Update in Dementia

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Dr. Gill has no conflicts or professional relationships to disclose.

Learning Objectives

1. Explain the difference between dementia and Alzheimer’s disease, identify warning signs and state the common causes of dementia
2. Discuss the pathology and the clinical presentation of Alzheimer’s disease, frontotemporal dementia and dementia with Lewy bodies
3. State risk factors for the development of Alzheimer’s disease and supports available.
4. Identify pharmacological and non-pharmacologic treatments and for Alzheimer's disease.

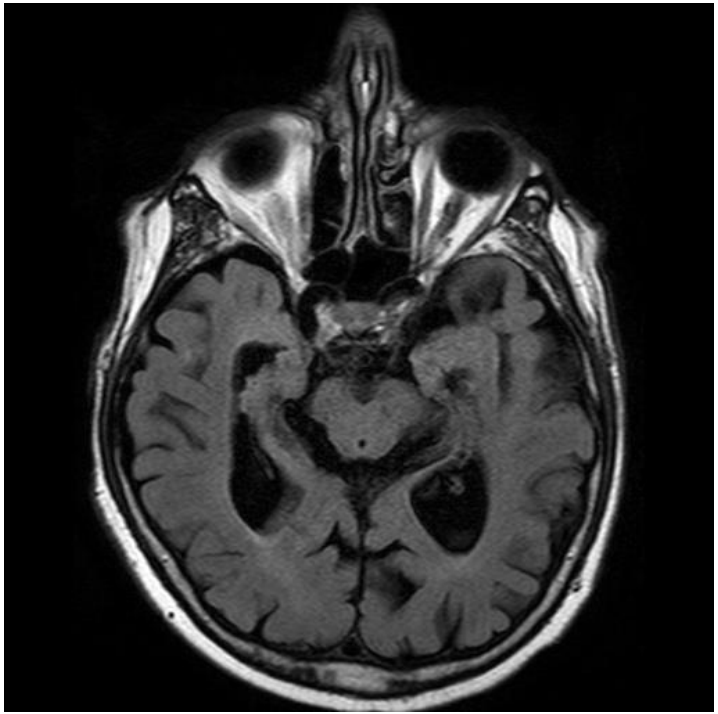
Case

Harold, a 67 year old gentleman, presents with his son. They are both concerned he has Alzheimer's disease.

He often misplaces his keys and cannot find them. He is increasingly repetitive and has word finding difficulty. He does not drive much, but has gotten lost several times recently. His son helps pay the bills.

On examination he has short term memory loss and naming difficulties. MMSE 26/30

He does not report any depression or anxiety symptoms. CBC, CMP, TSH and B12 levels normal.

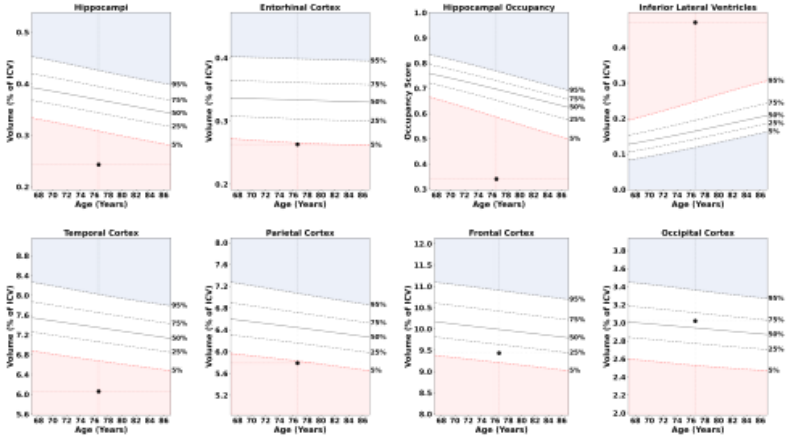


Brain Structure Volumes

	Volume (cm^3)	Normative Percentile
Hippocampi	4.09	1
Entorhinal Cortex	4.42	4
Superior Lateral Ventricles	101	99
Inferior Lateral Ventricles	7.92	99
Whole Brain	1152	19
Hippocampal Occupancy Score (HOC)	0.34	1

	Volume (cm^3)	Normative Percentile
Temporal Cortex	102	1
Parietal Cortex	97.4	4
Frontal Cortex	159	14
Occipital Cortex	50.8	63
Anterior Cingulate Cortex	9.5	91
Posterior Cingulate Cortex	5.57	11

Normative Reference Charts

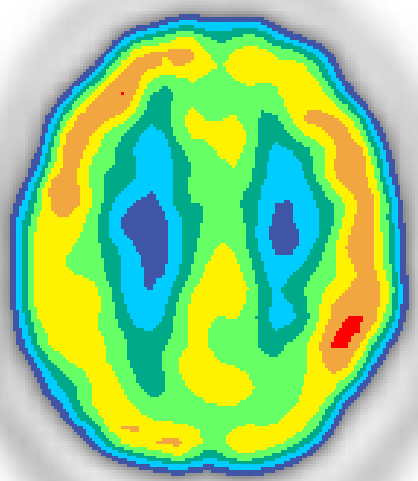


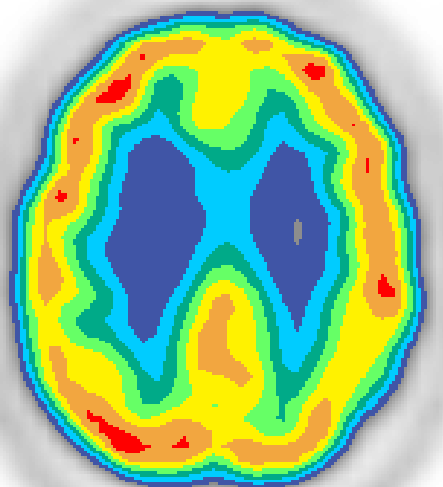
Poll

How certain are you that Harold has Alzheimer's disease?

1. Trick question--he doesn't have Alzheimer's disease
2. 0 percent because he likely has underlying Alzheimer's disease, but is in the MCI phase so we cannot call it Alzheimer's disease
3. 60 percent
4. 90 percent
5. 100 percent

FDG PET Scan





Z-score mapping

Atlas	Structure	Z-Score	L Z-Score	R Z-Score	L-R % Diff	L-R % Diff Z-Score
Single Brain Atlas	Temporal Operculum	-3.34	-2.27	-3.45	5.28	1.08
Single Brain Atlas	Superior Medial Frontal Gyrus	-3.27	-4.84	-1.77	-14.56	-6.51
Single Brain Atlas	Temporal Pole	-2.52	-0.58	-4.53	29.9	4.84
Single Brain Atlas	Heschl Gyrus	-2.48	-2.3	-2.06	-13.96	-0.82
Single Brain Atlas	Posterior Cingulate Gyrus	-2.45	-1.99	-2.63	7.09	1.56
Single Brain Atlas	Cingulate Gyrus	-2.24	-1.81	-2.64	2.07	1.8
Single Brain Atlas	Precuneus	-2.23	-1.8	-2.35	4.17	0.4
MIM Probabilistic Atlas	Posterior Cingulate Gyrus 8/10	-2.08	-1.22	-2.38	8.84	2.14
Single Brain Atlas	Subcallosal Area	-2.07	-2.08	-2	-5.07	-1
Single Brain Atlas	Anterior Cingulate Gyrus	-1.78	-1.55	-2.09	5.28	1.65
Single Brain Atlas	Posterior Orbital Gyrus	-1.62	-0.15	-2.29	30.04	2.82
MIM Probabilistic Atlas	Precuneus 8/10	-1.49	-0.74	-1.81	8.03	1.43
Single Brain Atlas	Amygdala	-1.41	-0.64	-1.94	6.85	2.46
Single Brain Atlas	Superior Parietal Lobule	-1.24	-1.9	-0.43	-8.92	-2.64
Single Brain Atlas	Hippocampus	-0.92	0.07	-1.72	9.29	2.65
Single Brain Atlas	Postcentral Gyrus	-0.68	0.62	-1.82	10.03	2.95
Single Brain Atlas	Inferior Medial Frontal Gyrus	-0.65	-1.85	0.56	-12.39	-4.2

CSF results

Alzheimer's Disease Evaluation, CSF

p-Tau/Abeta42 — SDL

⚠ 0.034 ratio — High

Reference Value ≤0.023

AD Interpretation — SDL

The elevated p-Tau/Abeta42 ratio is consistent with the presence of pathological changes associated with Alzheimer's disease.

The p-Tau/Abeta42 ratio provides better concordance with amyloid Positron Emission Tomography (PET) imaging when compared to Abeta42, phospho-Tau and total-Tau individually. A cut-off of 0.023 provides optimal balance between NPA (negative % agreement) and PPA (positive % agreement) when compared to amyloid PET results. A p-Tau/Abeta42 ratio of ≤0.023 has a 92% NPA with normal amyloid PET. A ratio of >0.023 has a 92% PPA with abnormal amyloid PET.

Failure to adhere to the sample collection instructions provided in the Lab Test Catalog may result in falsely reduced Abeta42 concentrations; potentially affecting subsequent interpretations as well as the p-Tau/Abeta42 ratio.

The pTau assay measures p-Tau181 (Tau phosphorylated at threonine 181), which has been shown to be a marker of AD pathology.

