EXHIBIT D

Update on the Diagnosis and Treatment of Alzheimer's Disease

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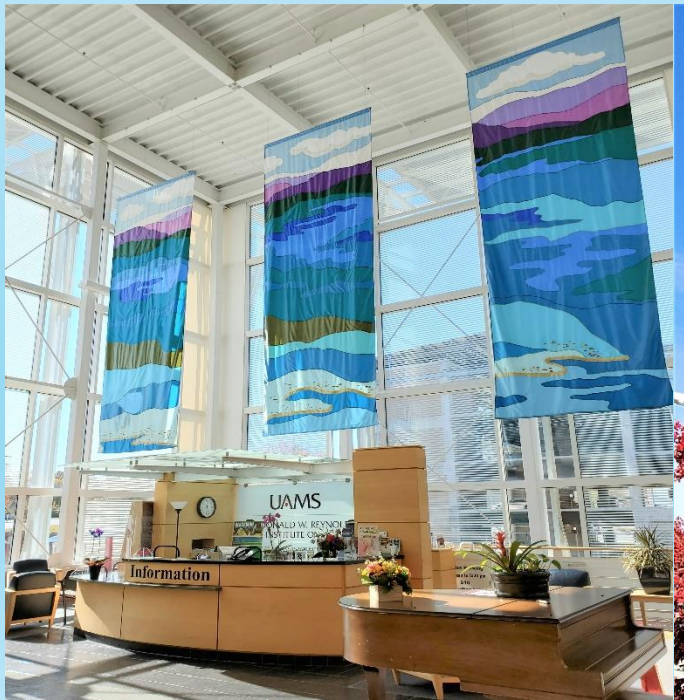
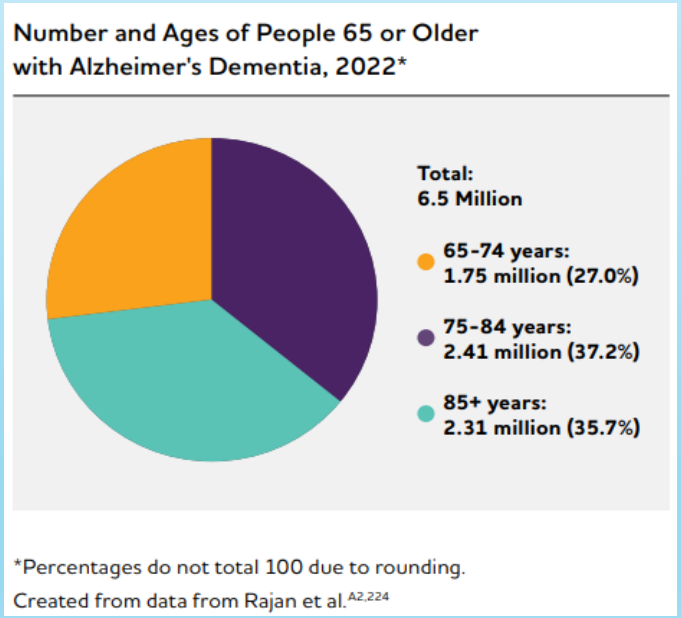
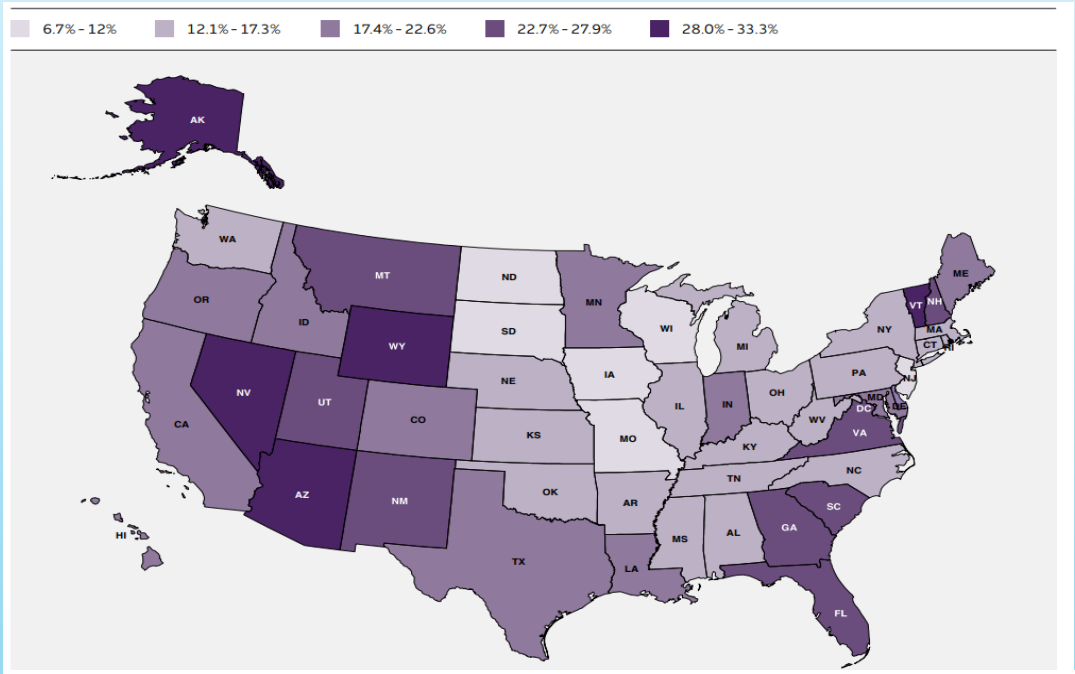


Major neurodegenerative disorders or dementias
Focus on Alzheimer's disease

In the U.S. AD is the 5th leading cause of death in > 65yrs.

