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at the Sanders-Brown Center on Aging

The ABCs of Dementia

Family Caregiver Training

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Dementia

- an illness of the brain resulting in impairments in multiple spheres of cognition

- Does not imply an etiology or diagnosis

- Our job is to find out why and find a way to help

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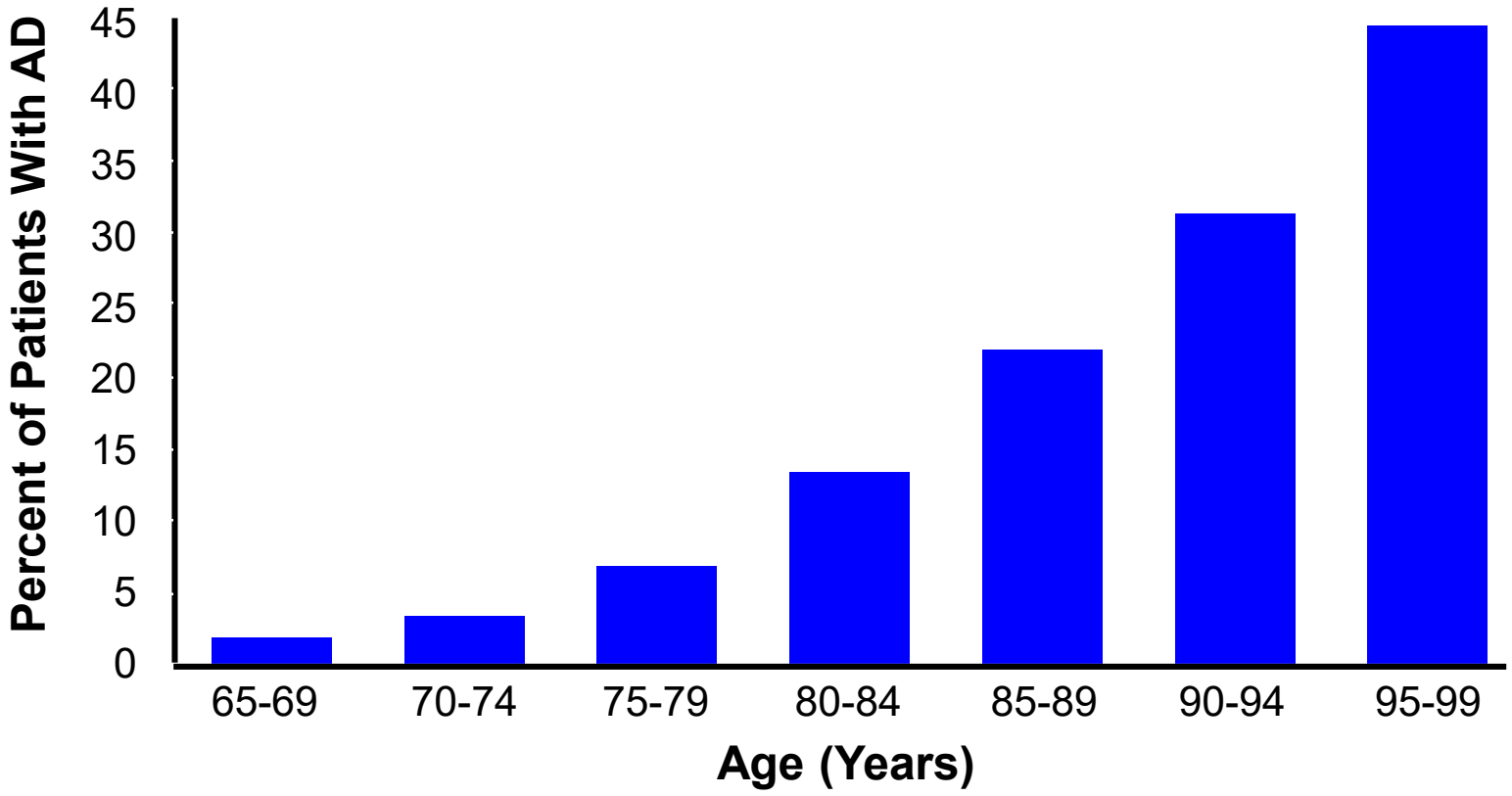
DEMENTIA PREVALENCE INCREASES AS WE AGE



Adapted from Ritchie K, Kildea D. *Lancet*. 1995;346:931-934.

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Dementia-barriers to diagnosis

- patient is typically unaware of symptoms
- evaluation may be time consuming and not well compensated financially
- belief that memory loss and cognitive decline are part of normal aging
- belief by physicians and general public that AD is not treatable

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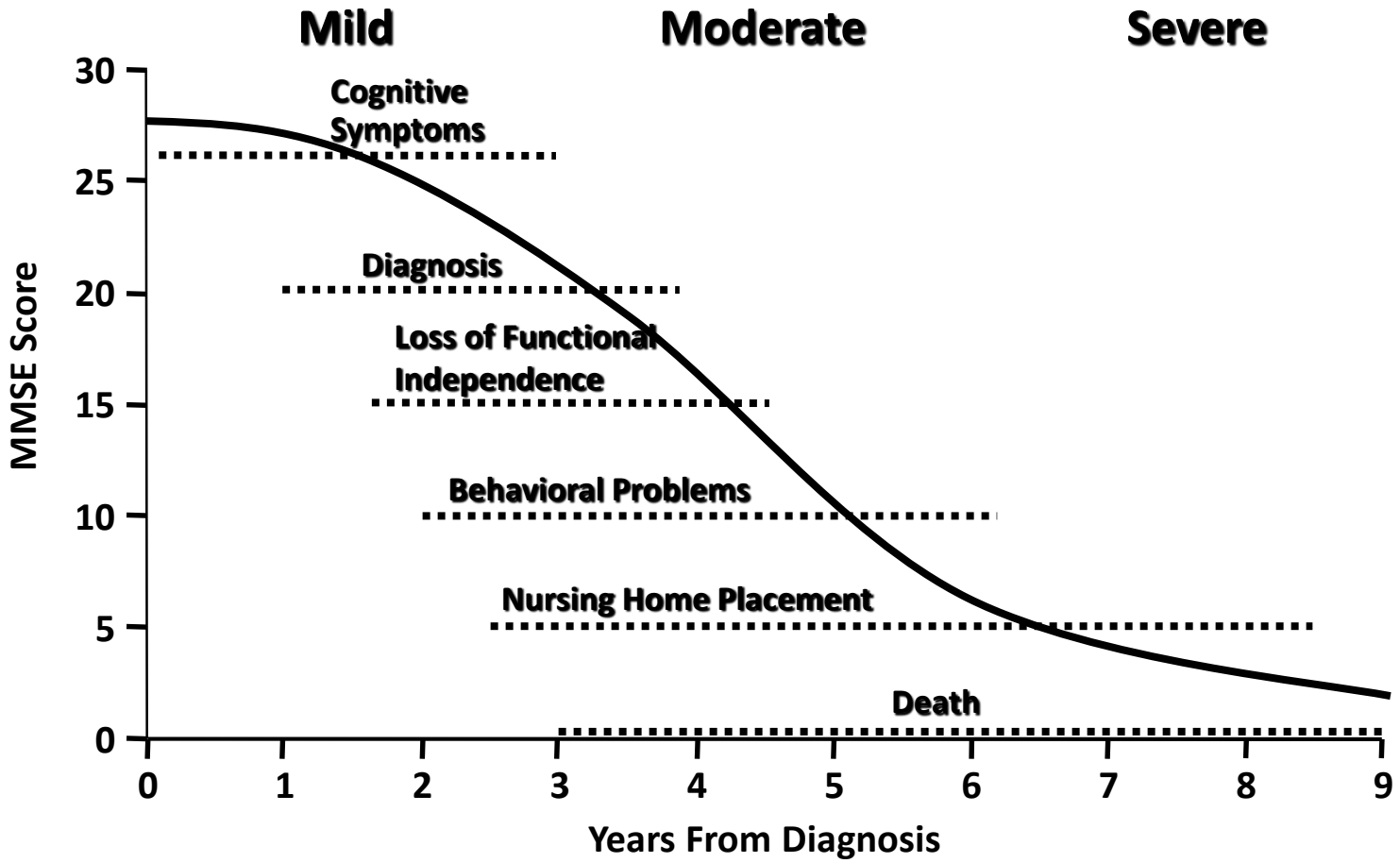
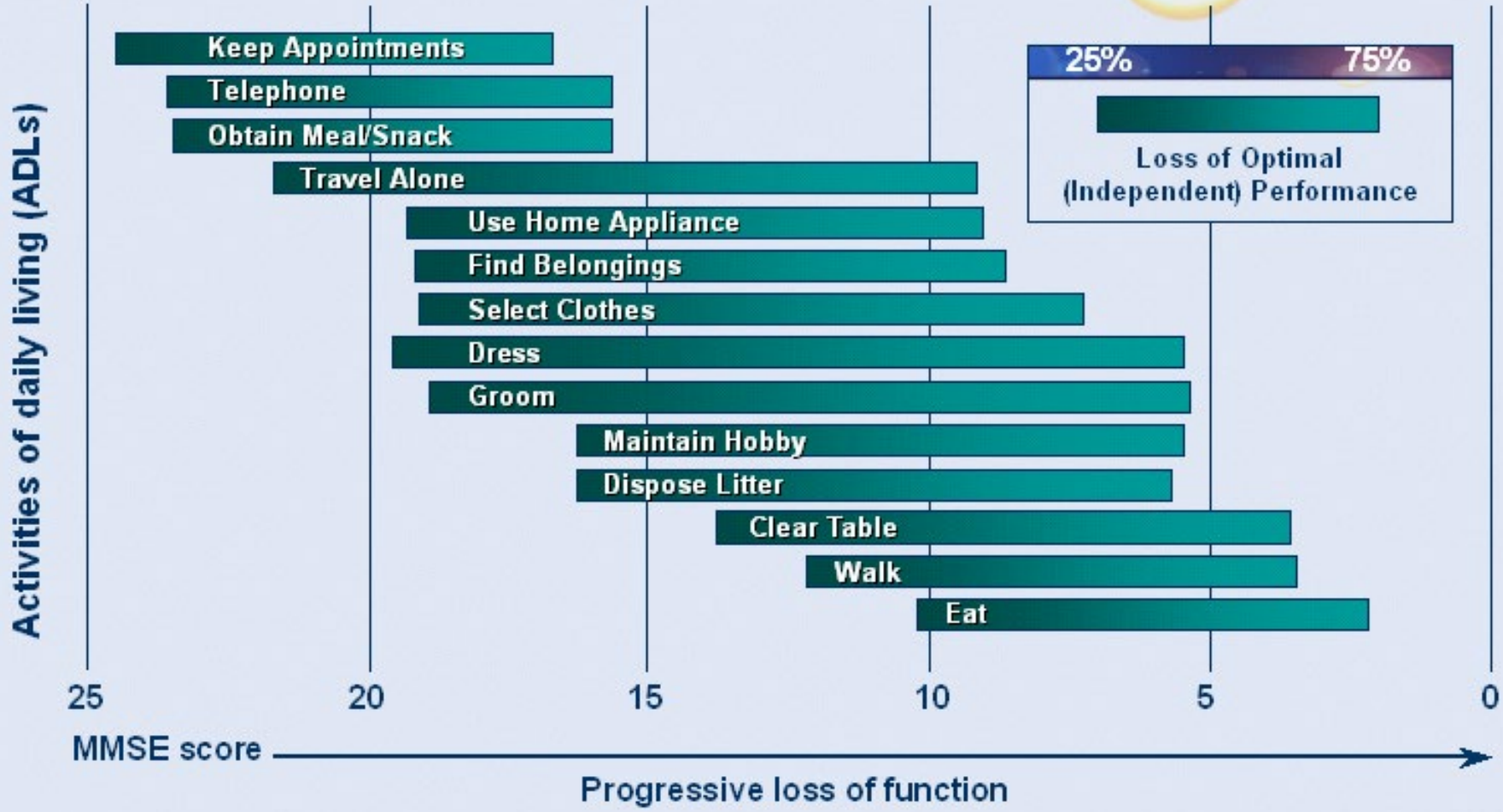
Disease Progression in dementia