Abeta42 — SDL

⚠ 854 pg/mL — Low

Reference Value >1026

Total-Tau — SDL

⚠ 332 pg/mL — High

Reference Value ≤238

Phospho-Tau(181P) — 1 SDL

⚠ 29.1 pg/mL — High

Reference Value ≤21.7

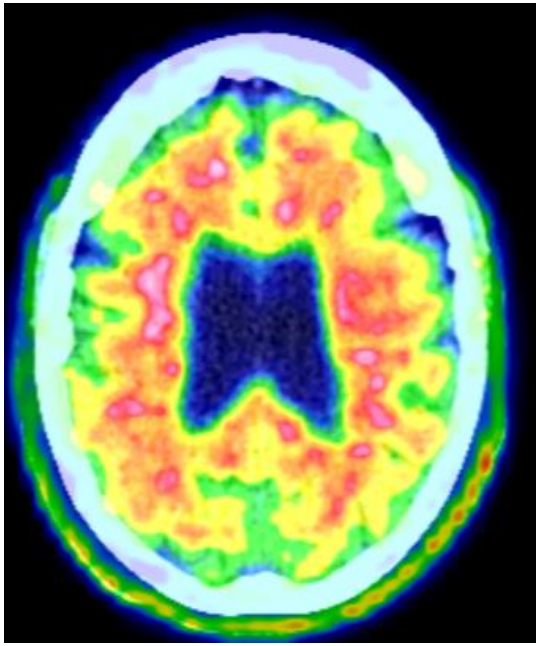
ADDITIONAL INFORMATION

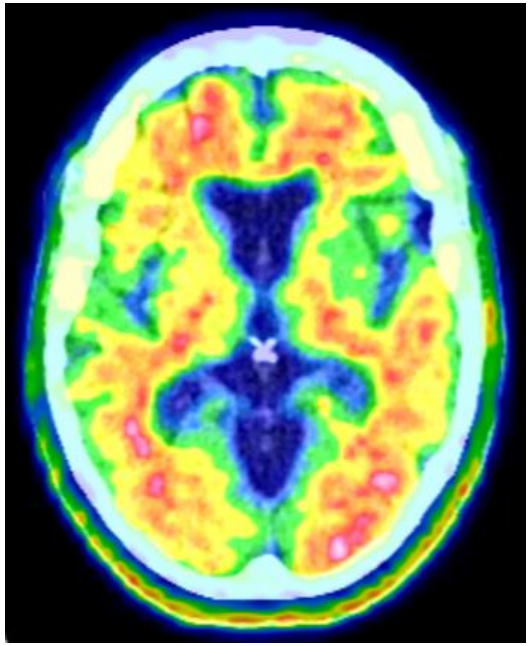
The testing method is an electrochemiluminescence assay manufactured by Roche Diagnostics Inc. and performed on the Cobas system.

Values obtained with different assay methods or kits may be different and cannot be used interchangeably.

Received: 09 Dec 2021 19:13 **Reported:** 09 Dec 2021 19:48

Amyloid PET scan





Structure	SUVR	Normal Values *Mean (Range)*
Anterior Cingulate Gyrus	1.6	0.99 (0.84 - 1.14)
Inferior Medial Frontal Gyrus	1.38	0.91 (0.81-1.01)
Lateral Temporal Lobe	1.58	0.99 (0.88-1.11)
Posterior Cingulate Gyrus	1.45	0.94 (0.82-1.05)
Precuneus	1.88	1.00 (0.91-1.10)
Superior Parietal Lobule	1.4	0.97 (0.86-1.09)
Average	1.55	0.97 (0.89-1.04)
Reference Structure: Cerebellum		

Diagnostic accuracy

Test	Studies (Patients Analyzed), *n*	Median AD Prevalence (Range)	Abnormal Cut Point Definition	Median Sensitivity (Range)*	Median Specificity (Range)*
AD vs. non-AD					
Amyloid PET	4 (426)	0.64 (0.33–0.79)	†	0.91 (0.79–0.98)	0.92 (0.76–1.0)
FDG PET	2 (182)	0.64 (0.57–0.70)	‡	0.89 (0.84–0.94)	0.74 (0.73–0.74)
MRI MTA	2 (161)	0.33 (0.24–0.42)	§	0.91 (0.91–0.91)	0.89 (0.84–0.94)
SPECT	3 (205)	0.56 (0.48–0.64)	‖	0.64 (0.57–0.94)	0.83 (0.76–0.92)

Fink et al. Ann Intern Med. 2020

CSF:

	AD+ vs AD− Unadjusted Models		
Biomarker	AUC	95% CI	*p* Value
Lumipulse CSF p-tau181/Aβ42	0.97	0.92–1.00	<0.001
Lumipulse CSF p-tau181	0.82	0.69–0.94	0.002
Lumipulse CSF Aβ42	0.91	0.83–0.99	0.002
Lumipulse CSF t-tau	0.73	0.58–0.88	0.01

Safransky et. al. Neurology. 2024

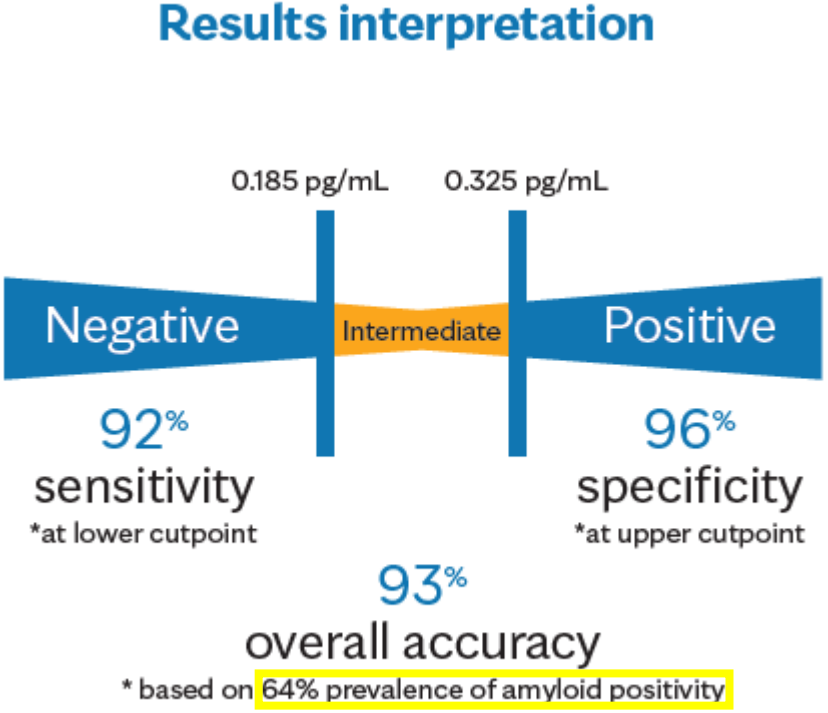
Blood test

Mayo Clinic PT217

But…
Assuming sensitivity and specificity of 90%:

5% prevalence at age 65 means that of those patients with a positive test 32% will actually have AD

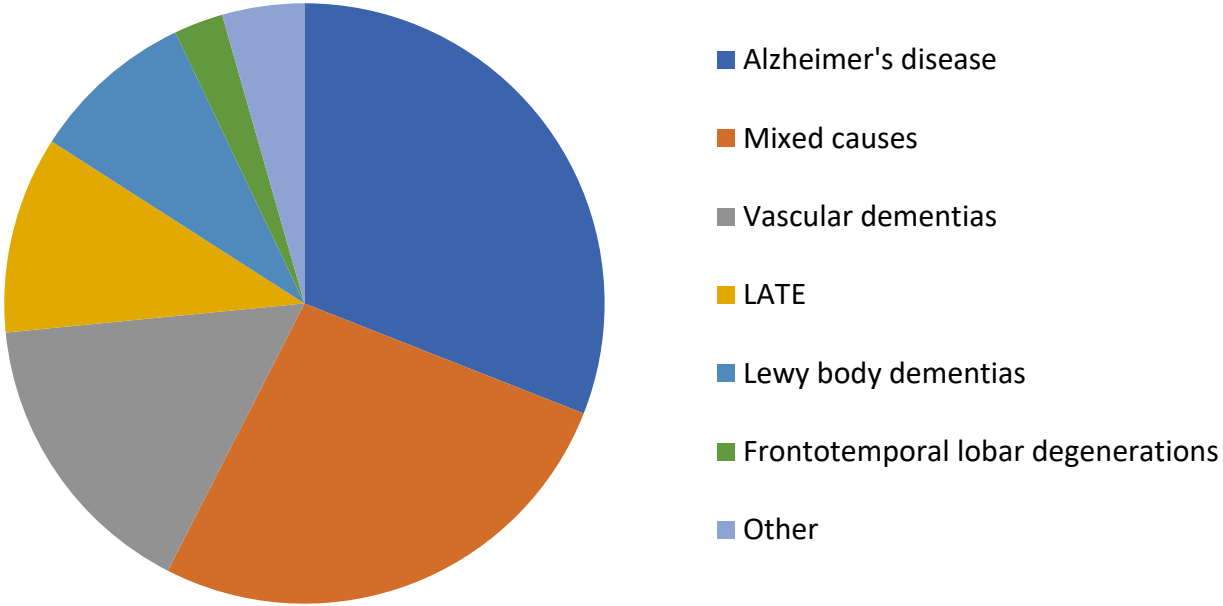
33% prevalence at age 85 means that of those patients with a positive test, 82% will actually have AD