5 million people suffer from Mild Cognitive Impairment due to AD





State	Projected Number with Alzheimer's (in thousands) 2020	2025	Percentage Increase 2020-2025
Arkansas	58	67	15.5

Projected increase in AD prevalence

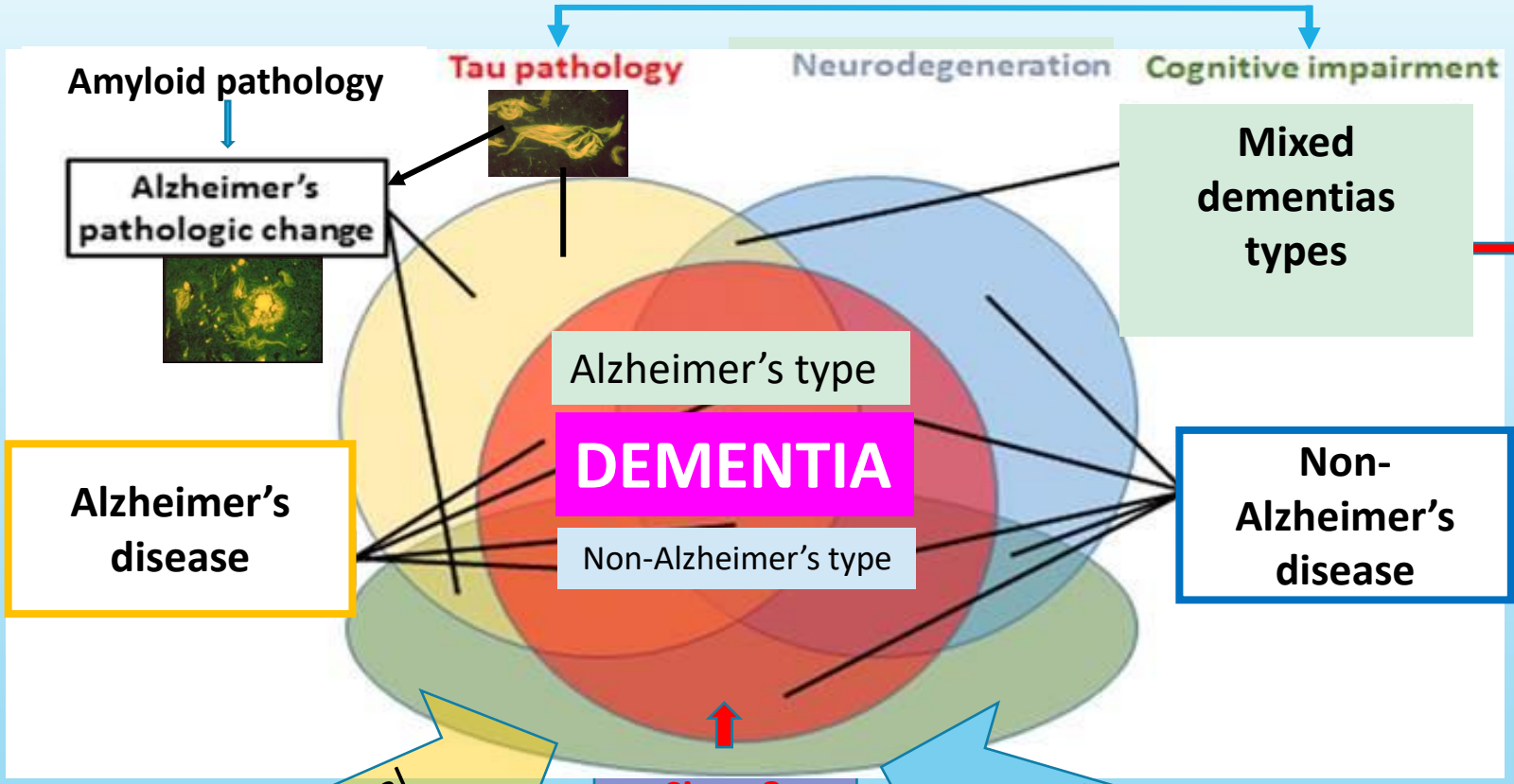
20 new cases of AD every minute worldwide

Shouldn’t the diagnosis of Alzheimer's disease be straightforward?

- Alzheimer's dementia may be misdiagnosed by experts in up to 30% of cases.
- We know this because patients misdiagnosed with AD did not display classic neuropathologic changes of plaques and tangles on autopsy and some had normal amyloid PET and normal CSF. Hence, their dementia was not due to AD.
- Symptoms with predominant memory changes or amnestic dementia is not specific for AD and could be due to other types of dementias e.g. vascular.
- Non-memory related cognitive difficulties with visuospatial, language and executive function might be an early feature of AD and could be mistaken for frontotemporal or other dementias,
- 30-40% of cognitively normal older adults have some AD neuropathological changes at autopsy but they never experienced memory issues.

Nelson PT et al, 2011, Serrano-Pozo et al, 2014, Rodrigue KM et al 2012 Dubois B et al, 2010, Gaugler et al 2013, BD James et al 2020

Biological and clinical overlap of Alzheimer's disease and non-Alzheimer's dementias



- Vascular -angiopathy or strokes, bleeding
- TBI - Trauma, infections (Covid 19), inflammation
- Frontotemporal (FTD), Tau proteinopathy, TDP43
- Lewy Body dementia
- Hippocampal sclerosis

Adapted from Jack et al, Alzheimer's and Dementia, 2018

Features needed for a diagnosis of dementia are based on DSM-5 Criteria for major neurocognitive disorders (dementia)

- **Significant cognitive impairment in at least one of the following domains:**
  - **Learning and memory**
  - **Language**
  - **Executive function**
  - **Complex attention**
  - **Perceptual-motor function**
  - **Social cognition/emotion**
- **The impairment must be acquired and represent a significant decline from previous level of functioning**
- **The cognitive deficits must interfere with independence in everyday activities**
- **The cognitive disturbances do not occur exclusively during the course of delirium or should not be accounted for by another mental disorder (e.g. major depression, Schizophrenia)**

Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5), 2013.

Risk factors

Definite (non-modifiable)

- Age 5% 65-75; 33% over 85
- Gender – slightly more in females (survival effect)
- Family Hx – (Dominantly inherited AD, DIAD)
- APOE4 (1 allele, risk x 3, 2 alleles risk x 12)
- ABCA7 (risk x2)
- Down's Syndrome – trisomy 21

Geneti Percentage of Blacks/African Americans and European Americans with Specified APOE Pairs

APOE Pair	Blacks/African Americans*	European Americans
e3/e3	45.2	63.4
e3/e4	28.6	21.4
e3/e2	15.1	10.2
e2/e4	5.7	2.4
e4/e4	4.5	2.4
e2/e2	0.7	0.2

Created from data from Rajan et al.[70]