MMSE Scores Correlate With Functional Ability



Adapted with permission from Galasko et al. *Eur J Neurol.* 1998;5:S9-S17.

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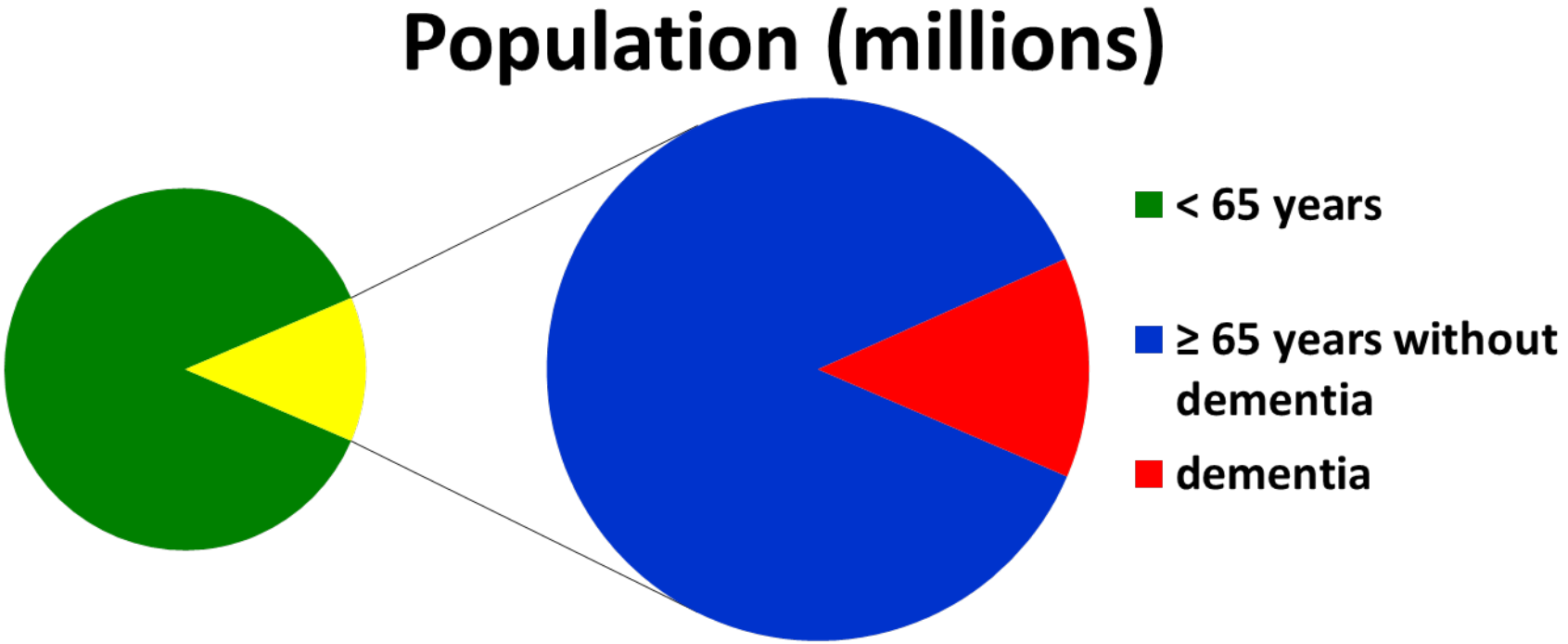
Dementia



12.9% of the US population is over 65 years of age

13.1% of the US population over 65 years is demented

=5.8 Million!

http://www.aoa.gov/Aging_Statistics/ ; https://www.alz.org/downloads/facts_figures_2019.pdf