Results may be affected by CKD
Lower levels in African American population

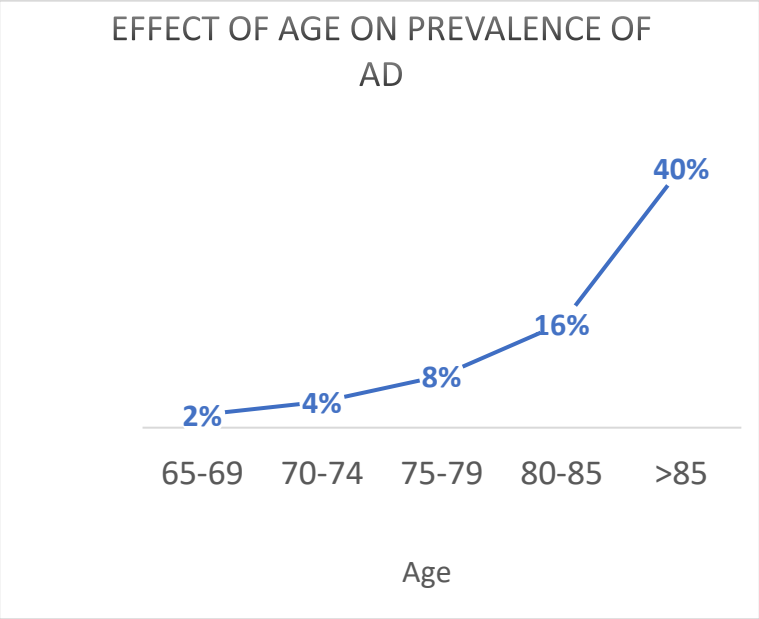
We can be certain of a diagnosis of AD while a patient is still alive

Estimated causes of dementia



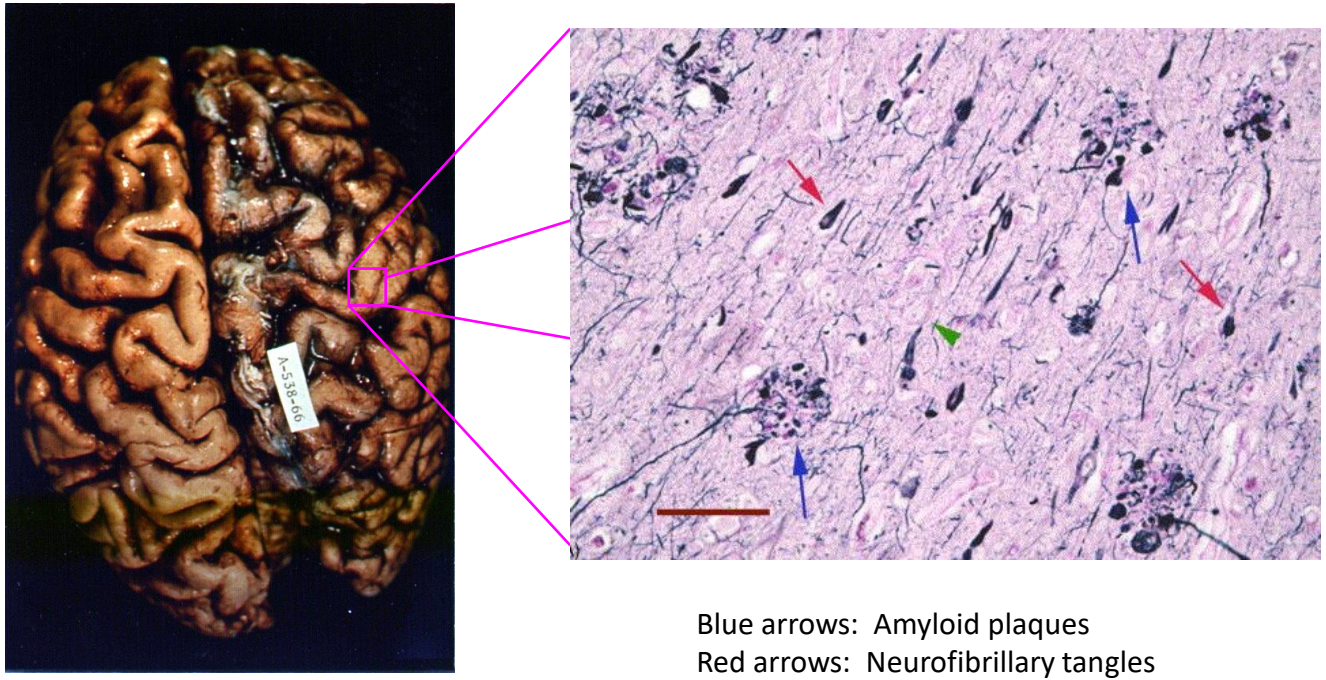
LATE = Limbic predominant age-related TDP-43 encephalopathy

Risk factors for AD

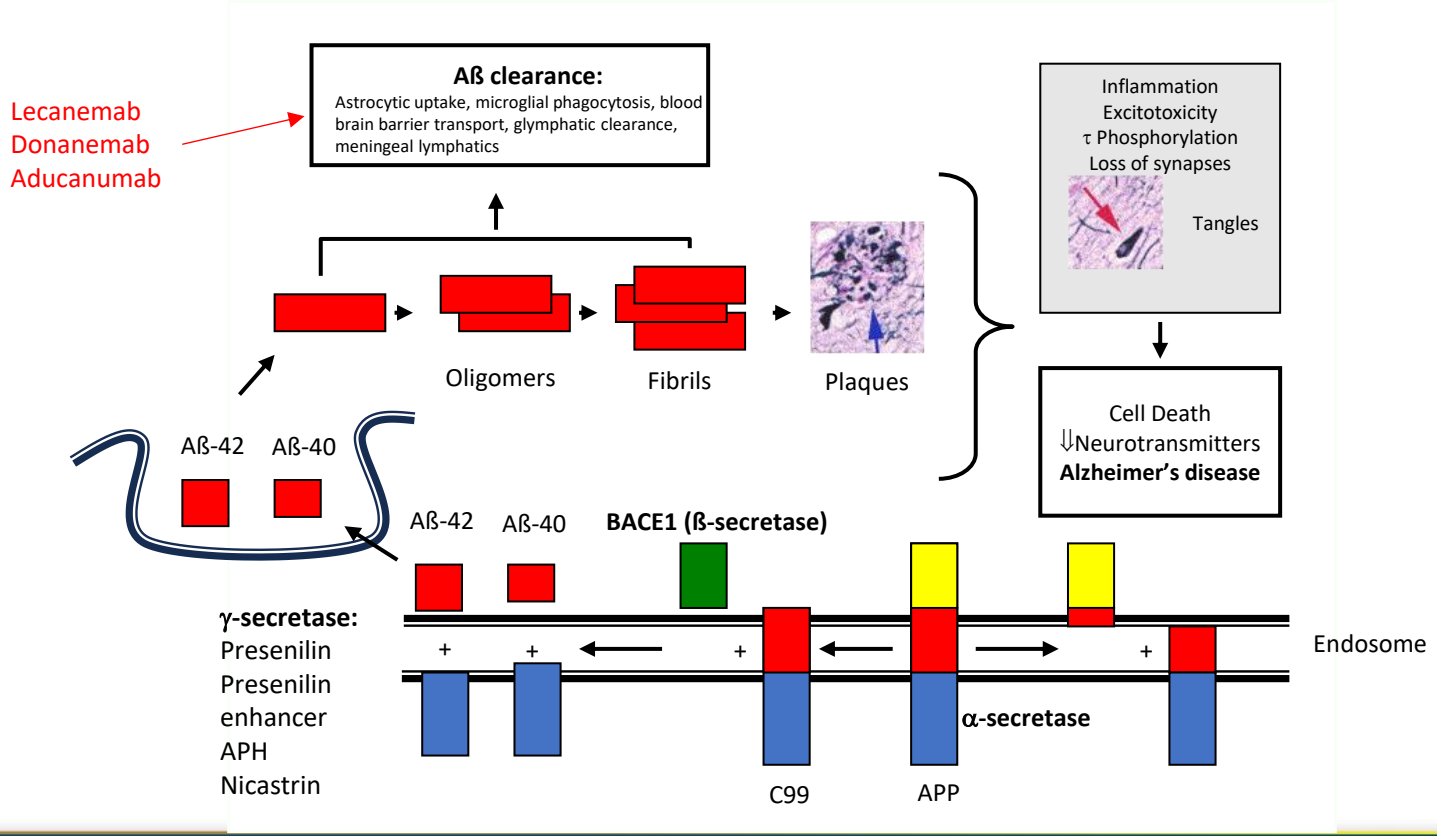


- Age
- Family history/genetics
- Apolipoprotein E status
- Vascular risk factors:
  - Diabetes
  - Smoking
  - Midlife hypertension
  - Midlife hypercholesterolemia
  - Midlife obesity
- Alcohol intake
- Decreased physical activity
- Low “cognitive reserve”
- Head trauma

Alzheimer's disease



Blue arrows: Amyloid plaques
Red arrows: Neurofibrillary tangles


Lecanemab
Donanemab
Aducanumab
Aß clearance:
Astrocytic uptake, microglial phagocytosis, blood brain barrier transport, glymphatic clearance, meningeal lymphatics
Inflammation
Excitotoxicity
τ Phosphorylation
Loss of synapses
Tangles
Oligomers
Fibrils
Plaques
Cell Death
⇓Neurotransmitters
Alzheimer's disease
Aß-42
Aß-40
Aß-42
Aß-40
BACE1 (ß-secretase)
γ-secretase:
Presenilin
Presenilin
enhancer
APH
Nicastrin
α-secretase
C99
APP
Endosome