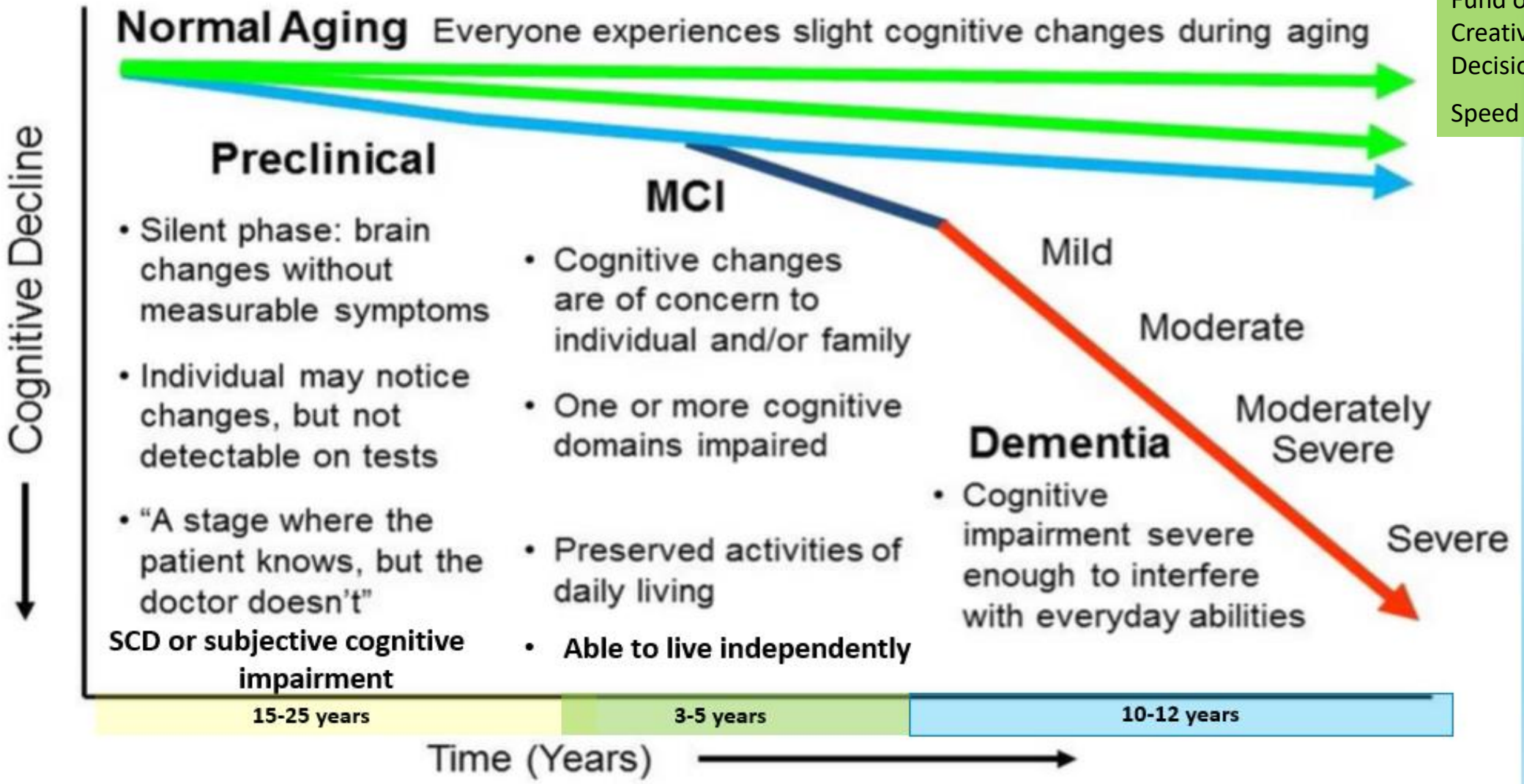
*Percentages do not total 100 due to rounding

DIAD (age of onset, 30-60) approx. 1%.
AD, type 1 is caused by mutations in the APP gene (DIAD)
AD, type 3 is caused by mutations in the PSEN1 gene (DIAD)
AD, type 4 is caused by mutations in the PSEN2 gene. (DIAD)
AD, type 2 is multifactorial interaction of a number of genes with environment & lifestyle. Late-onset AD