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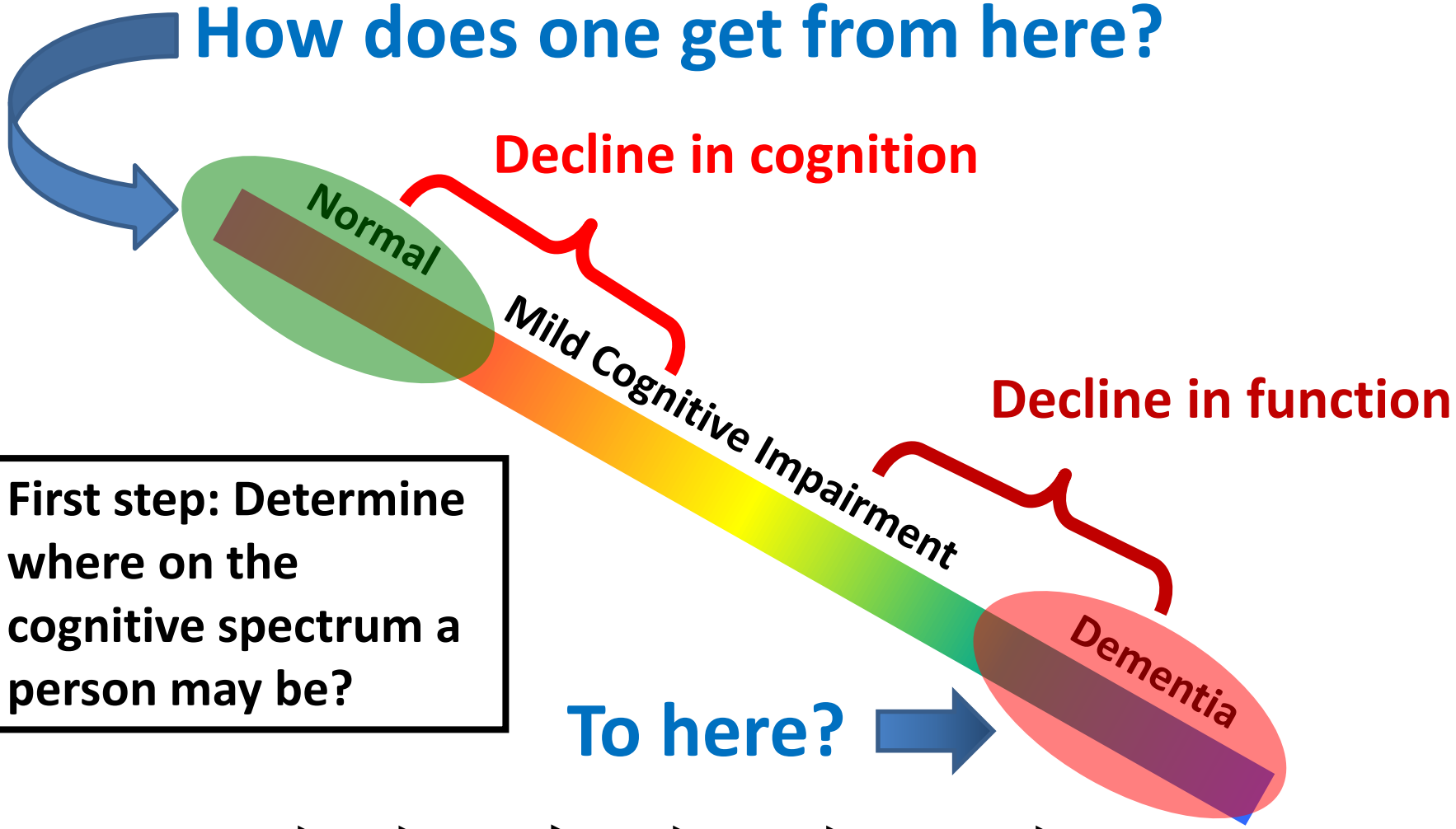
Are they normal or are they impaired?

How does one get from here?



First step: Determine where on the cognitive spectrum a person may be?

To here?

Normal ▶ mild MCI ▶ moderate MCI ▶ severe MCI ▶ mild dementia ▶ moderate dementia ▶ severe dementia?

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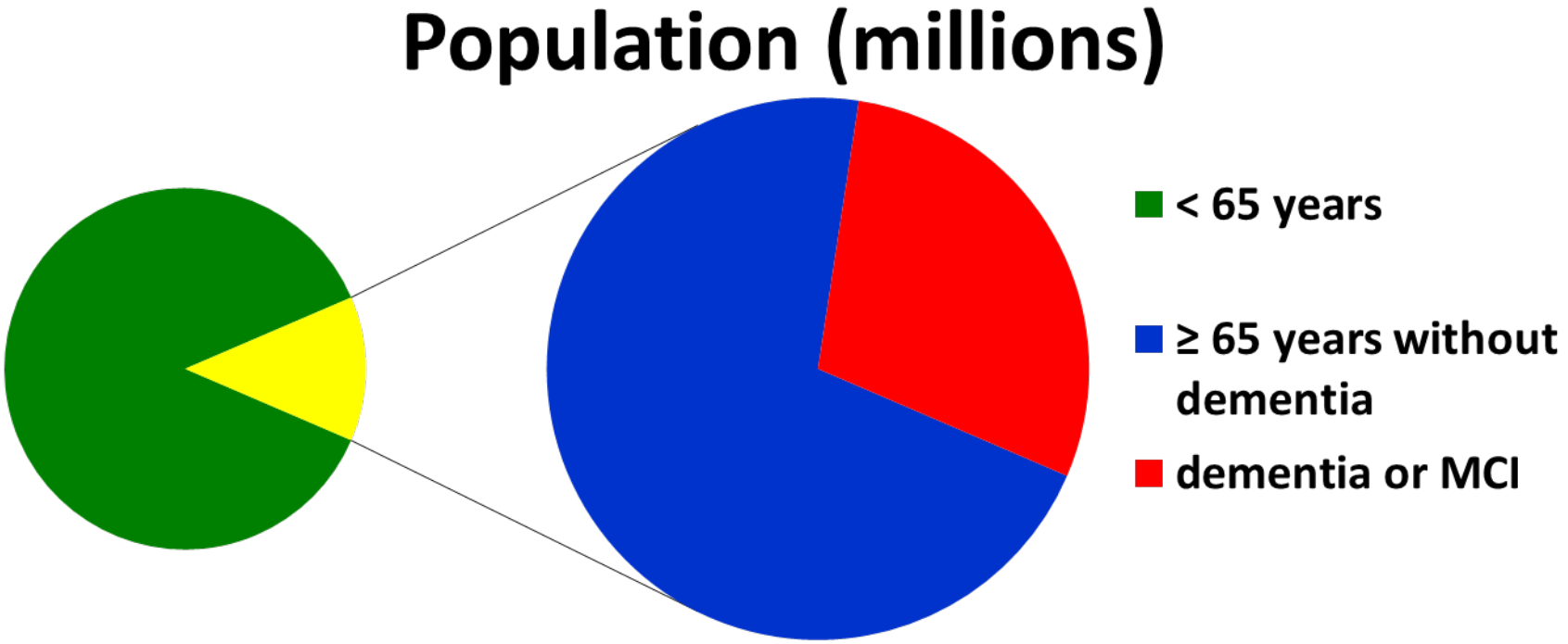
Dementia or MCI



12.9% of the US population is over 65 years of age

29% of the US population ≥65 years has MCI or dementia

>12 Million!

Petersen et al, Neurology. 2010 Sep 7;75(10):889-97

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Causes of Dementia

Neurogenerative conditions

- Alzheimer's disease
- Frontotemporal Dementia
- Dementia with Lewy bodies
- Vascular dementia
- HIV
- Normal pressure hydrocephalus
- Corticobasal ganglionic disease
- Parkinson's disease
- Huntington's disease
- Creutzfeldt-Jakob disease
- Other (leukodystrophy, Hallervorden-Spatz, etc.)

Other medical causes of dementia

- Alcoholic dementia
- Chronic drug intoxications
- Endocrinopathy
- Vitamin deficiency
- Infection
- Tumors
- Other brain lesions
- Seizures
- Multiple Sclerosis
- Pseudodementia

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AD8 (screen tool)

1. Does your family member have problems with judgment (problems making decisions, bad financial decisions, problems with thinking, etc.)?
2. Does your family member show less interest in hobbies/activities?
3. Does your family member repeat the same things over and over (questions, stories, or statements)?
4. Does your family member have trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)?
5. Does your family member forget the correct month or year?
6. Does your family member have trouble handling complicated financial affairs (balancing checkbook, income taxes, paying bills, etc.)?
7. Does your family member have trouble remembering appointments?
8. Does your family member have daily problems with thinking or memory?

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ROS for Dementia Evaluation

Mood: depression, anxiety
- May be cause or may be a target for treatment?

Behavior: personality change, OCD, inappropriate behaviors
- May be FTD, may just need to be treated?

Psychosis: hallucinations, delusions, paranoia
- May be DLB, may just need treatment?

Sleep: OSA, insomnia, DEB/RBD, circadian rhythm
- DEB may be diagnostic, others may need treatment?

Physical/Motor: Parkinsonism, MND, focal deficits
- Diagnostic or a symptom needed to be treated?

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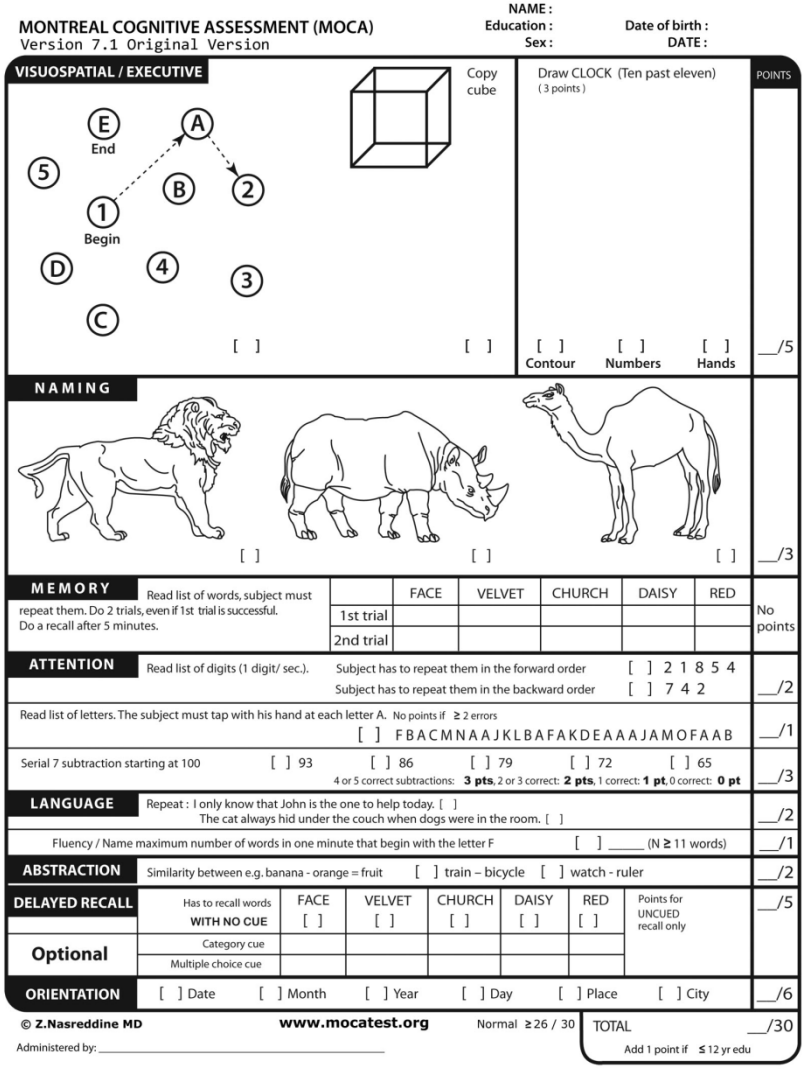
Montreal Cognitive Assessment