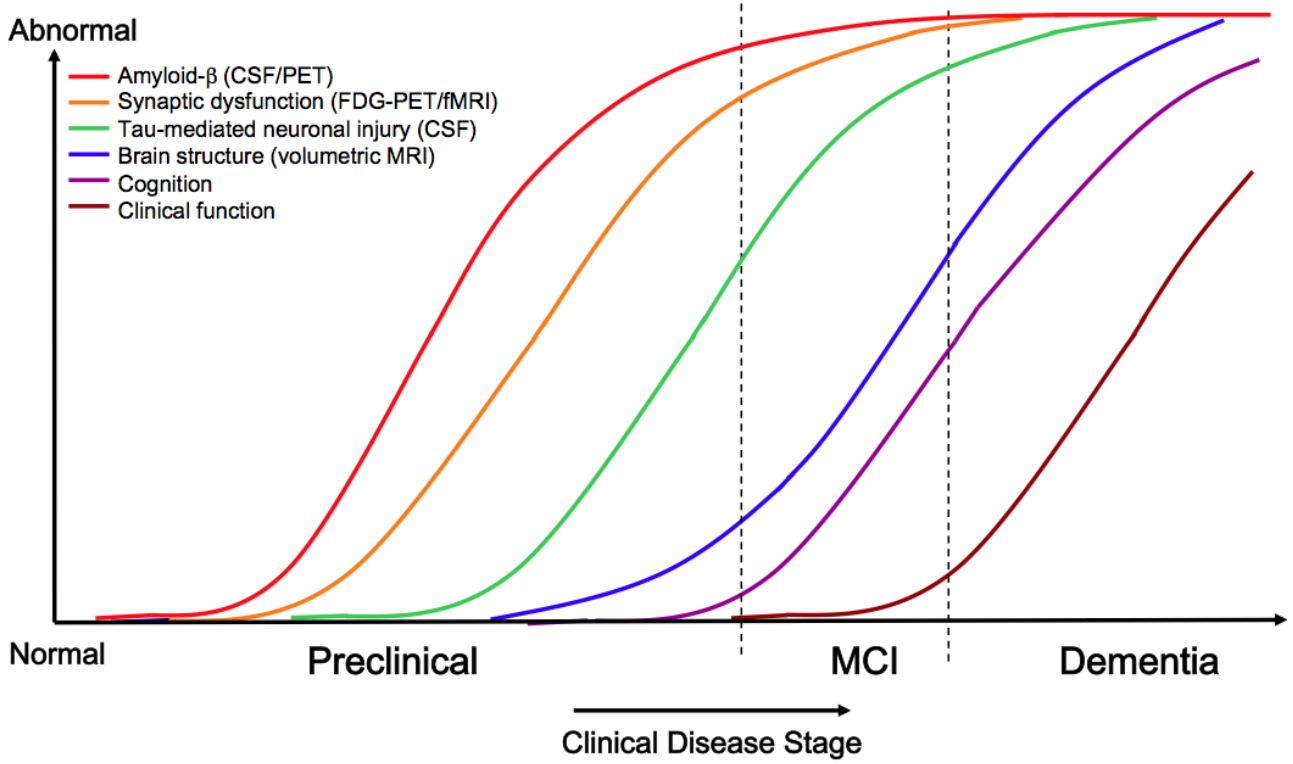


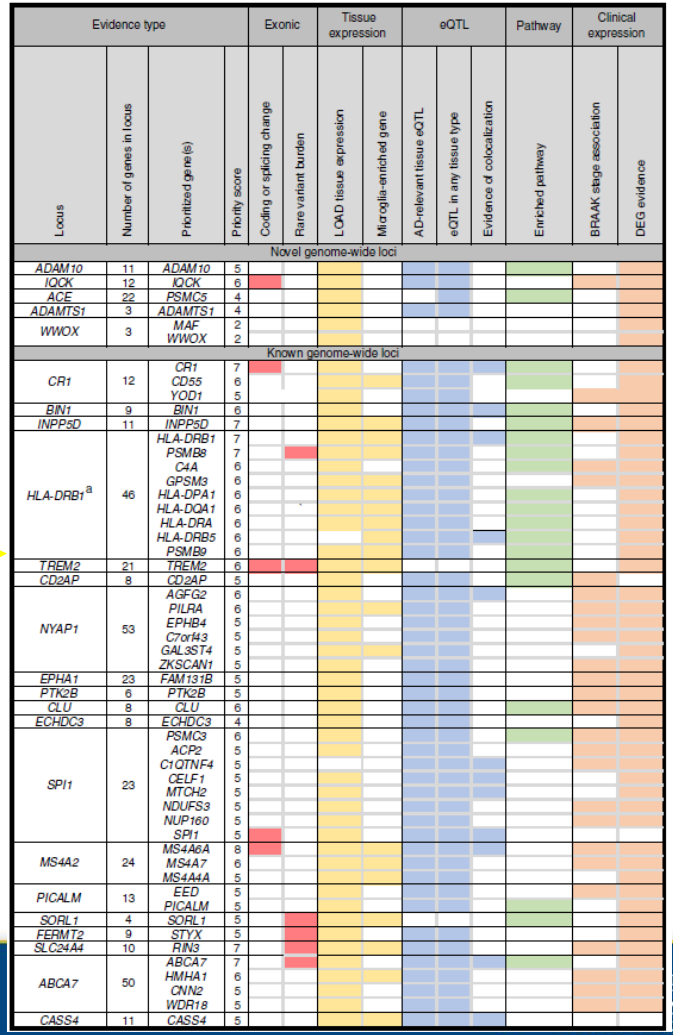
Figure adapted by AA from C. Jack. MCI = mild cognitive impairment

Genetics

	Genetic cause	Percent of cases
Chromosomal	Down syndrome	<1%
Early onset familial	Presenilin 1 Presenilin 2 Amyloid Precursor Protein Other	<2%
Late onset familial	Apolipoprotein E other	15-25%
Unknown	Presumed genetic/environment interactions	~75%

Three alleles of apoliprotein E: APOEε2, APOEε3, and APOEε4.

- One ε4 allele increases risk of AD by ~2-3 times, two alleles increases risk of AD by ~10 times
- But…frequency of APOEε4 in late onset AD ~50%



Kunkle et al. Nat Genetics. 2019

New suggested criteria

Stage 0 Asymptomatic, deterministic gene[a]

No evidence of clinical change. Biomarkers in normal range.

Stage 1 Asymptomatic, biomarker evidence only

Performance within expected range on objective cognitive tests.

No evidence of recent cognitive decline or new symptoms.

Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function

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)

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).

Stage 4 Dementia with mild functional impairment — **Mild**

Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.

Stage 5 Dementia with moderate functional impairment — **Moderate**

Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.

Stage 6 Dementia with severe functional impairment — **Severe**

Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

Jack, et al. Alz Dement. 2024

We can make a diagnosis of Alzheimer's disease in patient with normal cognition

Should we even be doing cognitive screening?

Treatment of Alzheimer's disease

Traditional medical treatment of AD

	Donepezil	*Galantamine*	*Rivastigmine*	*Memantine*
Indication	Mild-Severe AD	Mild-moderate AD	Mild-moderate AD, mild-moderate PDD	Moderate-severe AD
Mechanism of action	Acetyl-cholinesterase inhibitor	Acetyl-cholinesterase inhibitor, nicotinic receptor modulator	Acetyl- and butyryl-cholinesterase inhibitor	Non competitive NMDA receptor blocker
Dosing	Once a day	Once a day	Twice a day pill or patch	Twice a day

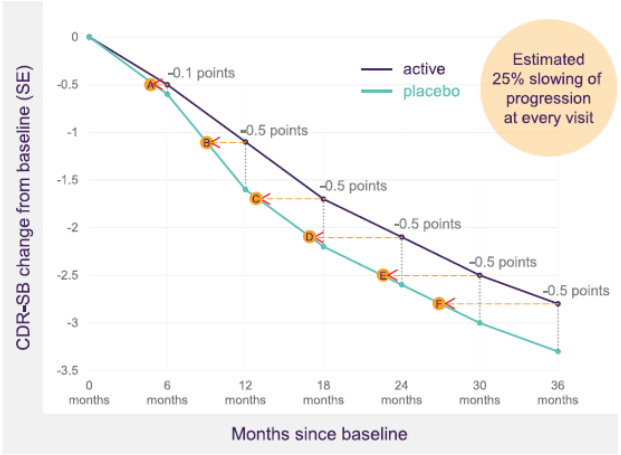
Additional points:

- None are disease modifying
- Do not prevent MCI or dementia
- Are “off label” when used in patients with MCI

New treatments

Lecanemab and donanemab are anti-amyloid monoclonal antibody IV infusions approved by the FDA for mild cognitive impairment and mild dementia due to Alzheimer's disease. They have not been shown to improve cognition, but may slow the progression of Alzheimer's disease.

Have risks of ARIA (brain swelling and bleeding)



	A	B	C	D	E	F
points	-0.1	-0.5	-0.5	-0.5	-0.5	-0.5
months difference vs. placebo	-1.5	-3	-4.5	-6	-7.5	-9

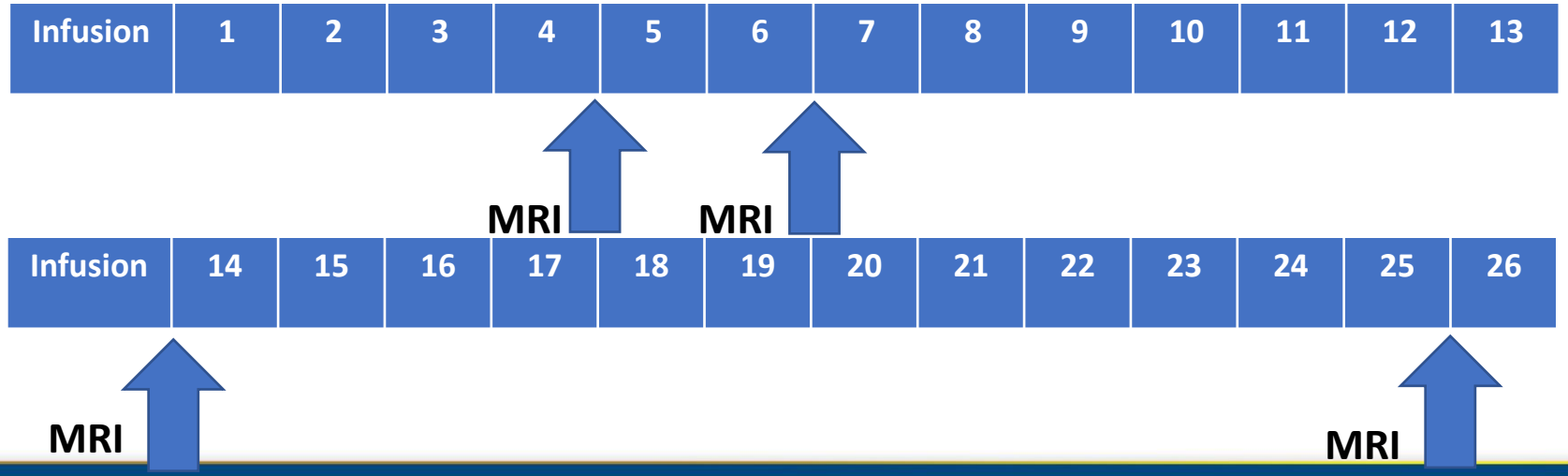
Petersen, et al. Alz Dement. 2023

Lecanemab administration

Baseline:
MMSE (or equivalent)
CDR
MRI
CSF Amyloid/pTau/Tau or Amyloid PET
APOE genetic testing