Difference between Normal Aging, MCI and Dementia

Experience
Fund of knowledge
Creativity
Decision making

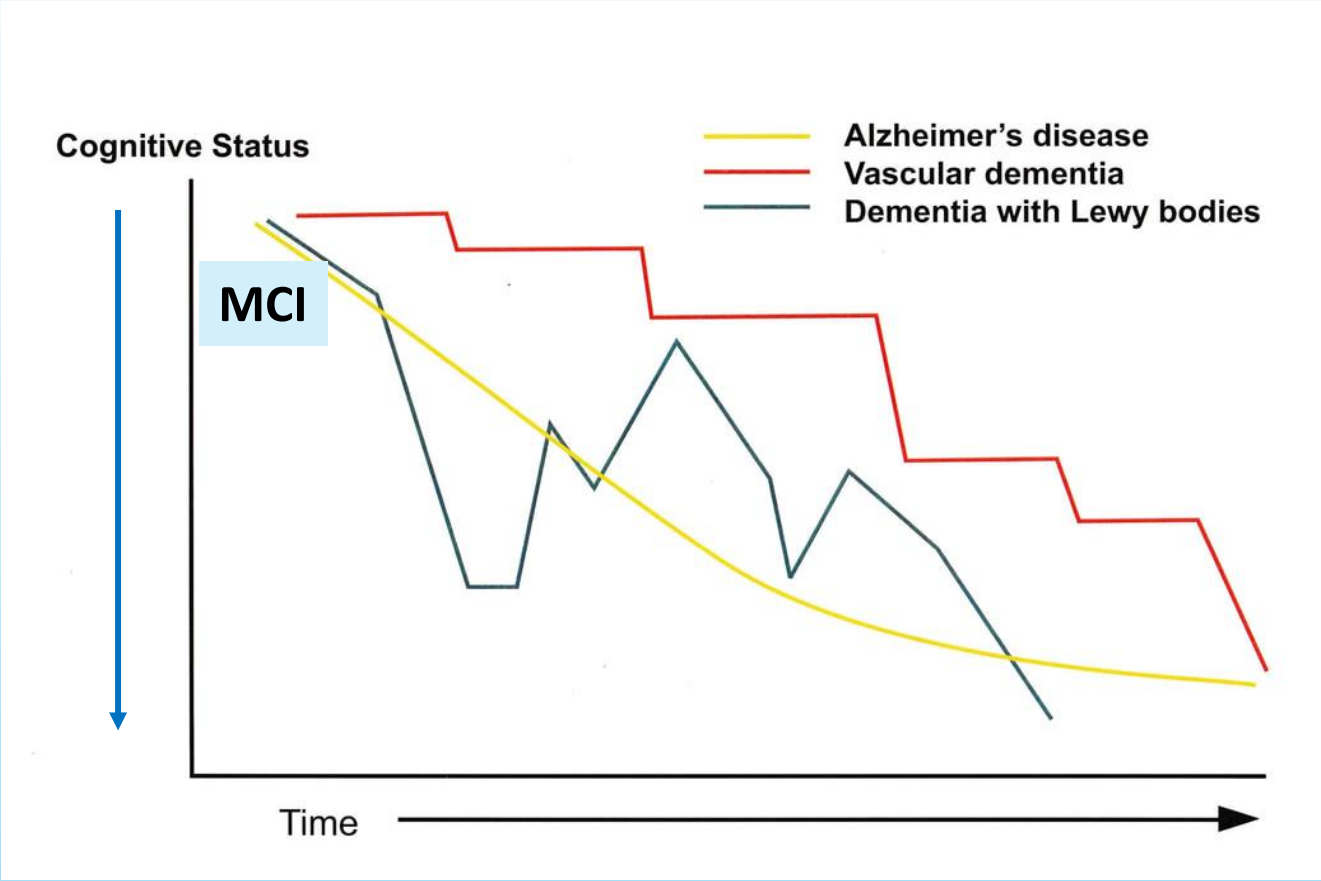
Speed of processing



Alzheimer's Disease continuum – duration of each part influenced by age, genetics, gender +other factors

Prognosis and typical progression

- Approx 50% of individuals with MCI do not develop dementia.
- In some instances, MCI is reversible.
- In MCI that progress to dementia, approx. 1/3 have MCI due to AD.



- Accurate diagnosis of MCI due to Alzheimer's disease is crucial in identifying individuals who might benefit from early treatment.
- Initiation of treatment earlier in the disease process may be associated with lower overall health care costs and reduced need for costly assisted living, nursing home and other types of residential care

Steps in dementia diagnosis

History

- Patient's perspective
- Caregiver 's perspective

- **Examination** (physical and cognitive)
  - Exclude confounding and potentially reversible factors

Laboratory tests

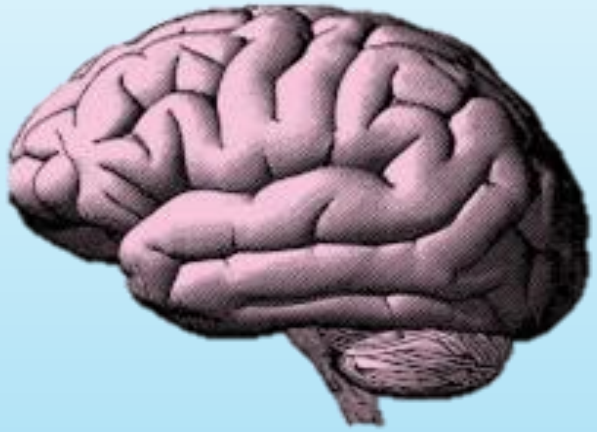
Brain Imaging

Special tests

Are there “reversible” causes of cognitive decline, MCI or dementia?

Confounding factors in the diagnosis of dementia

3 common types of brain dysfunction



The brain has more than 100 chemicals

Acetylcholine, Serotonin, Dopamine, Norepinephrine, Glutamate,
GABA, Histamine, Endorphins, Oxytocin, Vasopressin

Depression **Dementia** **Delirium**

(acute confessional state)

Delirium as a reversible cause of memory loss or cognitive decline

Can persist for days, weeks or months

- **C**onstipation
- **O**perations (anesthesia, pain)
- **N**utrition (anemia, B1, B12 folate, deficiency)
- **F**luids (dehydration or over-hydration)
- **U**rinary tract infections (other common infections like pneumonia)
- **S**leep, obstructive sleep apnea, sleep deprivation
- **E**nvironment (hospitalization) electrolytes, endocrine issues like thyroid disorders
- **D**rugs (opioids, medications for sleep/anxiety, alcohol, chemotherapy)

Repeated or long-standing delirium increases the risk for dementia

Screening tests (cont…)

Mini-mental State Examination (MMSE)

11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. MMSE was most widely used until recently (copyright).

Sensitivity (Se) of 79.8%, a specificity (Sp) of 81.3%,

Scores: Normal > 25-30; Mild dementia 20-24; 13-19 Moderate dementia; less than 13 severe dementia

Limitations of MMSE: illiteracy/low education, poor hearing and vision, paralysis, aphasia, Parkinson's

Montreal Cognitive Assessment (MoCA) for MCI or dementia

The results of MoCA for sensitivity, specificity, positive and negative predictive values, and classification accuracy are superior compared to the MMSE (copyright and certification needed)

Sensitivity (Se) of 90%, a specificity (Sp) of 87%

Scores: Normal 26-30; MCI 18-25 MCI; Dementia, moderate 10-17; Dementia, severe <10

Same limitations as MMSE

Screening tests (cont…)

AD8. This screening test is designed as an informant screening tool, but may be administered to the patient. It consists of eight questions about changes in the person's thinking, memory and behavior.

QDRS – Quick Dementia Rating Scale. Scores in the "normal" range suggest that a dementing disorder is unlikely, but a very early disease process cannot be ruled out.

Self administered or informant.

If screening tests are negative, borderline or there are overlapping features of clinical diagnosis, detailed cognitive evaluation is very useful.

Neuropsychological tests (NPT) NPT can help determine the cause of dementia. Different dementia types have distinguishable NPT profiles.

NPT also provides valuable opportunities for cognitive rehabilitation, patient and caregiver counseling (Cognitive behavioral therapy, CBT).

Laboratory tests

- CBC - Anemia or polycythemia
- Hypothyroidsm
- Homocysteine
- B1, B12, folate & D deficiency
- Lipids
- Glucose, A1C
- Infections, esp urinary tract
- BMP
- Renal insufficiency
- CSF exam (not routine)

If irregular pulse, tachy or bradyarrhythmia, check EKG

Clinical impression and presumptive diagnosis

Subjective Cognitive Impairment (SCD)

- characterized by self-perceived decline in cognition, but cognitive performance scores are in normal range

Mild Cognitive Impairment (MCI) - approx. 50% progress to Major Neurocognitive disorder or dementia within 5-10 yrs

- scores below normal range with normal ADLs and usually normal IADLs

Major Neurocognitive disorder or Dementia

- scores below normal range with varying degrees of impairment in IADLs and ADLs

What is the etiology or underlying basis for MCI or dementia? Is it Alzheimer's disease?