- There are many brief bedside cognitive screens you could use
- In Neurology we typically use the MoCA
- Very sensitive to early decline
- Assesses a wide range of cognitive functions
- Downside: it takes about 15 minutes or so, so pieces may be better than the whole or nothing at all



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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Let's see if there are other exam findings…

- **Physical exam should look for major medical conditions tha could lead to cognitive decline**
  - Neurovascular (Heart & carotids)
  - Gross respiratory, jaundice, cachexia, rashes…
- **Neurologic exam should screen for:**
  - focal deficits (stroke or tumor)
  - Parkinsonism (DLB, PSP, CBD, MSA, FTD-17…)
  - MND/ALS (associated with FTD)
- **Specific examination findings in cognitive decline**
  - Frontal release signs
  - Praxis difficulties

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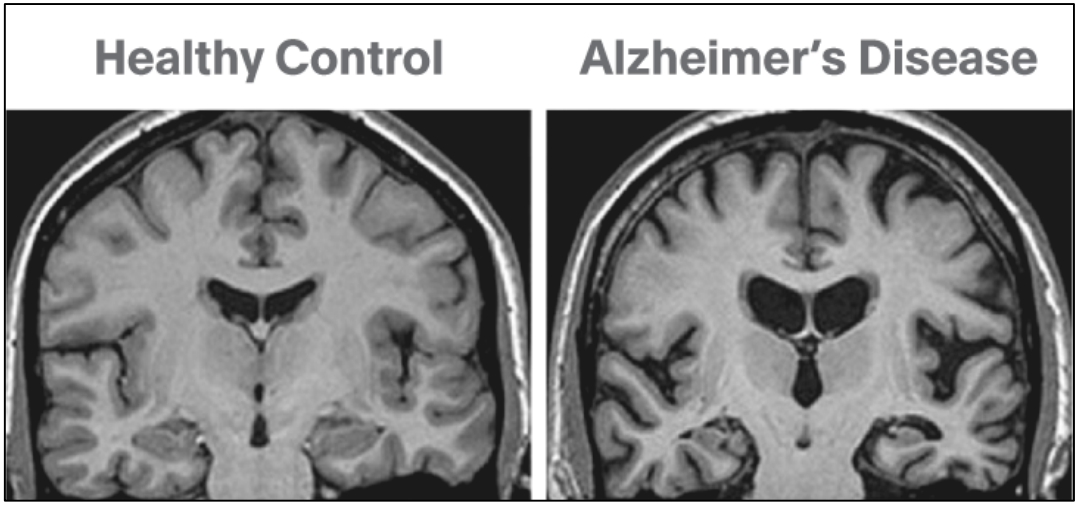
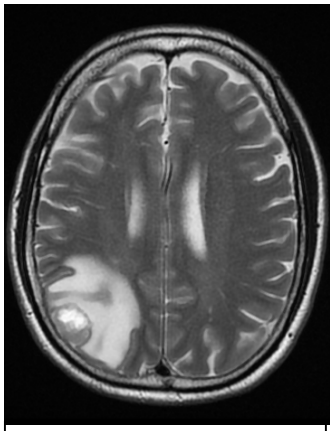
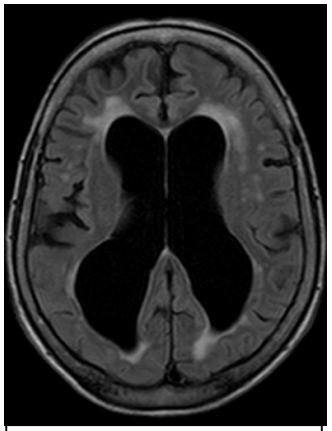
Imaging

