR score ranges from 0 to 3 and requires computation into an algorithm to stage dementia severity[9,10]
- CDR-SB scores, with total scores ranging from 0 to 18, can track changes within and between stages of dementia severity over time. It also provides more information than the global CDR score in patients with very mild and mild AD dementia[9,10]
- In the very early stages of AD (CDR 0.5), the annual rate of change in CDR-SB scores is around 1–2. This gives a narrow window, over an 18-month study period, to measure meaningful benefit[12]

CDR-SB Total Score	Disease Severity	Global CDR Score
0	Normal	0 (normal)
0.5–4.0 0.5–2.5 3.0–4.0	Questionable cognitive impairment to very mild dementia Questionable impairment Very mild dementia	0.5 (very mild)
4.5–9.0	Suggests mild dementia	1 (mild)
9.5–15.5	Suggests moderate dementia	2 (moderate)
16.0–18.0	Suggests severe dementia	3 (severe)

Table adapted from O'Bryant S, et al. Arch Neurol. 2008;65(8):1091–5[10]

Lecanemab vs placebo difference = 0.45/18 points, is that clinically meaningful to our patients?

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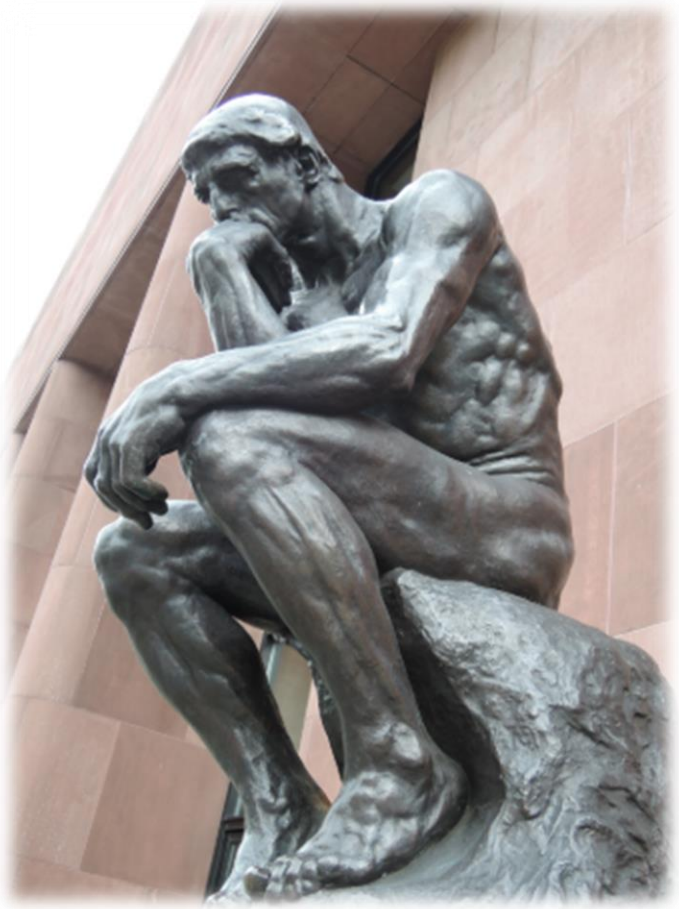


Is the amyloid hypothesis correct?

What else is involved in AD pathology beyond amyloid accumulation?

How do we approach mixed etiology dementias?

Is there a better way to track clinical outcomes in mild disease?

Lecanemab: Clarity-AD

Table 3. Adverse Events.*

Event	Lecanemab (N=898)	Placebo (N=897)
Overall — no. (%)		
Any adverse event	798 (88.9)	735 (81.9)
Adverse event related to lecanemab or placebo†	401 (44.7)	197 (22.0)
Serious adverse event	126 (14.0)	101 (11.3)
Death	6 (0.7)	7 (0.8)
Adverse event leading to discontinuation of the trial agent	62 (6.9)	26 (2.9)
Adverse event that occurred in ≥5% of participants in either group		
Infusion-related reaction	237 (26.4)	66 (7.4)
ARIA with microhemorrhages or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
Urinary tract infection	78 (8.7)	82 (9.1)
Covid-19	64 (7.1)	60 (6.7)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)

Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21

Lecanemab: Clarity-AD

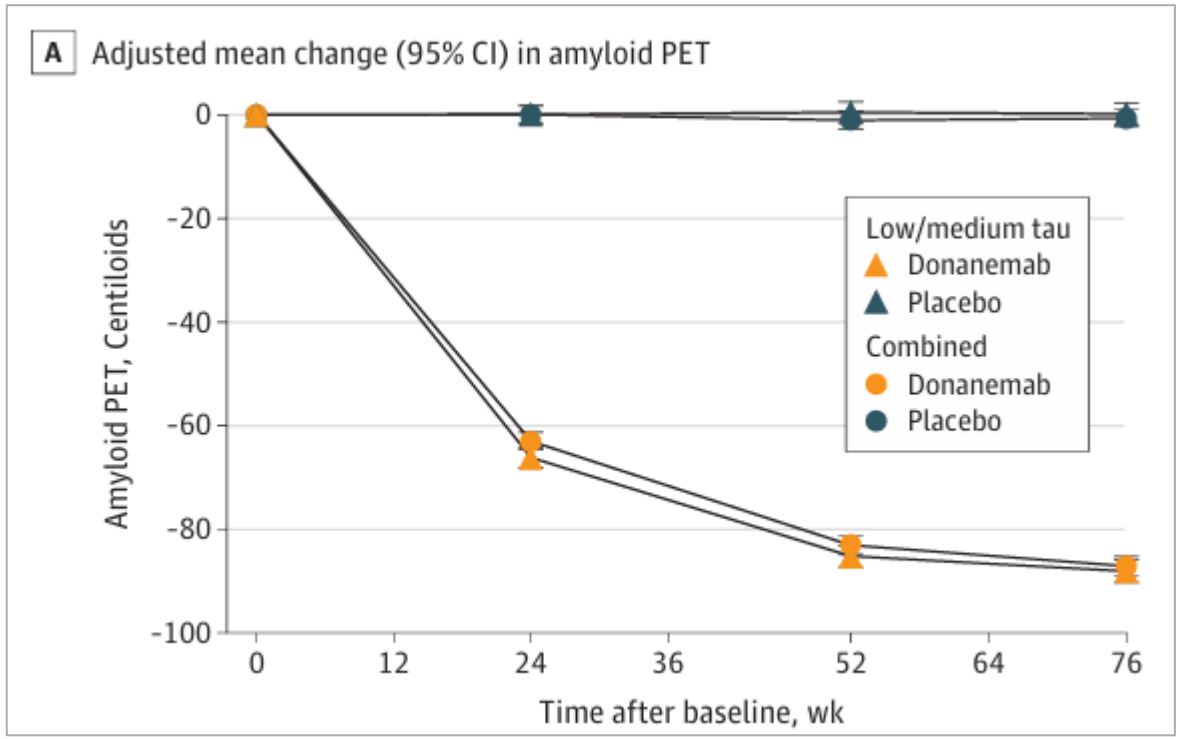
Table 3. (Continued.)