? prescribe

Registry enrollment
Infusion center coordination
Insurance prior authorization and appeal
Patient assistance program



ABC Behavior Prevention Tool

Antecedent: an event that precedes another

Behavior: an action

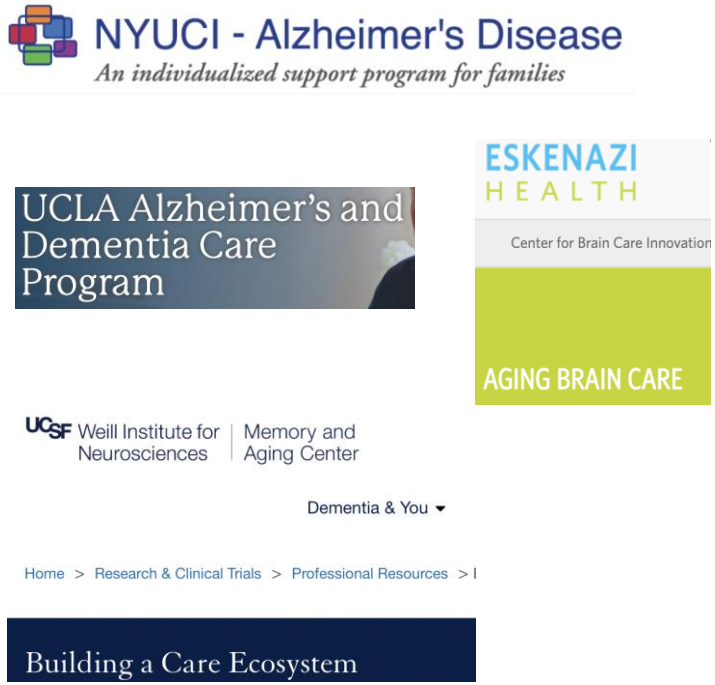
Consequence: what happens immediately following an action

Non drug treatments

- Collaborative care
  - Can improve quality of care and improve behavioral and psychologic symptoms of patients and caregivers.[1]
- Exercise plus caregiver training
  - Can improve physical health and depression in patients with AD.[2]
- Spirituality
  - Higher levels of spirituality and private religious practice is associated with a slower decline of AD.[3]
- Cognitive training and memory rehabilitation
  - Can improve cognition function[4]
- Enhanced counseling and support for caregivers
  - Can reduce nursing home placement[5]

[1]Callahan, et. al. JAMA. 2006, [2]Teri, et. al. JAMA. 2003, [3]Kaufman, et. al. Neurology. 2007, [4]Sitzer, et. al. Acta Psychiatr Scand. 2006, [5]Mittleman, et. al. Neurology. 2006

System wide approach to dementia



- Increase caregiver outcomes
- Reduces costs
  - Less hospitalizations
  - Less ED visits
  - Less nursing home placement
  - Less medication usage

Case

Sam is a 56 year old gentleman who developed forgetfulness and a right sided tremor about three years ago. Both of these have worsened over the past three years to the point where he is impaired by both his memory and slowness of movement.

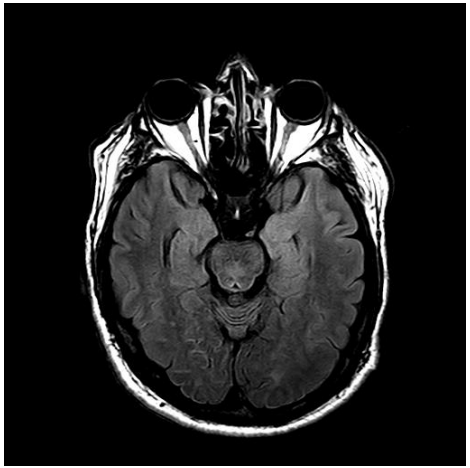
He frequently sees dead relatives in the room with him. His son says that he has been acting out his dreams violently for a number of years and has no sense of smell.

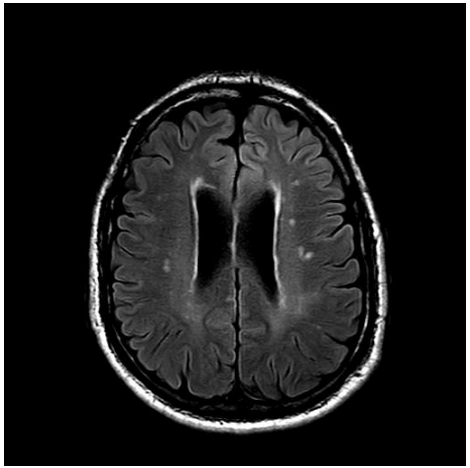
His examination is remarkable for bradykinesia, resting tremor and cogwheel rigidity along with memory and executive dysfunction. MMSE 26/30

Case

Case continued

CBC, complete metabolic panel, and TSH are normal. B12 412.





Poll

What's the diagnosis?

1. Alzheimer's disease
2. Dementia with Lewy bodies
3. Frontotemporal dementia
4. Mild cognitive impairment
5. Vascular dementia

What is the significance of the acting out of dreams and poor sense of smell?

Lewy Body Dementia diagnosis

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

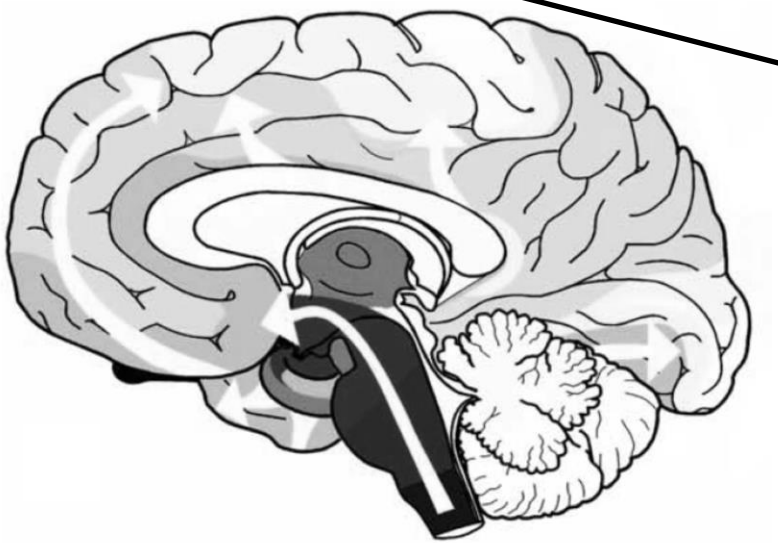
Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

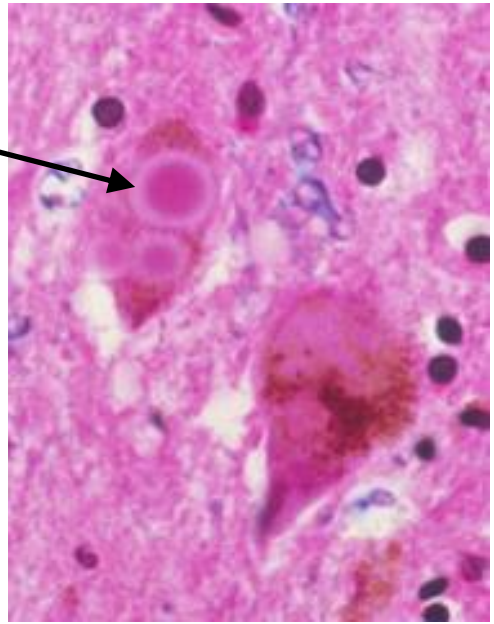
When patients meet all criteria, accuracy rates are about 80% of the time, but up to 40% or patients with Lewy body dementia will not meet these criteria