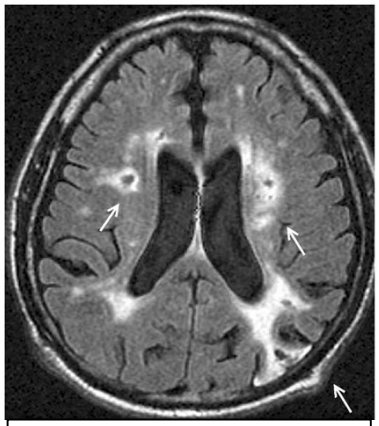




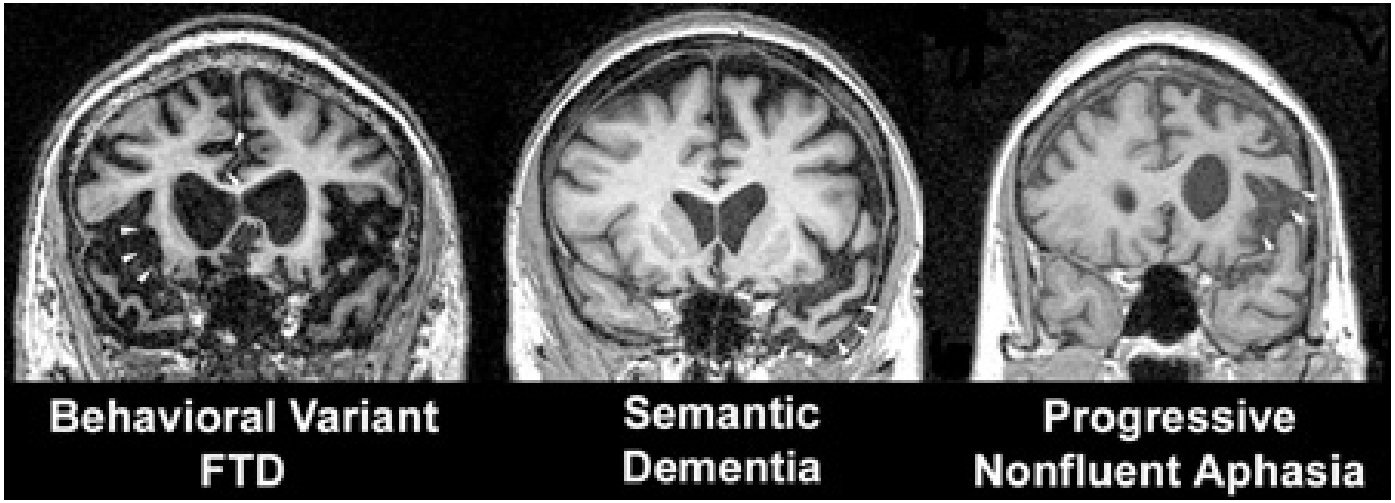
Tumor



NPH



VaD



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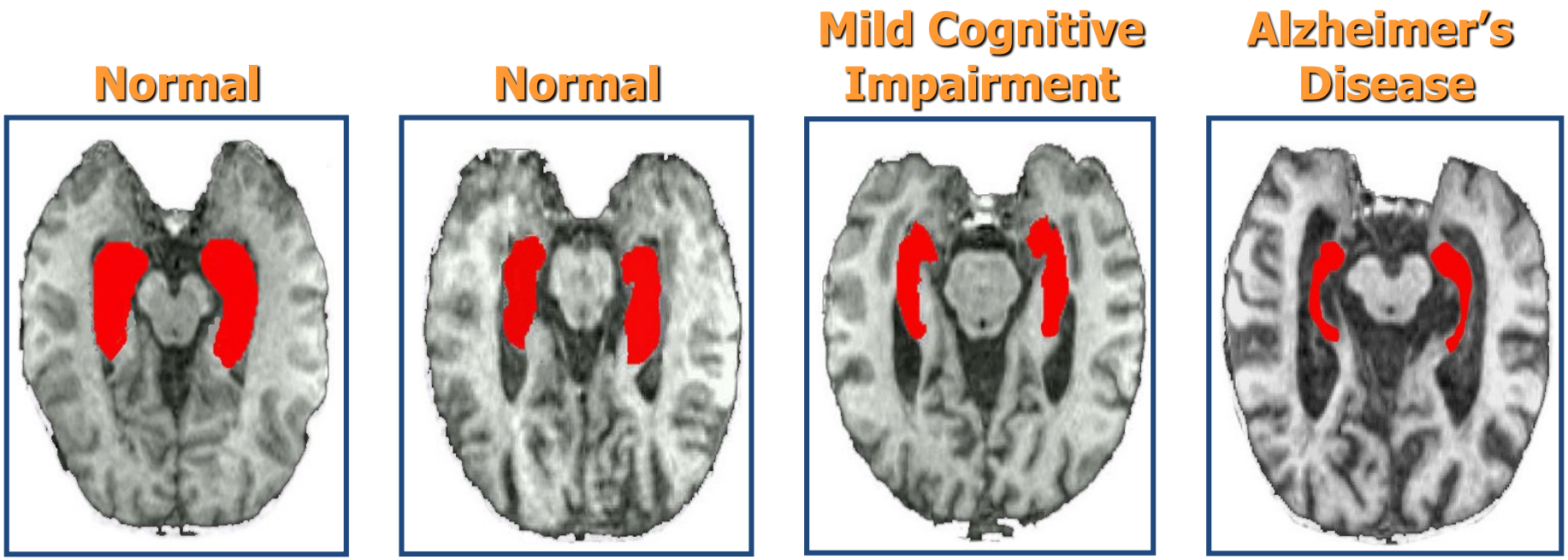
Hippocampal Size in Aging, MCI, and Alzheimer's Disease



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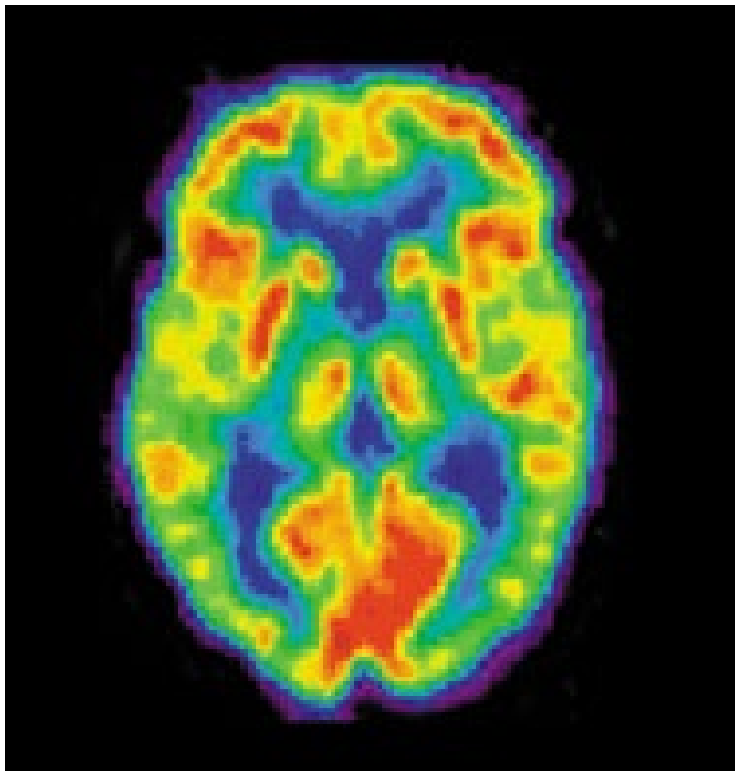
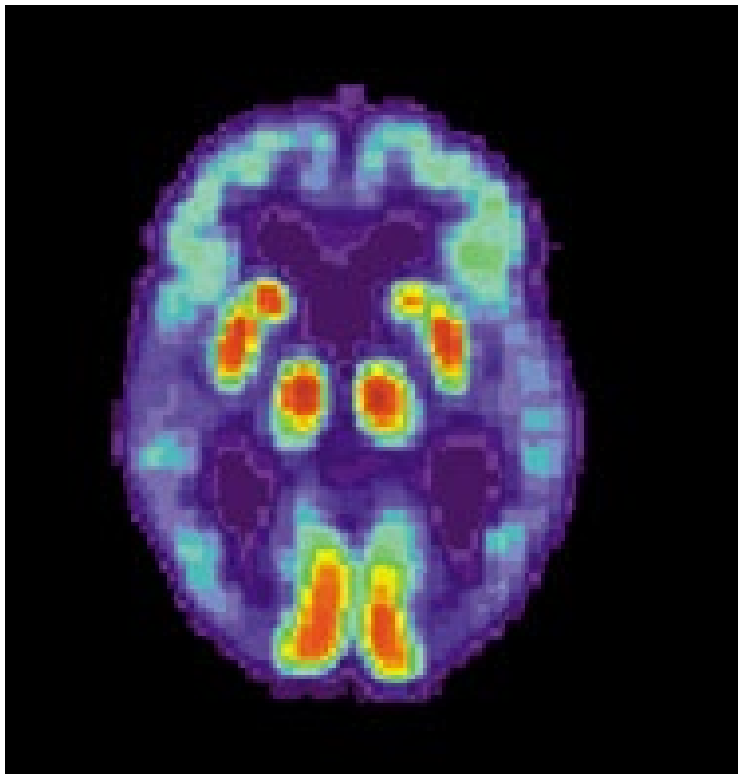
FDG-PET measure how the brain turns on (only for AD vs. FTD)



Normal



AD

ADEAR, 2003

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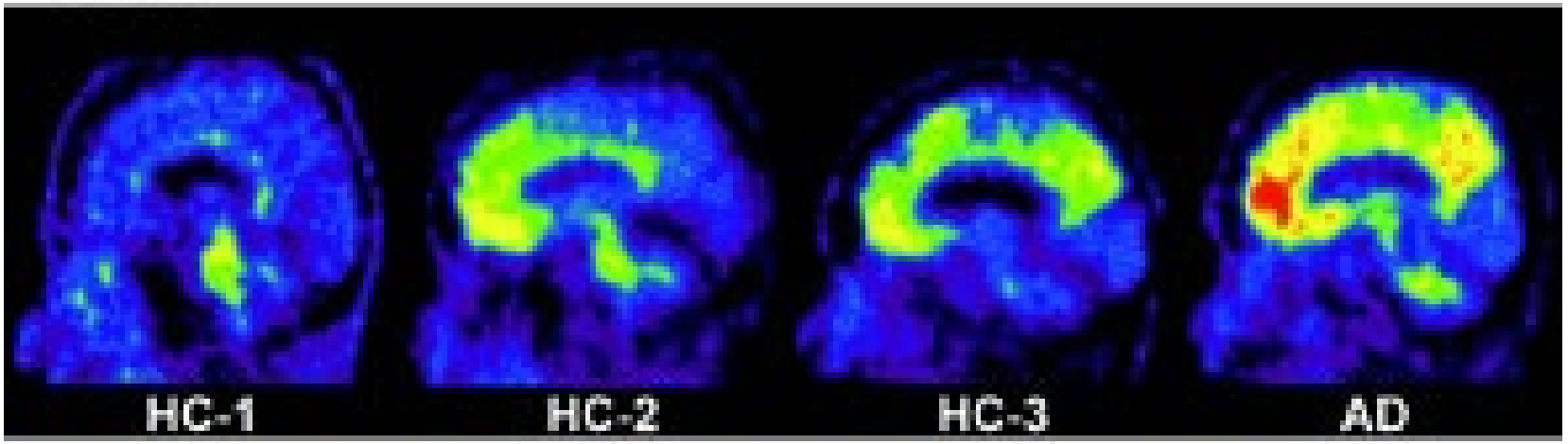
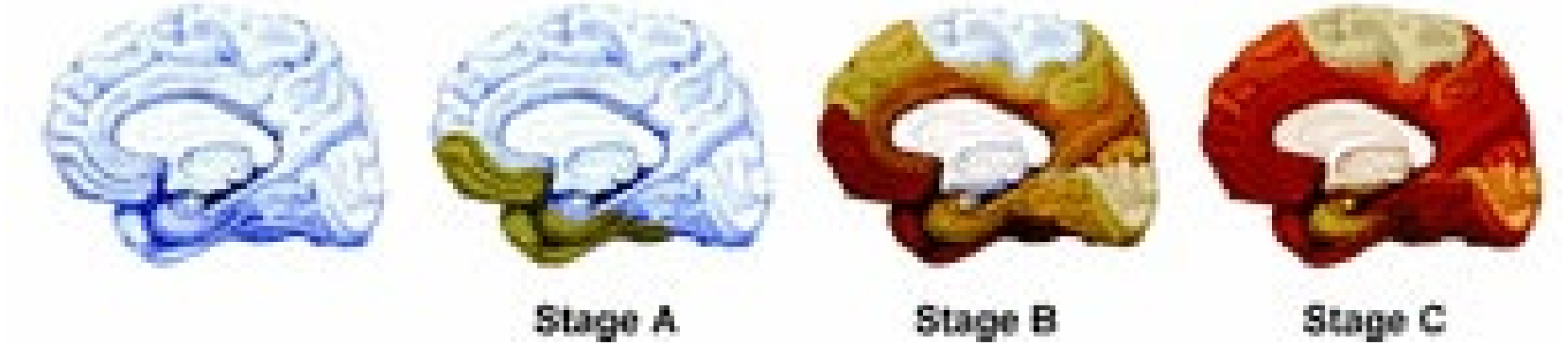
Amyloid PET can see AD
FDA approved but not covered by most insurance pay)

^{11}C-PIB



Plaque Progression



Rowe CC et al., Imaging beta-amyloid burden in aging and dementia. Neurology. 2007 May 15;68(20):1718-25.