Brain imaging in AD

Value of MRI, MRA, CT, CTA in dementia diagnosis

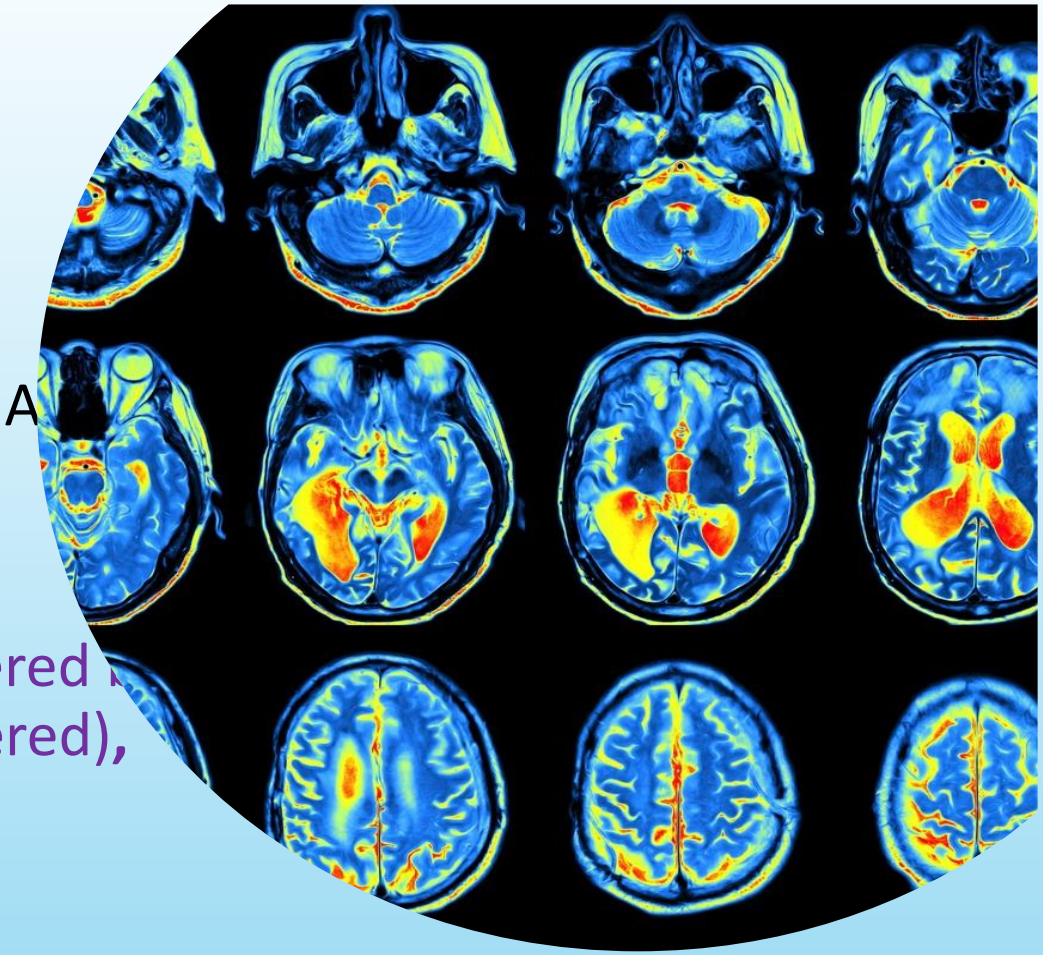
- Hippocampus portion of the brain is like the “hard drive” of the computer and is key for memory. Hippocampal shrinkage or atrophy maybe present before dementia onset and progresses with worsening of AD.

- When hippocampal size was found to be below normal in MCI patients, there was a 4-fold in the percentage of individuals converting to dementia within five years

- Other structural changes – bleeding, infarcts, tumors, aneurysms, microangiopathy, NPH

Alzheimer’s Association Neuroimaging Work Group Consensus Report

Value of PET scans in AD



- PET imaging with different tracers offers reliable biomarkers in dementia, esp useful in distingusing A from FTD
- Different PET tracers; **Amyloid PET scans** (not covered insurance, cost $4-$5,300), **FDG18 PET scans** (covered), Tau PET scans (research).
- PET imaging can give more accurate information regarding prognosis, management, and treatment.
- Other imaging techniques – DaT scans for Parkinson's

Berti MD, V., Pupi MD, A., & Moscani MD, L. (2013, July). *PET/CT in diagnosis of dementia*. NCBI. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3692287/

There are many possible causes of MCI or dementia directly related to intrinsic brain pathology

Clinical features might be helpful

- Alzheimer's disease (Familial, DIAD or Late onset) – amyloid & Tau
- Vascular dementia – (evidence of strokes or other cardiovascular factors)
- Lewy Body dementia – (early hallucinations)
- Frontotemporal dementia FTD (45-60yrs, Tau or TDP43, behavioral issues)
- LATE limbic age-related, TDP43 encephalopathy – hippocampal atrophy
- Parkinson's disease
- Mixed dementias
- Normal pressure hydrocephalus (NPH, gait abnormalities, urinary incontinence, dementia)

Factors outside the brain contributing to MCI and/or dementia

Identify, investigate and treat

- Hypertension or Hypotension
- Heart failure
- Brady or tachyarrhythmias
- CABG
- Anemia or polycythemia
- Hyperlipidemia
- Diabetes mellitus
- Sleep apnea or other sleep disorders
- Depression/anxiety
- Episodes of delirium
- Hearing or visual impairment
- Hypothyroidism or Hyperparathyroidism
- Liver disease
- Renal disease
- Infectious diseases: HIV, Covid-19, other viral infections
- Head trauma
- Chronic Traumatic Encephalopathy (CTE)
- Brain tumors, primary or metastatic
- Brain aneurysms
- Seizure disorder
- Vitamin deficiencies: B1, B12, folate, homocysteine
- Alcohol, smoking or substance abuse
- Polypharmacy
- Potentially inappropriate medications

Discuss with patient/caregiver

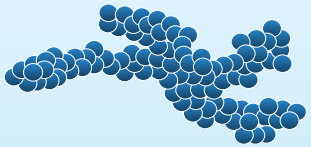
Special tests used for diagnosis of Alzheimer's disease