McKeith, et al. Neurology. 2017

Lewy Bodies

1. Parkinson's disease
2. Dementia with Lewy bodies
3. Multiple system atrophy
4. Pure autonomic failure

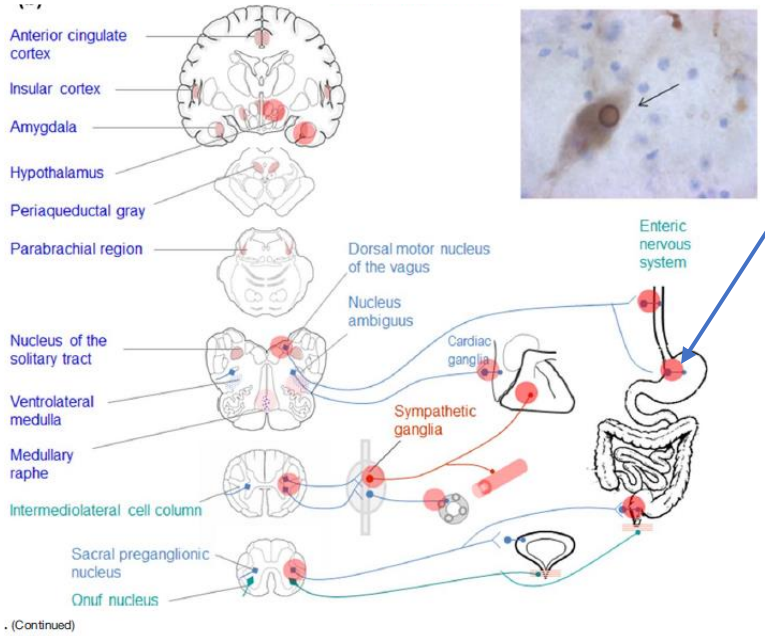




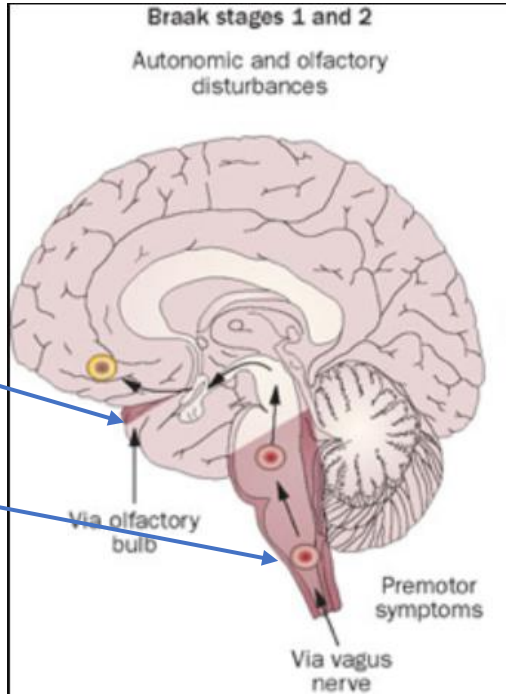
Lewy bodies contain Alpha synuclein protein, ubiquitin protein and other proteins

Braak, et. al. Neurobiolg Aging. 2003

Prodrome



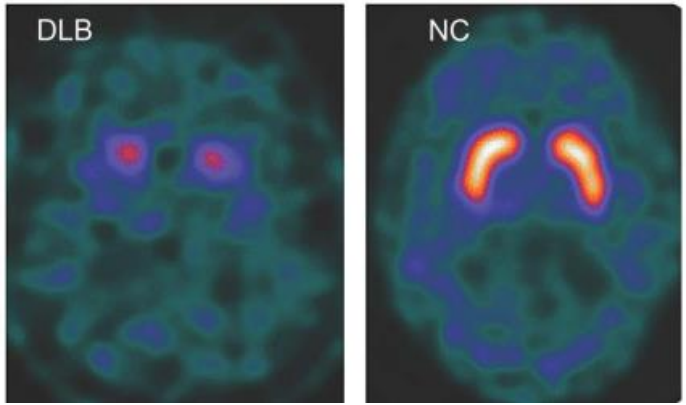
1. Constipation
2. Olfactory dysfunction
3. REM sleep behavior disorder



Coon, et. al. Mov Disord. 2018

What about additional testing?

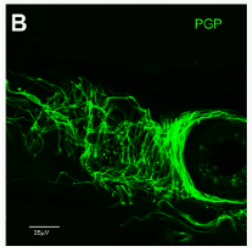
DaTScan



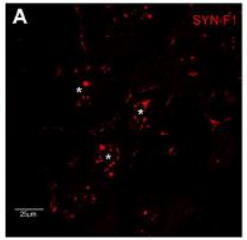
Accuracy 86% (sensitivity 80%, specificity 92%). but can't distinguish between DLB and PSP

Thomas, et. al. Neurology. 2017

Skin biopsy for alpha synuclein



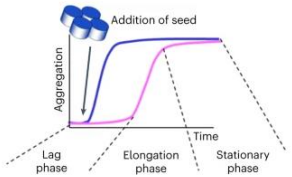
DLB patient

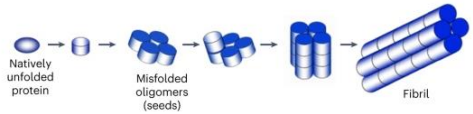


Normal

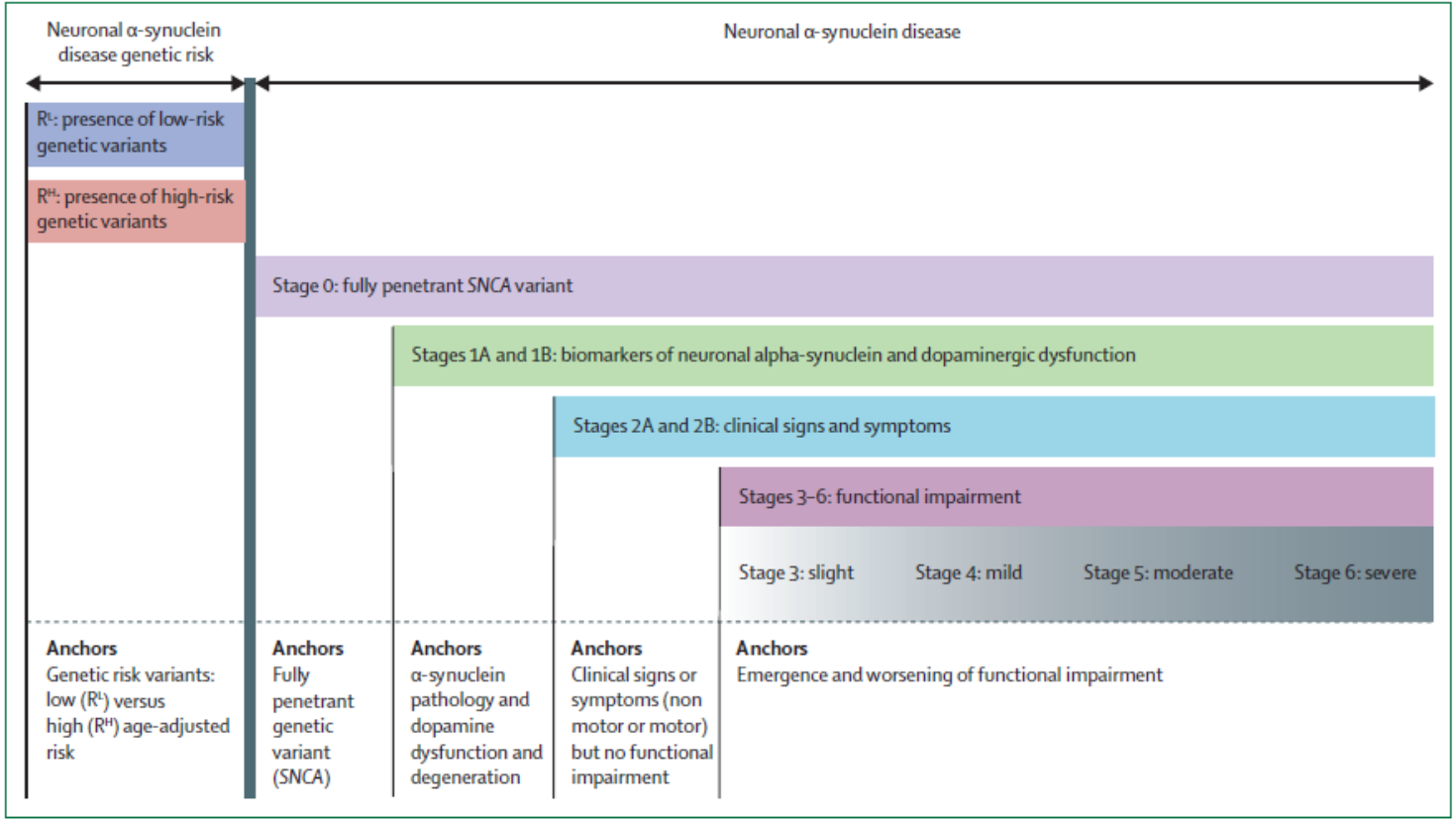
Donadio et al. Scientific Reports. 2018

CSF alpha synuclein seeding amplification assay





Concha-Marambio et al. Nat Protocols. 2023



Simuni et al. Lancet Neurol. 2024

Treatment (all off label)

Parkinsonism

- Levodopa

Cognitive impairment

- Cholinesterase inhibitors
- Namenda?

Hallucinations

- **ATYPICAL** antipsychotic medications (quetiapine, pimavanserin or clozapine)
- Cholinesterase inhibitors

REM sleep behavior disorder

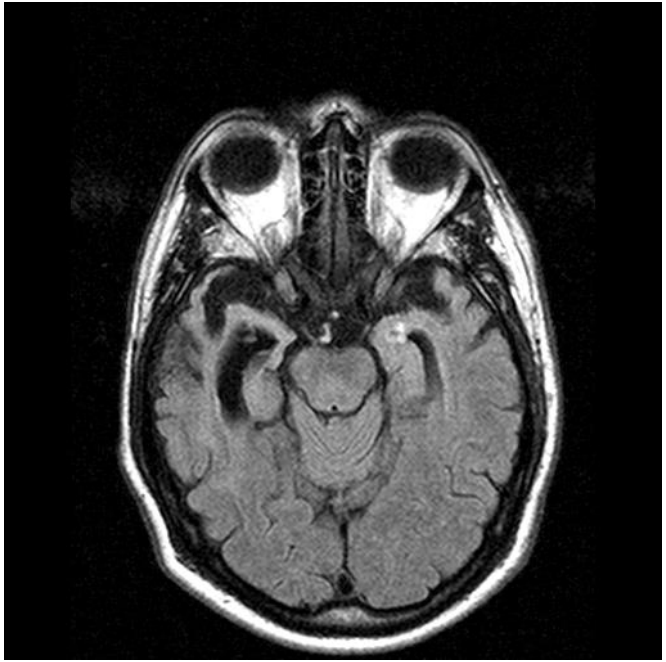
- Clonazepam
- Melatonin

Case

Case continued

59 year old brought in by his spouse with marked decreased emotionality toward his wife and poor insight into any problems.