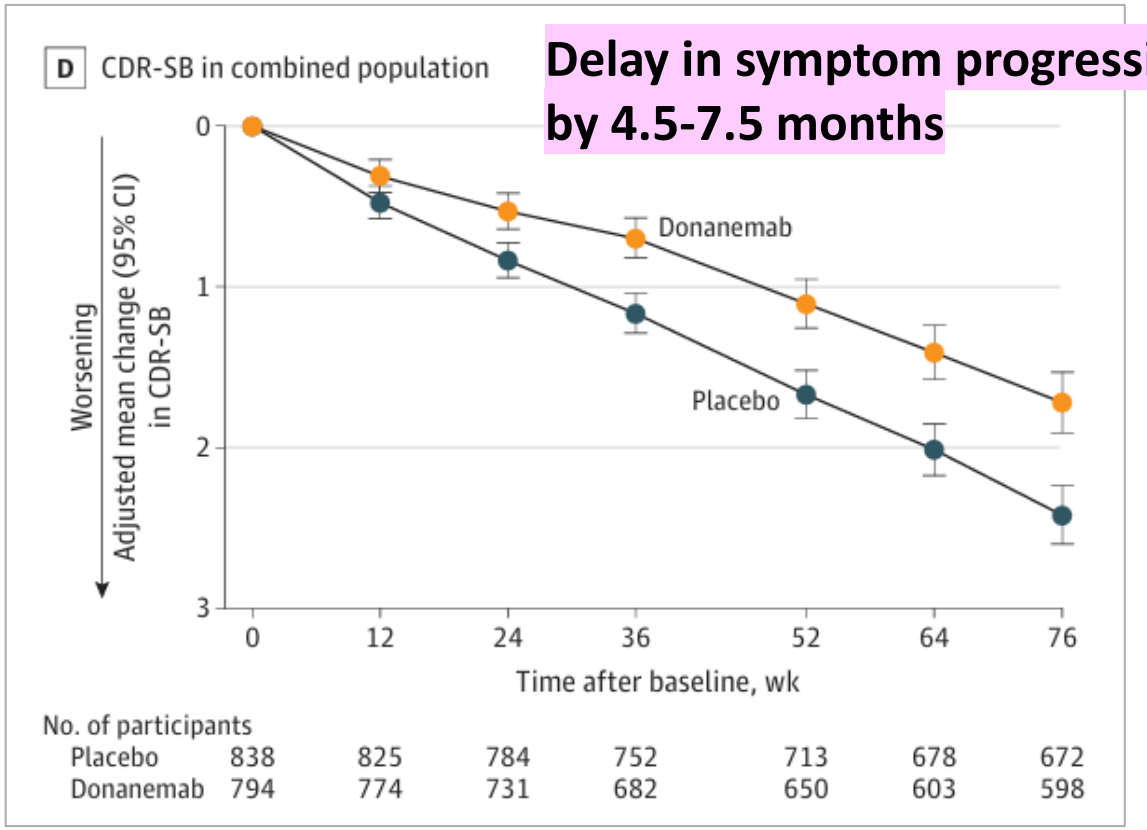
Event	Lecanemab (N = 898)	Placebo (N = 897)
ARIA-H according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	33/278 (11.9)	12/286 (4.2)
ApoE ε4 carrier	122/620 (19.7)	69/611 (11.3)
ApoE ε4 heterozygote	67/479 (14.0)	41/478 (8.6)
ApoE ε4 homozygote	55/141 (39.0)	28/133 (21.1)
ARIA-E or ARIA-H — no. (%)	193 (21.5)	85 (9.5)
Concurrent ARIA-E and ARIA-H — no. (%)	74 (8.2)	9 (1.0)

Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21

Donanemab: TRAILBLAZER-ALZ2

- 17.5-mo, double-blind, placebo controlled, n=1736, MCI/mild AD, avg age 73, 91% white





Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA.* 2023;330(6):512–527.

Donanemab: TRAILBLAZER-ALZ2

Table 3. Summary of Adverse Events (AEs) by Treatment Group

Event	Donanemab (n = 853)[a]	Placebo (n = 874)[a]
Overview of AEs, No. (%)		
Death[b]	16 (1.9)[c]	10 (1.1)
Death considered related to treatment[d]	3 (0.4)	1 (0.1)
Participants with ≥1 serious AE[e]	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	69 (8.1)	32 (3.7)
Participants with ≥1 treatment-emergent AE[f]	759 (89.0)	718 (82.2)
Treatment-emergent AEs ≥5% incidence, No. (%)		
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	65 (7.4)
COVID-19	136 (15.9)	154 (17.6)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)
Superficial siderosis of central nervous system	58 (6.8)	10 (1.1)
Dizziness	53 (6.2)	48 (5.5)
Arthralgia	49 (5.7)	42 (4.8)
Urinary tract infection	45 (5.3)	59 (6.8)
Diarrhea	43 (5.0)	50 (5.7)
Fatigue	42 (4.9)	45 (5.1)