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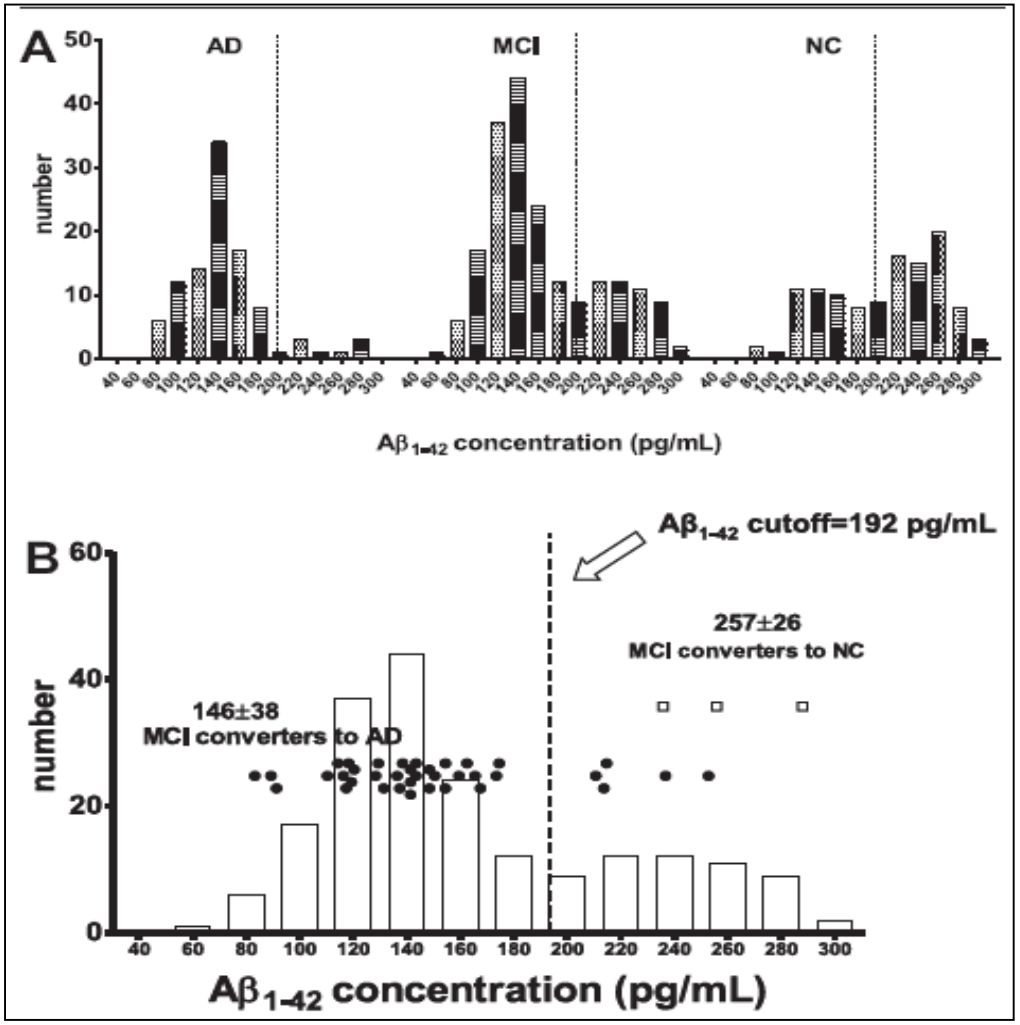
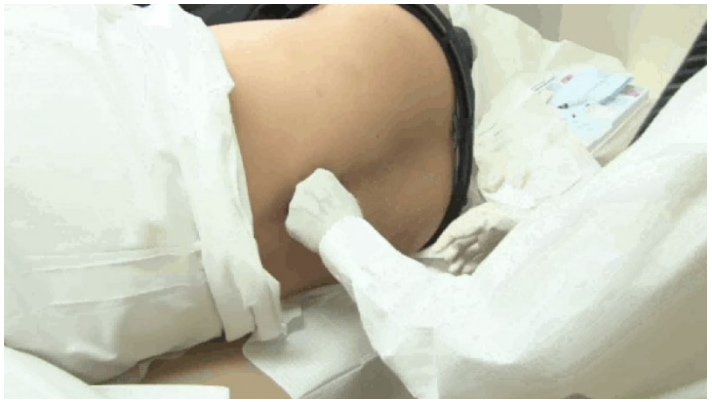
CSF is very accurate and available clinically





Shaw et al., Ann Neurol. 2009 Apr;65(4):403-13.

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Common Behaviors in Dementia

- Short term memory loss/repetition
- Lethargy/lack of initiative
- Emotional changes/mood swings/depression
- Agitation (anger, anxiety)
- Resistance to care
- Wandering/pacing
- Wanting to go home
- Shadowing
- Hallucinations, delusions, suspiciousness, paranoia
- Change in sleep patterns
- Rummaging, hoarding
- Loud verbal noises/yelling
- Abusive/combative behaviors

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Psychiatric symptoms in dementia