Mini Mental State Examination score of 29



Poll

What's the diagnosis?

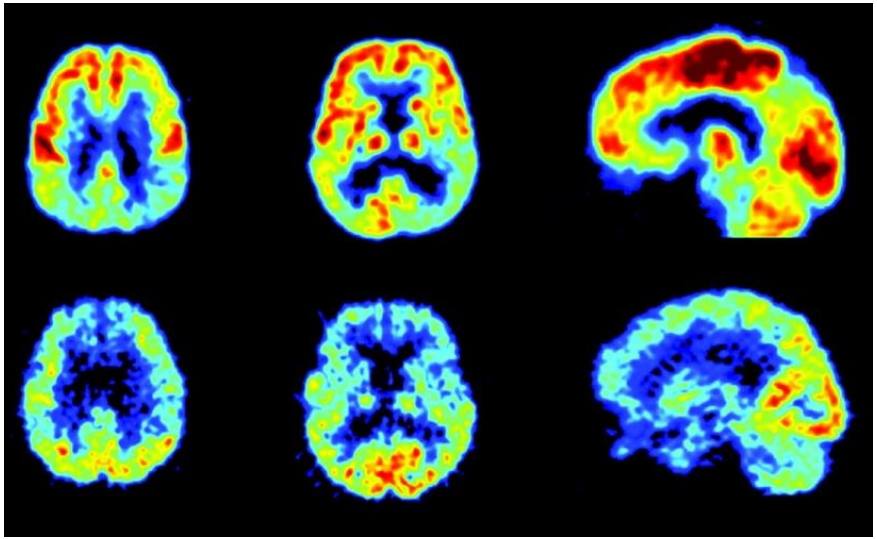
1. Alzheimer's disease
2. Dementia with Lewy bodies
3. Frontotemporal dementia
4. Mild cognitive impairment
5. Vascular dementia

Diagnostic tests

FDG-PET:

With proper presentation methods, FDG-PET can distinguish between AD and FTD with 90% accuracy.

Foster, et. al. Brain, 2007

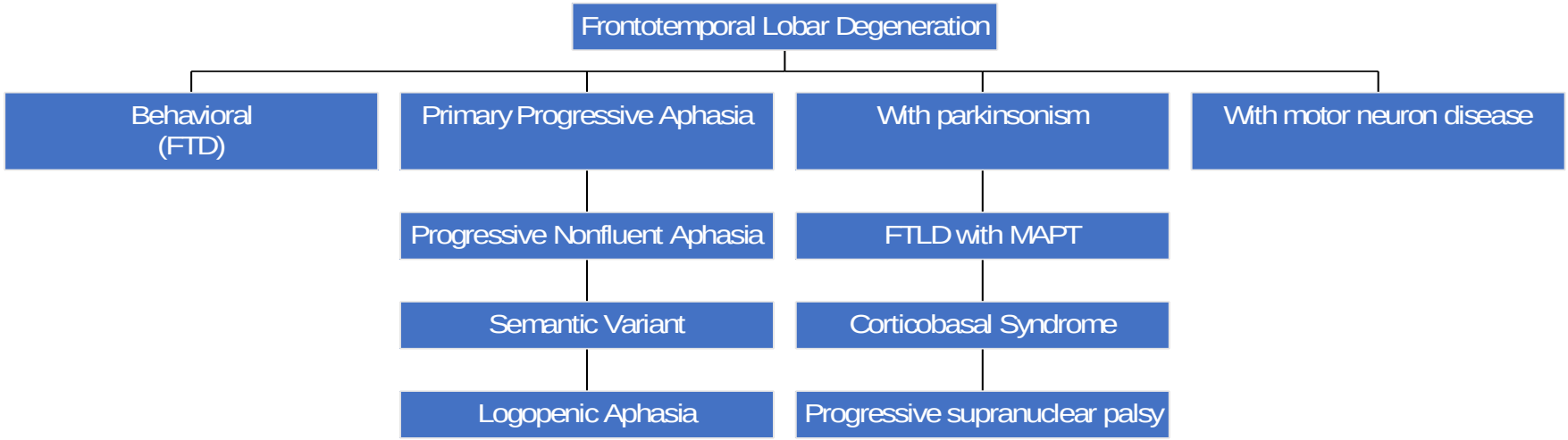


AD

FTD

Jagust, et. al. Neurology. 2007.

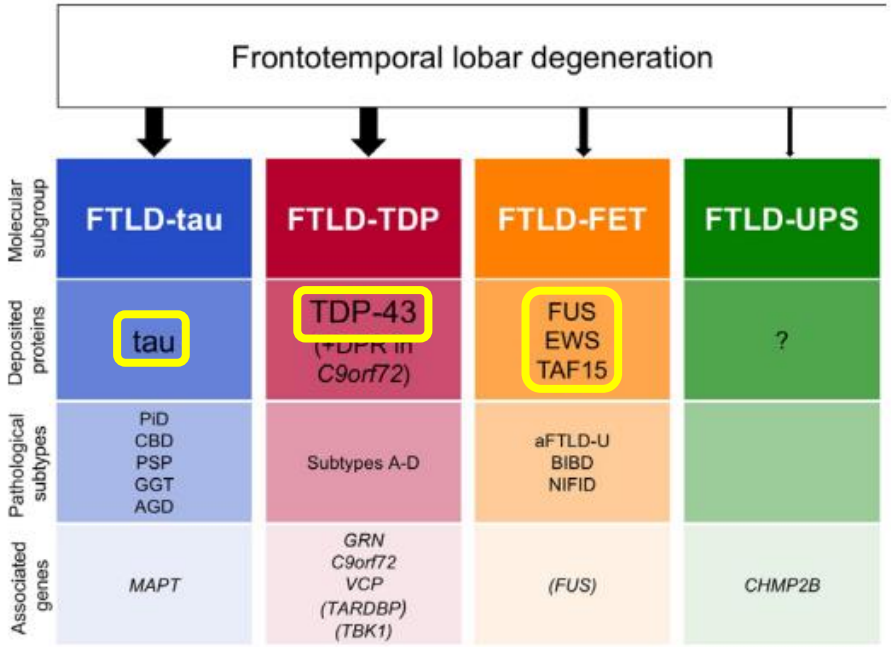
Clinical Classification



FTD = Frontotemporal dementia
FTLD = Frontotemporal lobar degeneration
MAPT = Microtubule associated protein Tau

Pathologic Classification

As many as 40 percent of patients with FTD may have a genetic cause



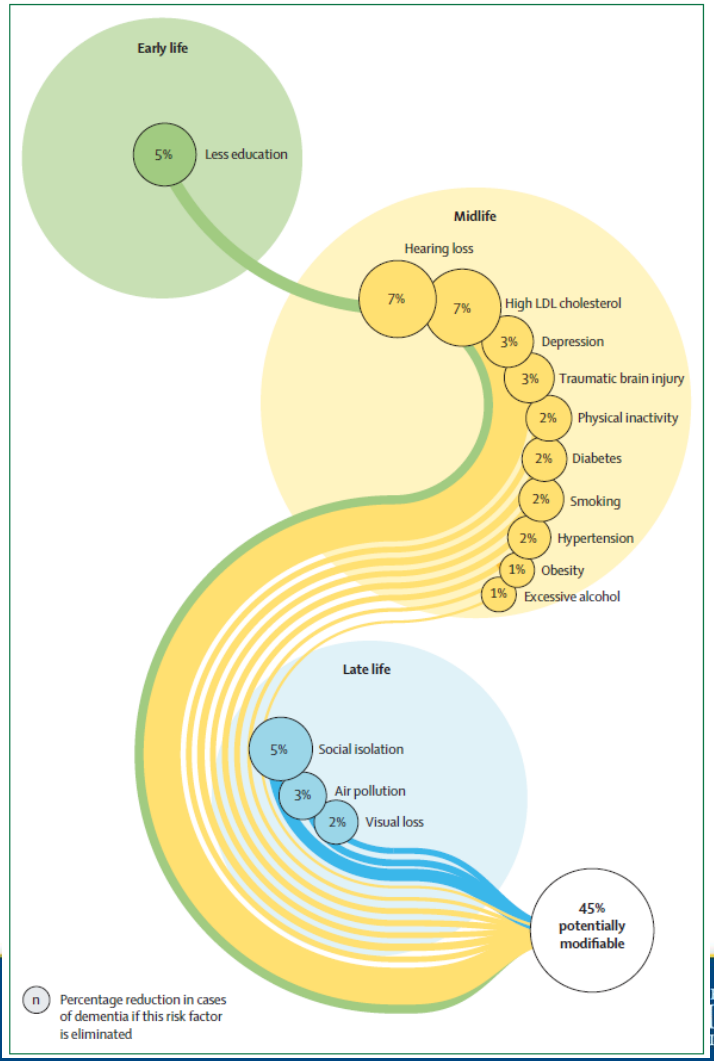
Neumann and Mackenzie. Neuropath and App Neurobiol. 2019

Prevention of dementia

1. Cognitive activity
2. Depression
3. Mediterranean diet
4. Obesity
5. Hypertension
6. Smoking
7. High cholesterol
8. Type 2 diabetes
9. Physical inactivity