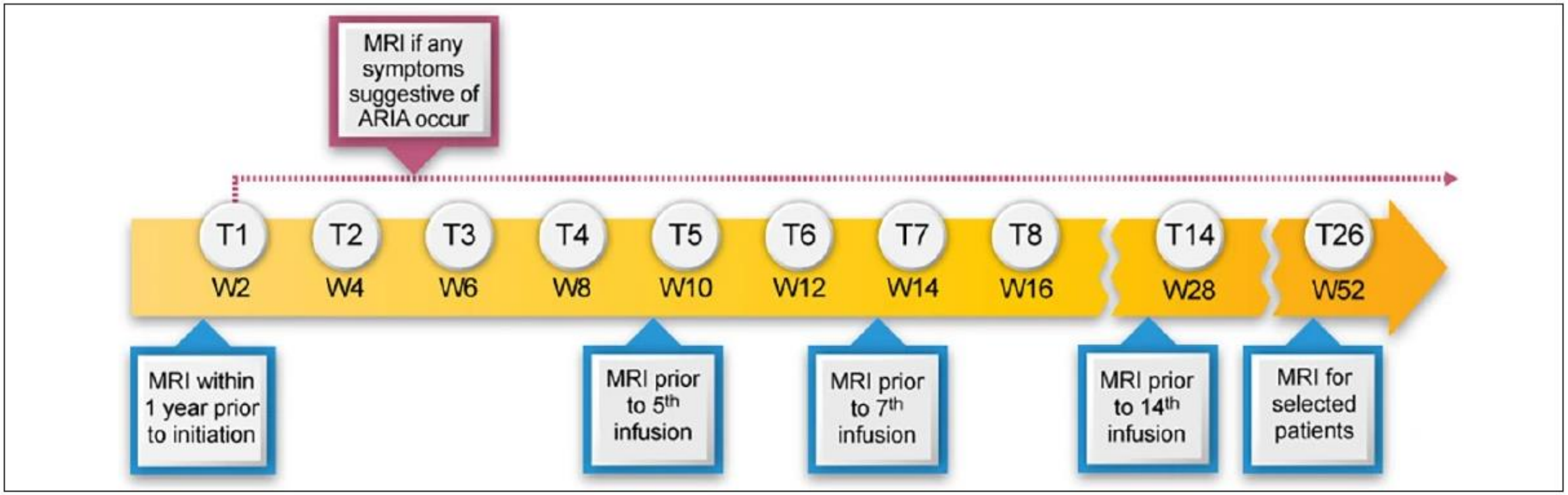
Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA.* 2023;330(6):512–527.

Donanemab: TRAILBLAZER-ALZ2

Overview of ARIA[g]		
Microhemorrhage or superficial siderosis present at baseline, No. (%)	124 (14.5)	161 (18.4)
ARIA-E by *APOE* ε4 allele status, No./total No. (%)		
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, No. (%)[h]	314 (36.8)	130 (14.9)
ARIA-E, No. (%)	205 (24.0)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	1 (0.1)[i]
ARIA-H, No. (%)	268 (31.4)	119 (13.6)
Microhemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral hemorrhage >1 cm	3 (0.4)	2 (0.2)

Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA.* 2023;330(6):512–527.