Biomarkers

- Changes in biomarkers (brain imaging, CSF or blood) may be evident 15-25 years before patients and caregivers express problems with memory

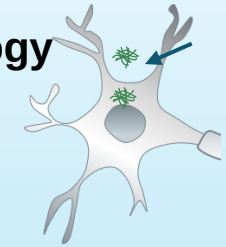
- Biomarkers are useful for identifying appropriate patients for interventions or treatment

Neurodegeneration cause by abnormal or misfolded proteins that accumulate or cause inflammation: potential protein biomarkers



Aβ pathology
- Aβ42
- Aβ40

Tau pathology
- t-tau
- p-tau

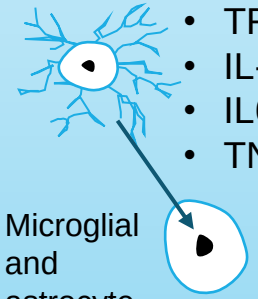


Neurofibrillary tangles

Synaptic dysfunction
- Neurogranin
- SNAP-25

N E U R O D E G E N E R A T I O N

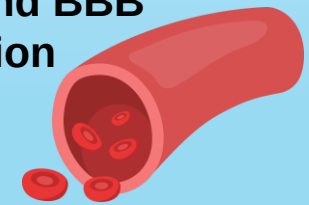
Inflammation
- TREM2
- IL-1ß
- IL6
- TNFα



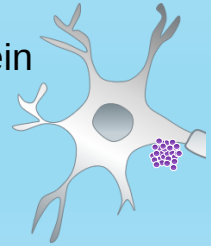
Microglial and astrocyte activation

GFAP - Glial fibrillary acidic protein is a blood biomarker for astrocytic activation and indicates neuroinflammation.

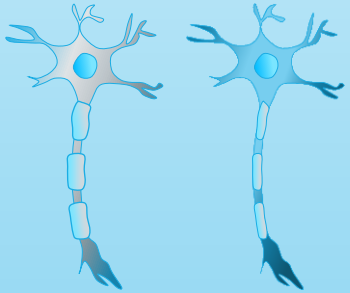
Vascular and BBB dysregulation
- PDGFRβ
- NO



α-Synuclein inclusions
- α-synuclein



Neuronal injury
- NfL



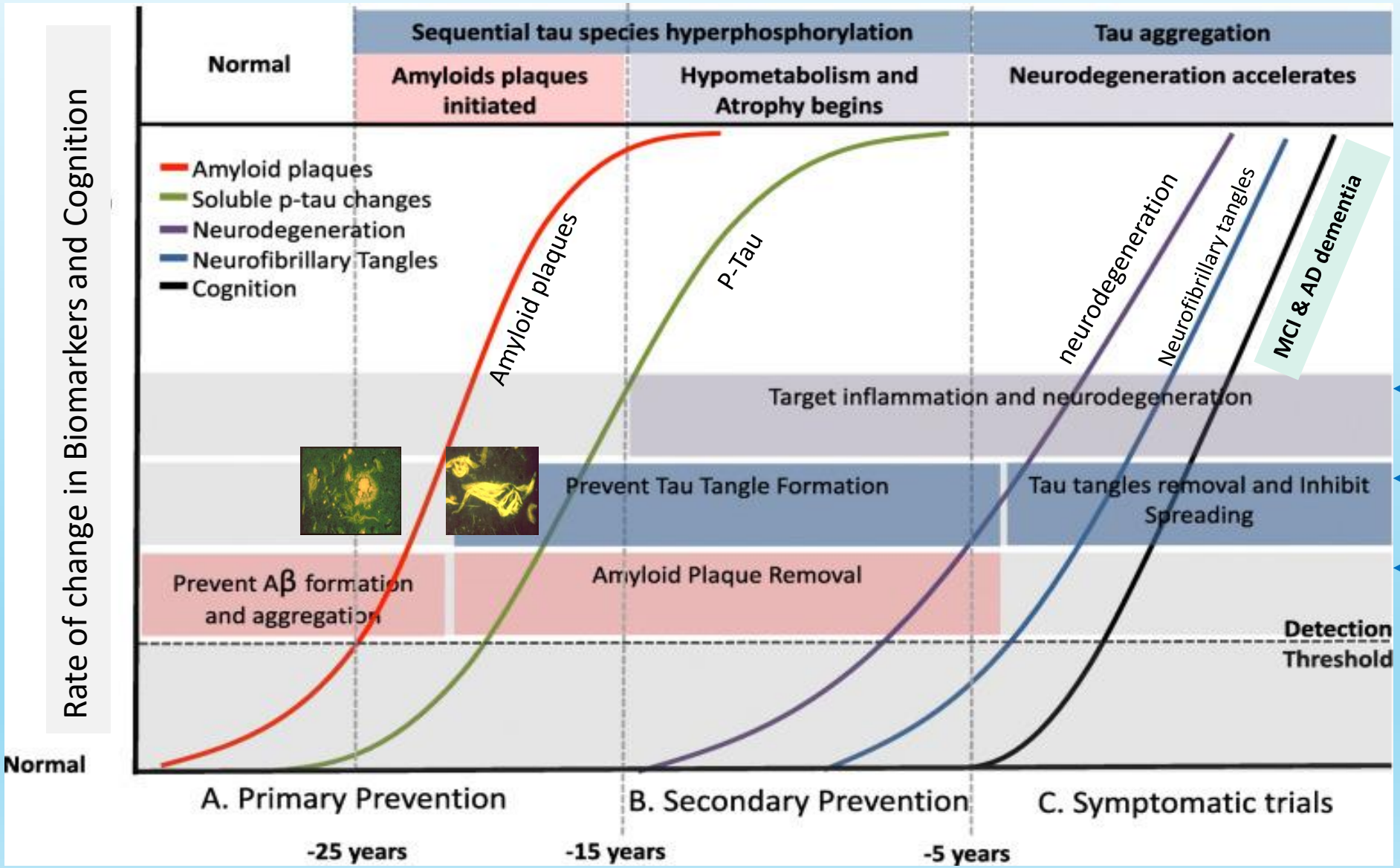
Healthy neuron

Injured neuron

Neurofilament light (NFL), part of neuronal cystoskeletan is modestly increased in AD in CSF and plasma

Adapted from Molinuevo et al, 2018

Using biomarkers in clinical trials to identify patients with AD earlier and track progress of treatment



The question is not, whether to intervene or not to intervene -

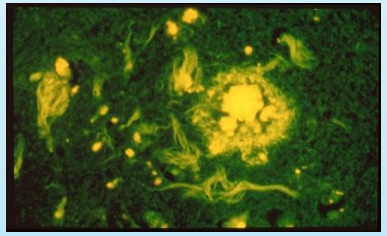
The question is when should we intervene?