Rolandi et al. Alz Res Ther. 2020

As much as 40% of dementia may be preventable



Livingston et al. Lancet. 2024

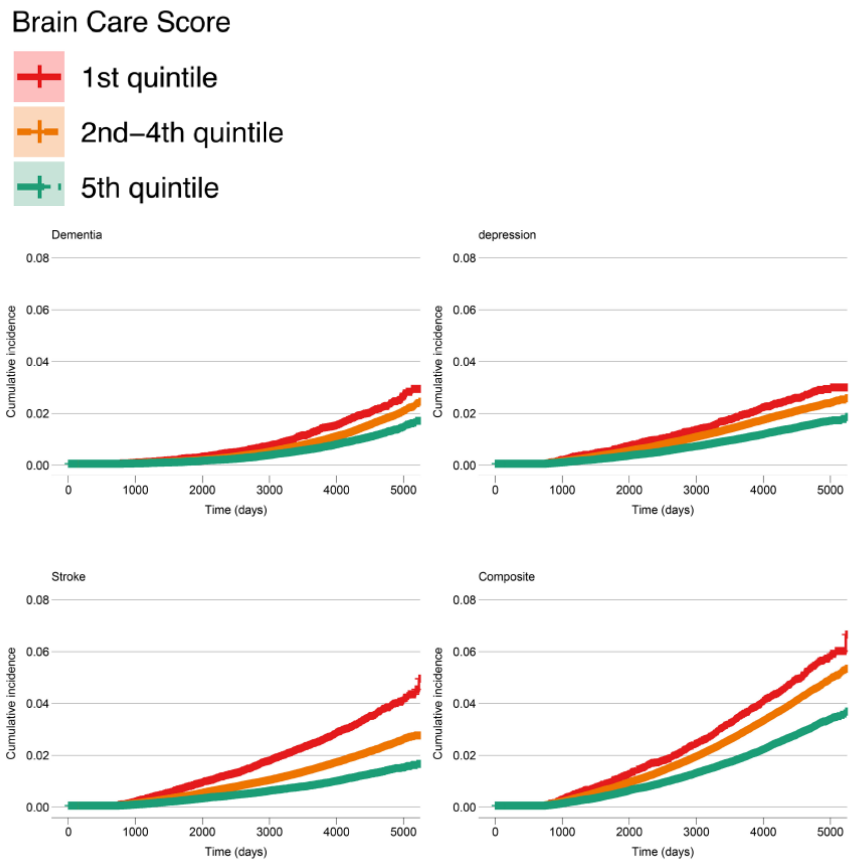
McCANCE
Brain Care Score™

MASSACHUSETTS GENERAL HOSPITAL
McCANCE CENTER FOR BRAIN HEALTH

Category		Criteria / Description	Rank	Score
Physical	Blood Pressure	Resting blood pressure greater than 140/90, with or without treatment	0	
		Resting blood pressure 120-139/80-89, with or without treatment	2	
		Resting blood pressure less than 120/80	3	
	Blood Sugar	Hemoglobin A1c greater than 6.4	0	
		Hemoglobin A1c between 5.7 and 6.4	1	
		Hemoglobin A1c less than 5.7	2	
	Cholesterol	190 or higher	0	
		No treatment required or less than 190 mg/dL	1	
		If cardiovascular disease is present, LDL is in accordance to the latest CDC recommendations	1	
	BMI	Lower than 18.5 kg/m^2	1	
		18.5-25 kg/m^2	2	
		25-29.9 kg/m^2	1	
		Greater than 30 kg/m^2	0	
Lifestyle	Nutrition	**Dietary habits:** • 4.5 servings of fruit and vegetables per day; • 2 servings of lean protein per day • 3 or more servings of whole grains per day • Less than 1,500 mg of sodium per day • Less than 36 oz of sugar sweet beverages (soda, juice, etc.) per week		
		Typical weekly diet does not include at least 2 of the recommendations above	0	
		Typical weekly diet includes 2 or more of the recommendations above	1	
		Typical weekly diet includes 3 or more of the recommendations above	2	
	Alcohol	4 or more alcoholic drinks per week	0	
		2-3 alcoholic drinks per week	1	
		0-1 alcoholic drink per week	2	
	Smoking	Current smoker	0	
		Never smoked or quit more than a year ago	3	
	Aerobic Activities	Less than 150 minutes of moderate or 75 minutes of high intensity physical activity per week	0	
		At least 150 minutes of moderate physical activity (ex. walking) or 75 minutes of high intensity physical activity per week	1	
	Sleep	Untreated sleep disorder and/or sleeps <7hrs per night	0	
		Treated sleep disturbances and 7-8 hours of routine sleep per night	1	
Social Emotional	Stress	High level of stress that often makes it difficult to function	0	
		Moderate level of stress that occasionally makes it difficult to function	1	
		Manageable level of stress that rarely makes it difficult to function	2	
	Social Relationships	I have few or no close connections other than my spouse or children	0	
		I have at least two people, other than my spouse or children, that I feel close with and could talk about private matters or call upon for help	1	
	Meaning in Life	I often struggle to find value or purpose in my life	0	
		I generally feel that my life has meaning and/or purpose	1	

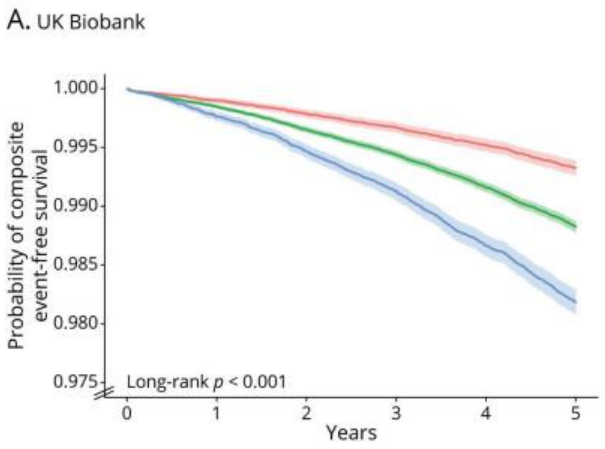
The components above reflect the latest, scientific based key contributors to brain health. It is important to discuss your score with a healthcare professional.

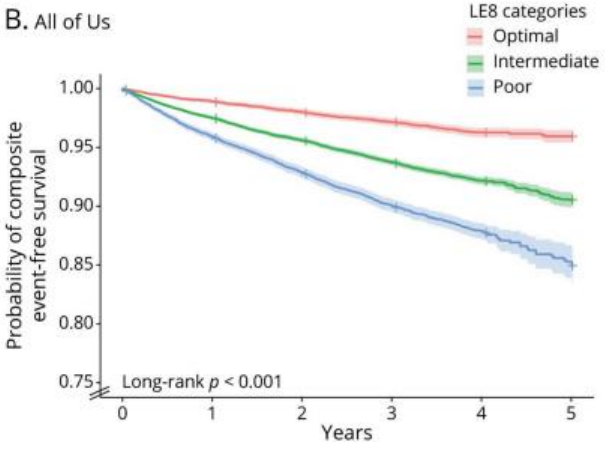
Total Brain Care Score (0-21)



Singh et al. Frontiers Psychiatry. 2024

UNIVERSITY of ROCHESTER MEDICAL CENTER

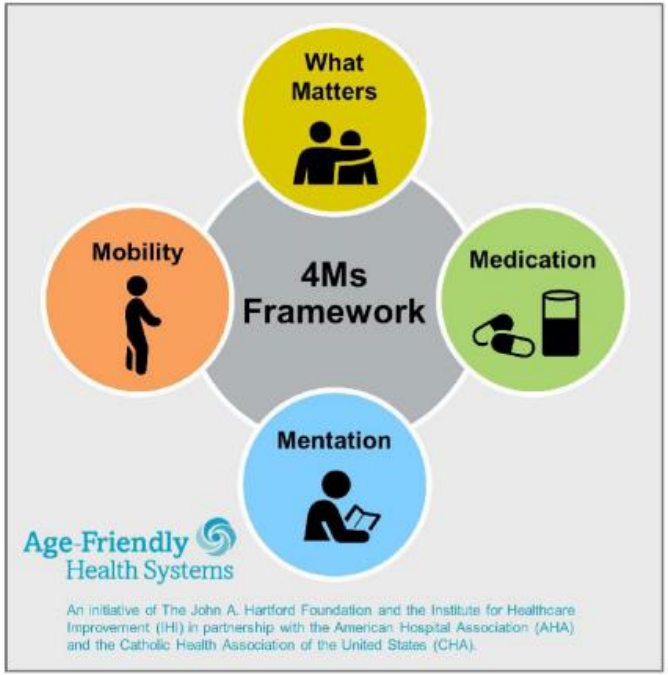




Two stage (discovery and replication) prospective study using composite outcome: new stroke of any type, dementia, or depression

Cliocchiotta-Tuozzi et. al. Neurology. 2024

Overlap with other programs



Six pillars of lifestyle medicine: (top right clockwise) nutrition, physical activity, relationships, sleep, risky substances and stress.

We can (and should) prevent dementia

URMC NeuroHealth initiative (NHI)

1. Formalize a Trans-Departmental NHI to foster collaboration and support coordinated, efficient NeuroHealth care and clinical research across URMC.

2. Improve access to high quality, coordinated, biopsychosocial medical and surgical NeuroHealth care in the Rochester and the Region

3. Scale delivery of personalized, cutting edge medical and surgical neurotherapeutics.

4. Expand the breadth of URMC NeuroHealth clinical trials – Access to NeuroHealth clinical trials for all who need them

5. **Develop a Neuroprevention program within the NHI to promote primary and secondary neuroprevention and wellness**

6. Promote NeuroHealth Equity in Rochester and the Region

What did we learn?

- Diagnosis of AD is still clinical, but there are a number of tests that may be able to help confirm a diagnosis.
- Many of the steps in the pathologic cascade of AD have been identified and involve the production of Aß, inflammation, excitotoxicity, synaptic degradation and cell death.
- There are treatments for AD and many support options.
- Protein deposition is a common feature in neurodegenerative disease and is seen in AD, DLB and FTD.

Questions?