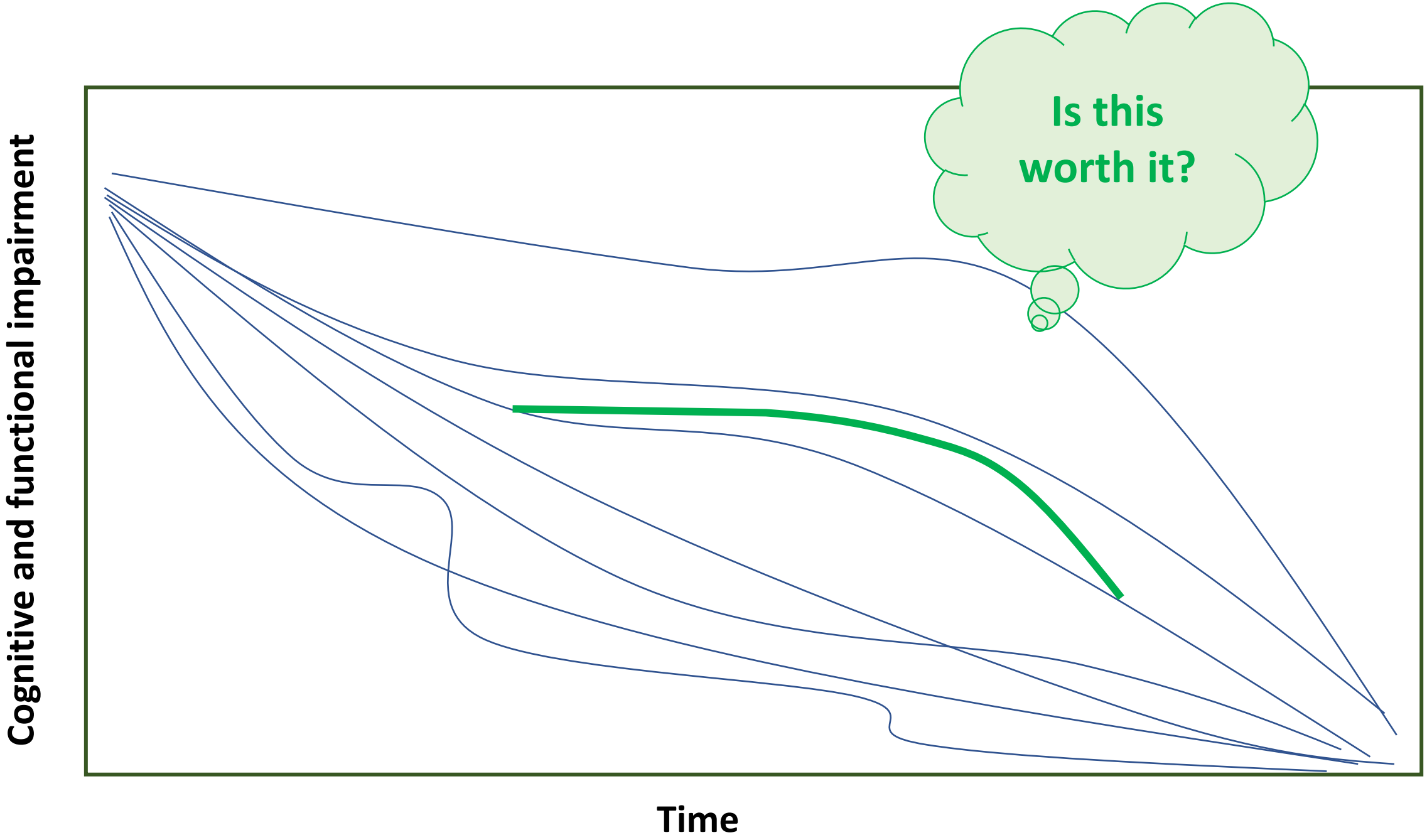
From: Lecanemab: Appropriate Use Recommendations



Lecanemab is administered by one-hour infusion (IV) every 2 weeks

- First infusion – observation for 4 hours
- Second infusion – observation for 3 hours
- Third infusion – observation for 2 hours
- Subsequent infusions – observation for 30-minutes
- Scheduled MRIs obtained at baseline, before dose 5, 7, 14, 26.
- Unscheduled MRI anytime there are symptoms concerning for ARIA

Cummings, J., Apostolova, L., Rabinovici, G.D. *et al.* Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis* **10**, 362–377 (2023)


Is this worth it?
Cognitive and functional impairment
Time

References

1. Chételat G, Arbizu J, Barthel H, et al. Amyloid-PET and ^{18}F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias. *Lancet Neurol*. 2020;19(11):951-962
2. Day GS. Diagnosing Alzheimer Disease. Continuum (Minneap Minn). 2024;30(6):1584-1613
3. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169.
4. Hall JR, Petersen M, Johnson L, O'Bryant SE. Characterizing Plasma Biomarkers of Alzheimer's in a Diverse Community-Based Cohort: A Cross-Sectional Study of the HAB-HD Cohort. *Front Neurol*. 2022;13:871947
5. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement*. 2016;12(3):216-224.
6. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD001190. DOI:10.1002/14651858.CD001190.pub3. Accessed 11 February 2026.
7. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med. 2012 Mar 8;366(10):893-903. doi:10.1056/NEJMoa1106668. PMID: 22397651.
8. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948. Epub 2022 Nov 29. PMID: 36449413.
9. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA.* 2023;330(6):512–527. doi:10.1001/jama.2023.13239
10. Skyles T, Bouchal SM, Giarratana A, et al. PET Imaging in Alzheimer Disease in the Era of Antiamyloid Therapy in the United States: Clinical Utility, Quantification, and Policy Landscape. *J Nucl Med Technol*. 2026;54(1):10-17

Websites:

- AGS response to 2024 revised criteria for AD: https://www.americangeriatrics.org/sites/default/files/inline-files/AGS%20Comments%20on%20Draft%20NIA-AA%20Revised%20Clinical%20Criteria%20for%20Alzheimer%27s%20Disease%20(8%2016%2023)%20FINAL_0.pdf

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