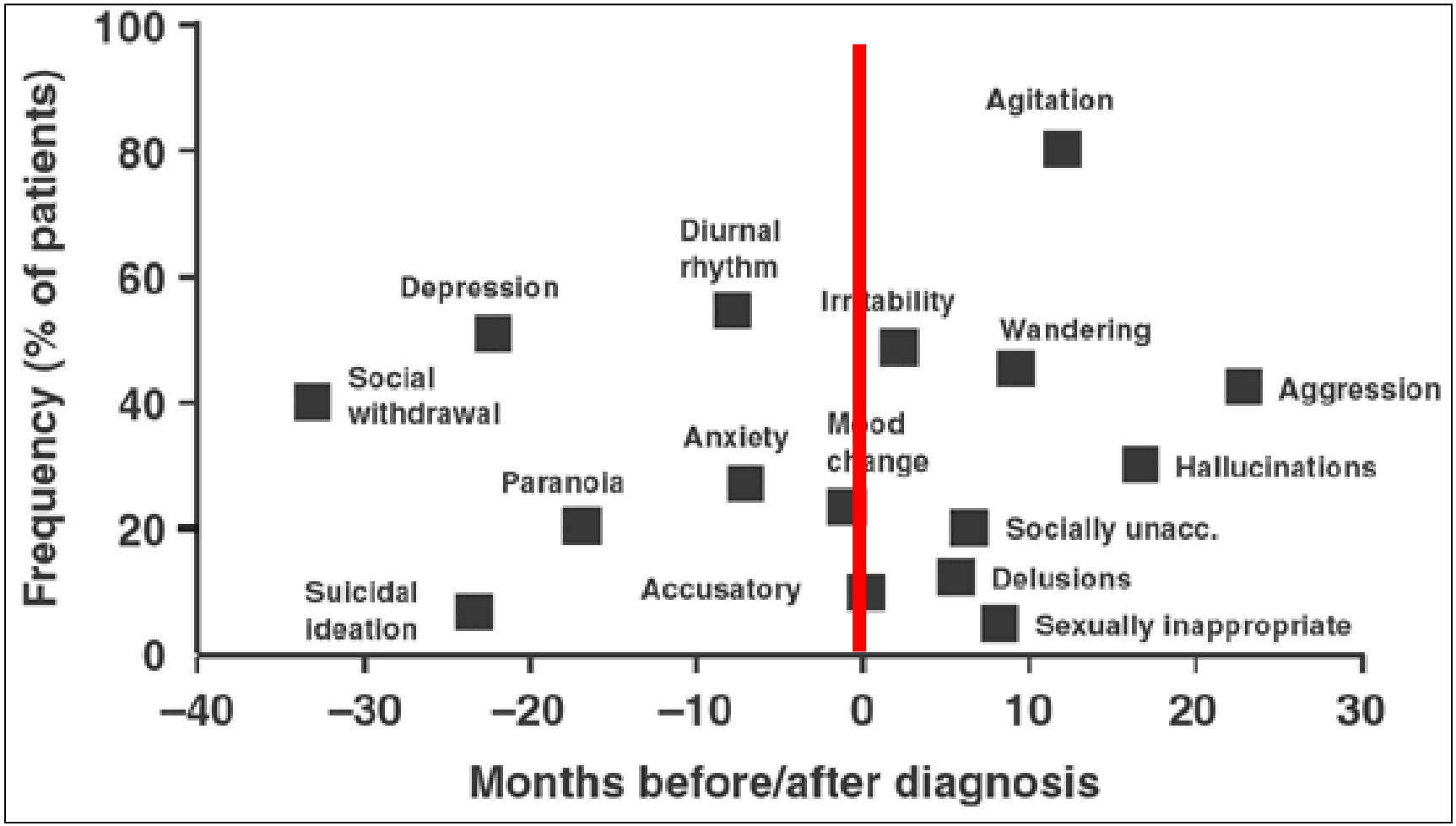

Figure from Medscape.com

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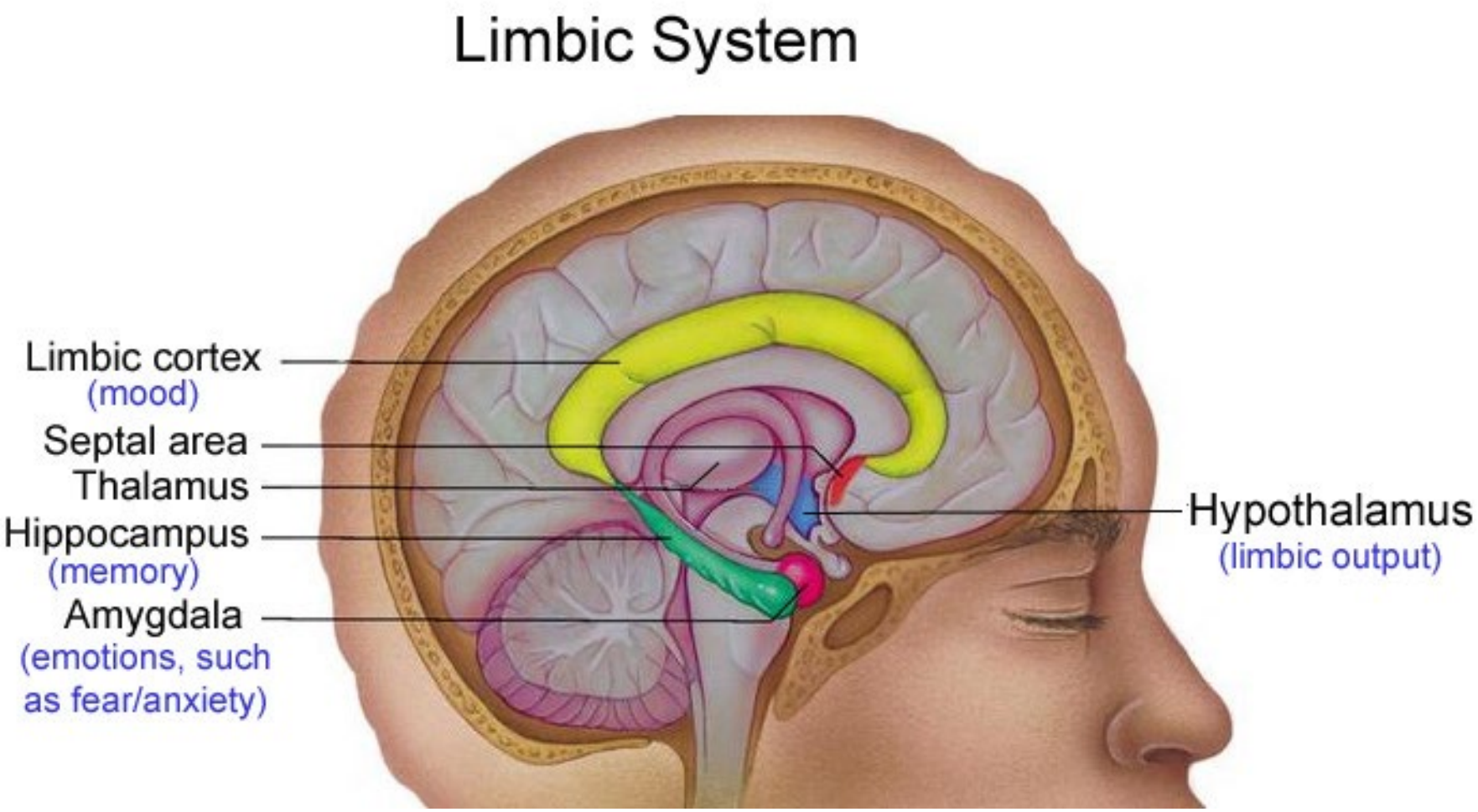
Why is behavior a problem?



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Importance of Behavioral & Psychological Symptoms of Dementia (BPSD)

- **BPSD account for 30% of cost associated with AD**
- **Strongly associated with caregiver depression**
- **Strongly associated with institutionalization**
- **Undermine caregiver's ability to provide care**
- **Vicious cycle between BPSD and caregiver stress is created with escalation of BPSD**

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Causes of BPSD

- **Psychosocial/psychological factors**
  - Behaviors may be an expression of unmet psychological needs
    - Thirst
    - Hunger
    - Pain
    - Distress
    - Feelings of abandonment
    - Fear

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Causes of BPSD

- **Environmental factors**
  - Excessive stimulation
  - Lack of daily structure/routine
  - Inadequate lighting
  - Confusing surroundings
  - Excessive demands
  - Distressing behavior of others
  - Loneliness/boredom

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Assessment of BPSD

- **History** (current sx's, etiol. of dementia, PMH)
- **R/O environmental disturbances** (changes in home situation, over-stimulation, sensory deprivation, change in staff, death of family member)
- **R/O contributing medical problem** (infection, dehydration, pain, sleep disturbance, etc.)
- **R/O drug effects** (interactions, intoxication, withdrawal, poor compliance)
- **Review prior psychiatric hx**

K. Meador, 2006

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Medications with Negative Cognitive & Behavioral Side Effects

- H1-Blockers (e.g. cimetidine, ranitidine)
- Antihistamines (bendryl and OTC sleep aids)
- Tricyclic antidepressants (e.g. Elavil)
- Phenytoin and some other seizure medicines
- Steroids (e.g. prednisone, prednisolone)
- Oxybutynin
- Opioids
- Theophylline
- Digoxin

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Treatment of BPSD- Prevention

- **Provide structured, secure and safe environment**
- **Maintain routines**
- **Encourage constructive activities and social interactions**
- **Attend to medical and physical condition**
- **Support caregiver**
- **Ensure adequate nutrition and sleep**

- ***Treat the dementia first!***
- ***Cholinesterase Inhibitors***
- ***Memantine***

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Behavioral Interventions for BPSD

- **Distract/redirect patient**
- **Adjust environment**
  - Avoid precipitating factors
  - Meet needs and limitations of the patient
- **Provide structure and consistency**
- **Avoid over-stimulation**
- **Planned activities to avoid boredom**

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Dementia and Communication

- Speak clearly and at a steady pace
- Keep language simple
- Engage eye contact
- Show an attitude of warmth and firmness
- Address by name and provide identifying information
- Use non-verbal cues (e.g. facial expression, touch, gesture)
- Observe and listen to identify most effective means of communication (e.g. verbal, visual,…)