Adapted from McDade et al, 2021

NIA-AA research framework for biological biomarkers

Mapping the the amyloid, Tau and Neurodegeneration (A,T,N) framework

Focus on Amyloid

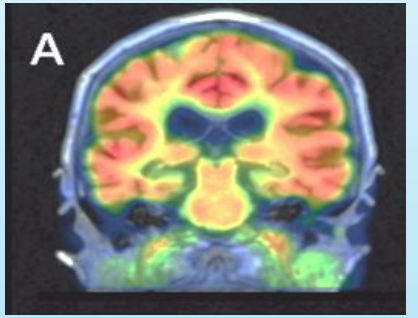


ß Amyloid-based plaques

Major pathological proteins – amyloid A:

Amyloid PET

CSF or plasma Aβ42/40

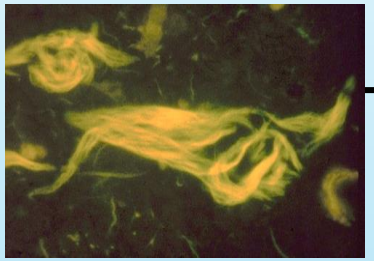


Amyloid PET scan

- As AD progresses and Aβ42 forms plaques its concentration in the CSF and blood is reduced.
- In AD patients Aβ42/40 ratio in CSF is 40% lower than normal controls

The A,T,N framework

Focus on Tau

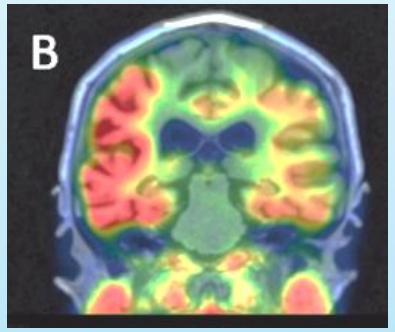


Tau-based Neurofibrillary tangles

Major pathological proteins –Tau T:

Tau PET,

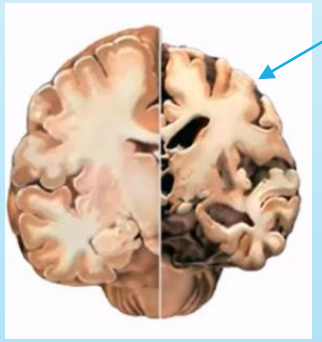
CSF or plasma P-tau



- Plasma pTau maybe high x2 to x4 fold in AD
- pTau increases early even before symptoms develop).
- It also accumulates in non-AD pathologies such as progressive supranuclear palsy (PSP), corticobasilar degeneration, chronic traumatic encephalopathy (CTE), cerebellar ataxia, FTD – hence, clinical correlation is important.

The A,T,N framework

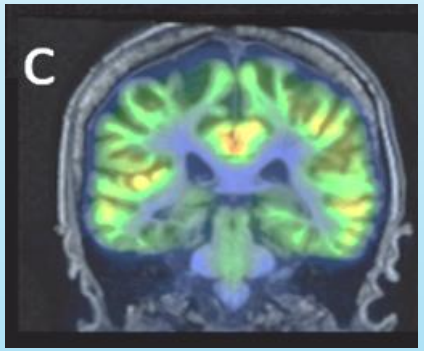
Focus on neurodegeneration: Imaging of brain atrophy, neuron loss and dysfunction



N: **Anatomical & metabolic**

MRI: atrophy

FDG PET: neuronal glucose use



Other neurodegeneration markers:

- **NFL in** plasma and CSF increase in DIAD 7 years before symptom onset.
- **GFAP** glial fibrillary astrocytic protein GFAP, is markedly increased in AD but may be increased in several other CNS pathologies.

NIA-AA research framework for biological biomarkers 2011

Biomarker profiles and categories

	AT(N) profiles	Biomarker category	
1	A-T-(N)-	Normal AD biomarkers	
2	A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
3	A+T+(N)-	Alzheimer's disease	
4	A+T+(N)+	Alzheimer's disease	
5	A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
6	A-T+(N)-	Non-AD pathologic change	
7	A-T-(N)+	Non-AD pathologic change	
8	A-T+(N)+	Non-AD pathologic change	

- Similar to cancer staging, dementia staging can be complex.
- Every individual can be placed into one of the 8 profiles based on biomarkers

The term "Alzheimer's continuum" is an umbrella term that denotes either Alzheimer's pathologic change with A+ positivity (pre-clinical) or clinical Alzheimer's disease.

Pre-clinical or clinical dementia, but not Alzheimer's disease.

C.R. Jack Jr. et al 2018.

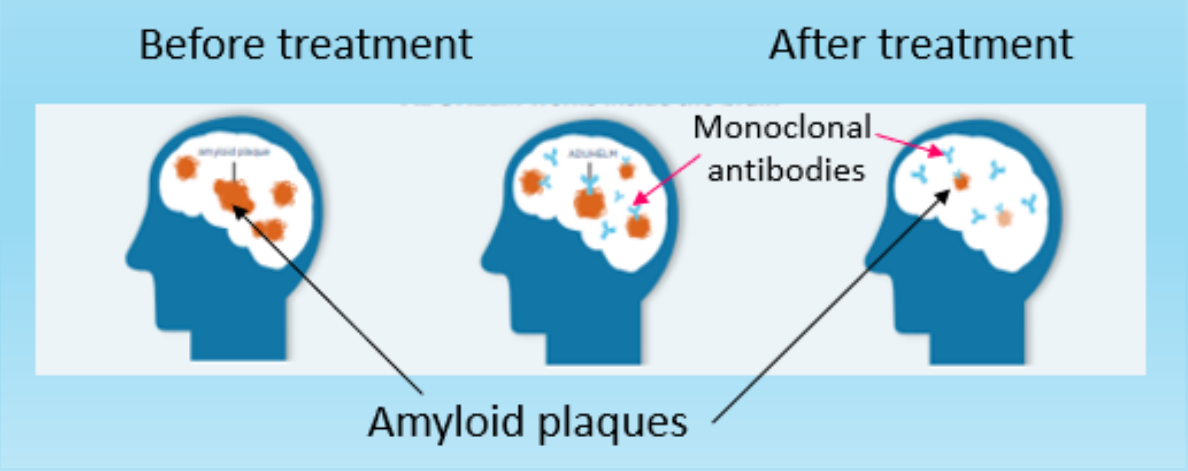
Common side-effects of Cholinesterase inhibitors

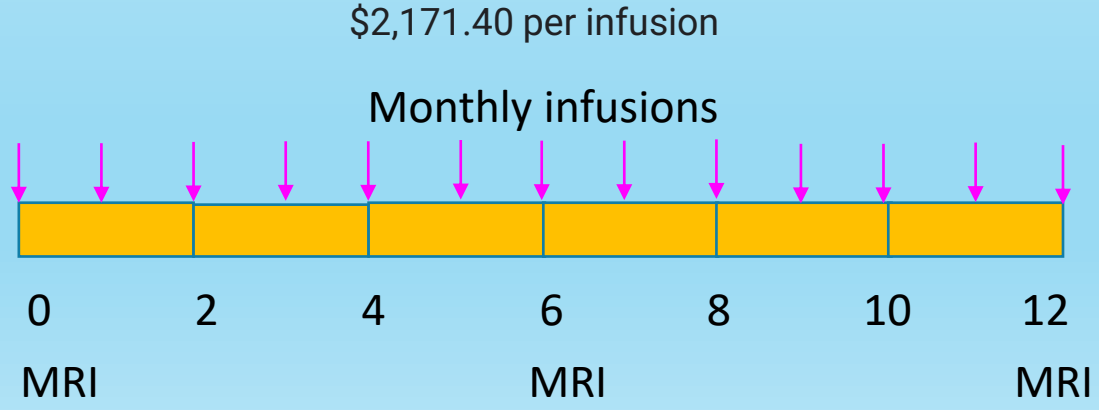
- Gastrointestinal
  - diarrhea, gastritis (rare – GI bleed)
- Cardiovascular
  - hypotension, bradycardia, dizziness -- can be serious
- Sleep
  - vivid dreams, nightmares
- Liver
  - increased enzymes
- Drug interactions
  - especially with beta-blockers, ppt bradycardia

Treating the root cause of disease
Monoclonal Antibodies against Amyloid

Aducanumab (brand name, Aduhelm) – accelerated FDA approval June 7, 2021

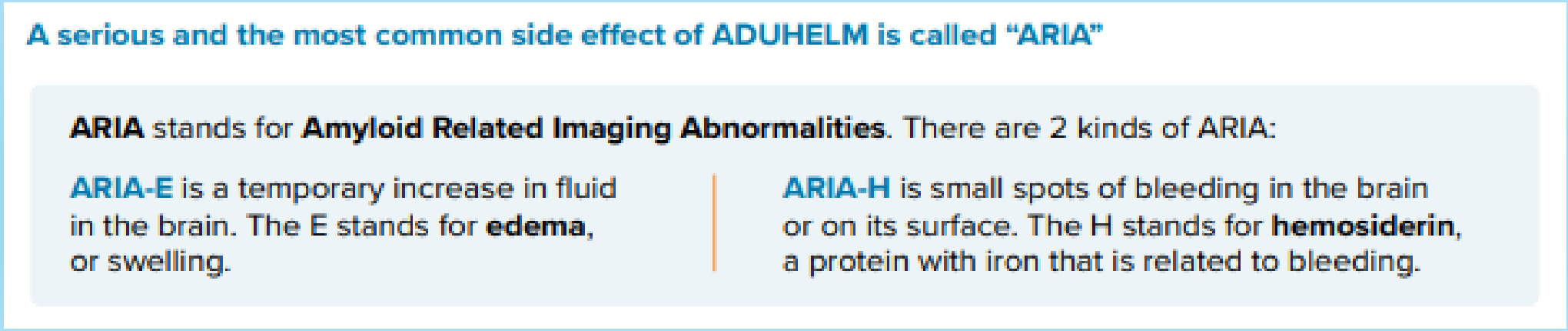
- A human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against the accumulated soluble and insoluble forms of amyloid-beta to reduce their levels in the brain
- Currently approved for MCI or early Alzheimer's disease that has been confirmed by either:
  - beta amyloid in CSF
  - beta amyloid on brain imaging – amyloid PET scan





Aducanumab administration

- Not approved for moderately severe dementia and non-AD dementia.
- Contraindicated in patients with strokes, bleeding tendencies or those on anticoagulants.
- Given as an IV infusion over 1 hour, every month for a year at a hospital infusion center or independent infusion centers.
- MRI required at baseline, 6 mos and 12 mos.
- Side-effects, allergic reactions, headaches, dizziness, vision change



41% of people taking ADUHELM in clinical studies had ARIA-E and/or ARIA-H compared to 10% of people who took placebo

Aducanumab – phase 4, real world clinical trials for confirming benefit and other therapies

- Drug companies are required to conduct additional studies to determine whether there is in fact clinical benefit after the drug is approved through the accelerated approval pathway,
- If the follow-up trial fails to verify clinical benefit, the FDA may withdraw approval of the drug.
- Many other monoclonal antibodies in phase 3 trials and might seek FDA approval within a year
- More than a 100 clinical trials – varying from drugs that treat gingivitis and modify gut bacteria to those that reduce inflammation

Clinical Trials related to MCI and Alzheimer's disease at the Walker Memory Research Center, Reynolds Institute on Aging, UAMS

1. An Observational Study Using Multimodal Sensors to Measure Cognitive Health in Adults and Distinguish Mild Cognitive Impairment From Normal Aging (Intuition) - Azhar/Wei
Distinguish Between Individuals With and Without MCI. To develop and validate a cognitive wellness score using multimodal passive sensor data and metrics derived from normal iPhone and Apple Watch usage.

2. Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults (PREVENTABLE) Wei/Azhar
a. Cardiovascular mortality measured as a composite of CV death, hospitalization for myocardial infarction/unstable angina, heart failure, stroke/TIA, or coronary revascularization
b. Cognitive disability as measured as a composite of MCI or probable dementia

3. Evaluation of the cognitive function and socioeconomic, biomedical, and genetic risk factors of Alzheimer's disease and related dementias (ADRD) in older Marshallese residents of Northwest Arkansas Wei/Azhar

4. Agitated Alzheimer's disease dementia. A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of AVP-786 (deudextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type Azhar/Wei

Thank You

Walker Memory Clinic phone number: 501-526-5884; fax
Thomas and Lyon Longevity Clinic: 501-686-6219