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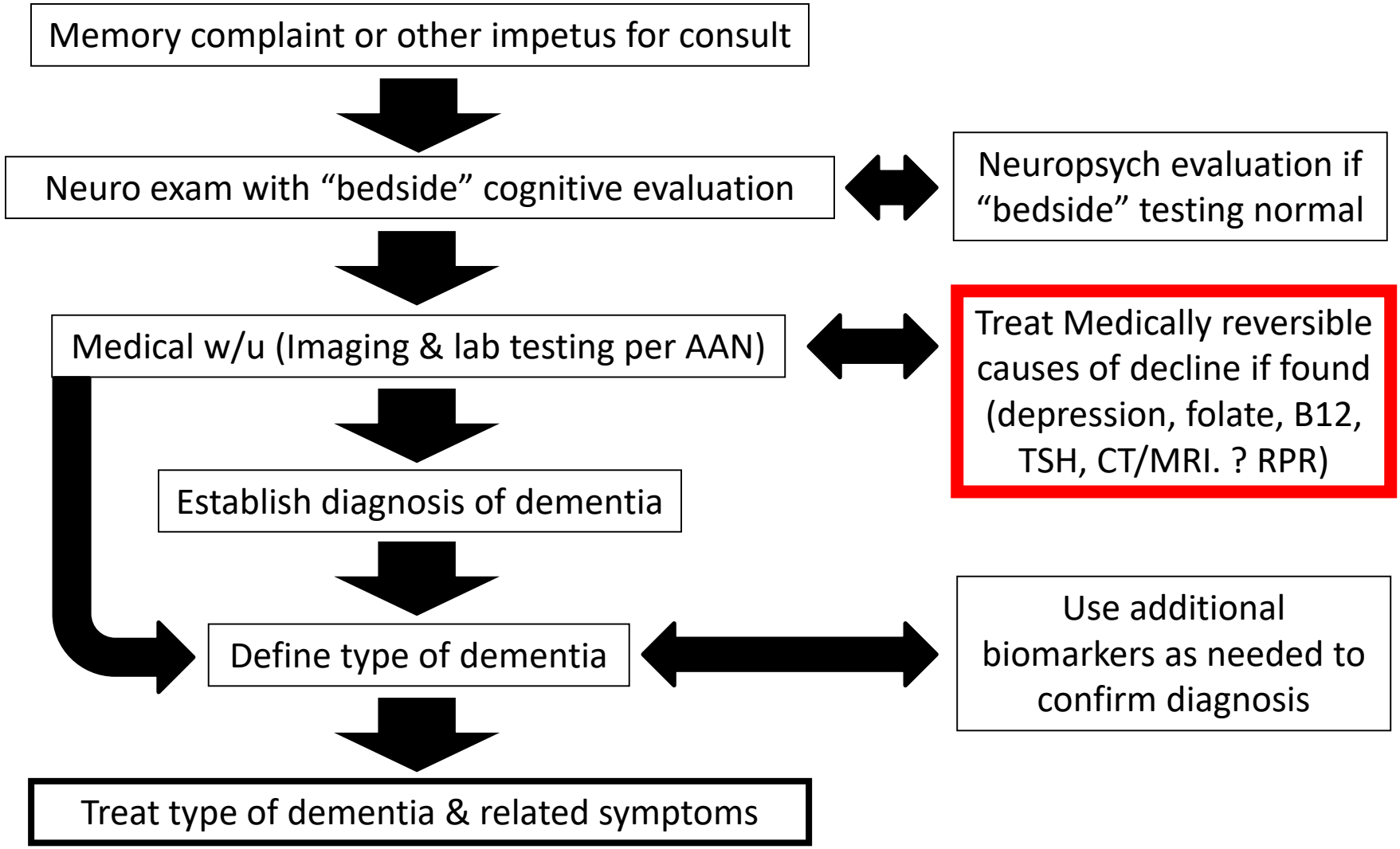
Algorithm for Dx



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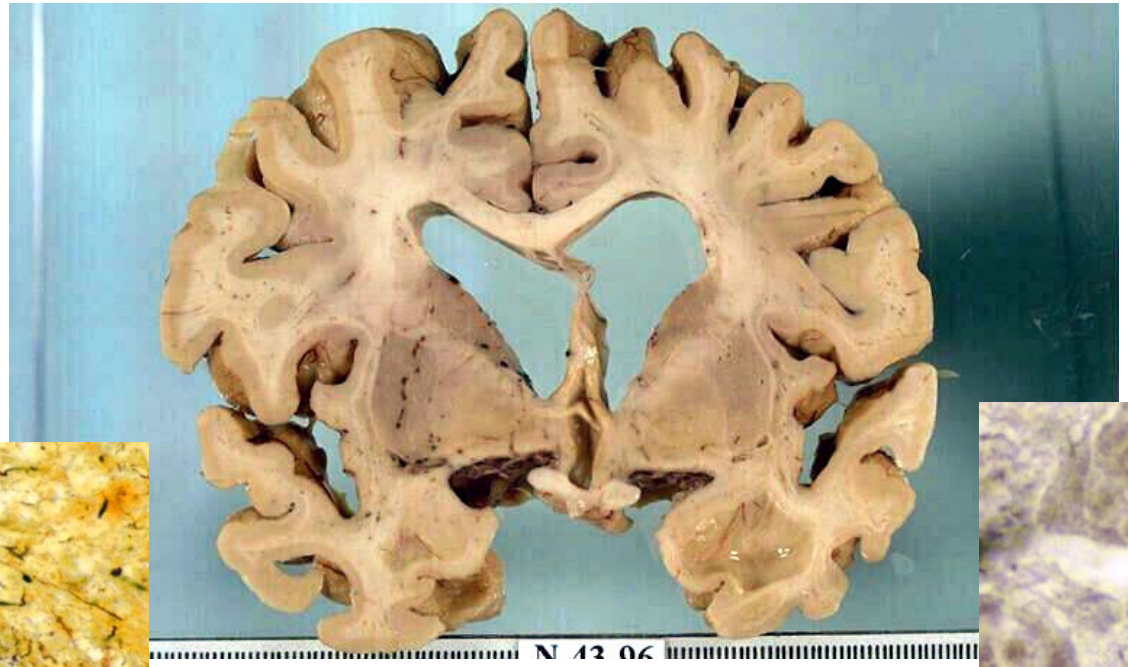
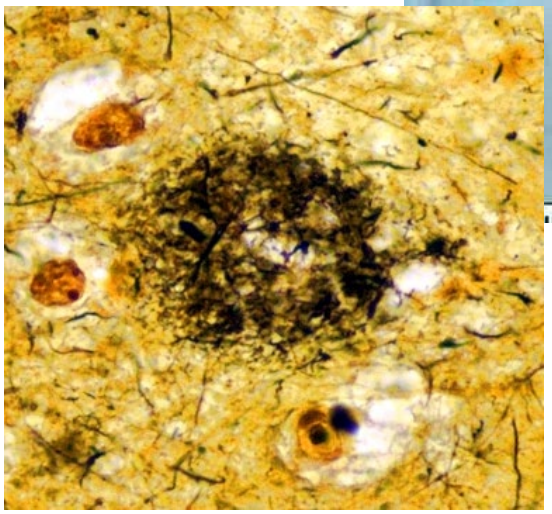
Alzheimer's Disease Pathology

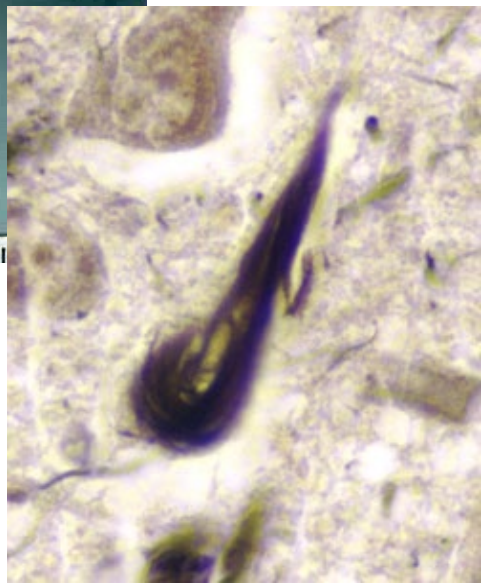
Cerebral atrophy





Neuritic plaque

Neurofibrillary tangle



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Let's see how the disease happens…

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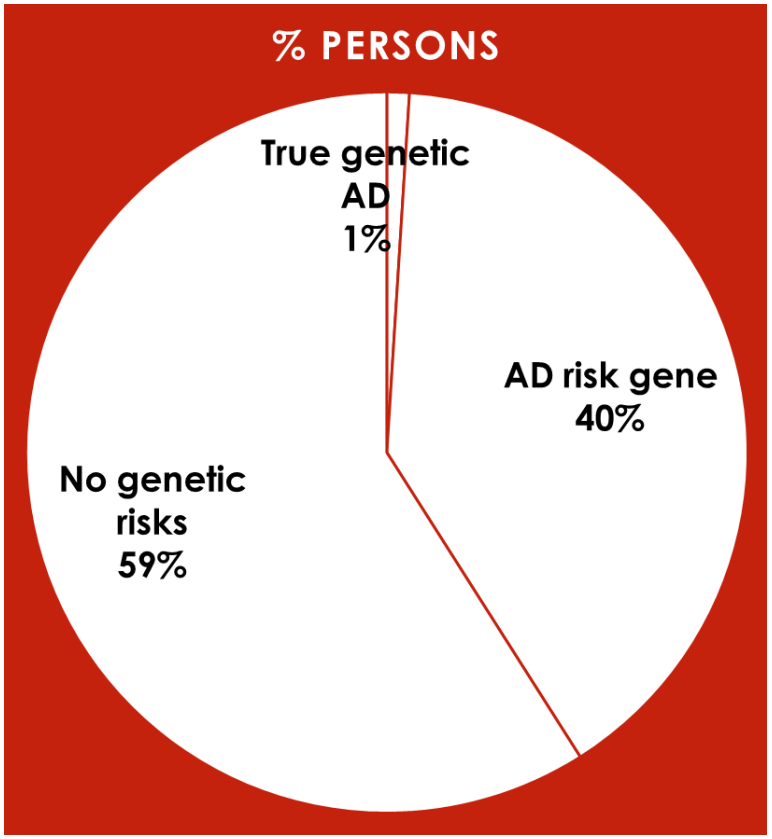
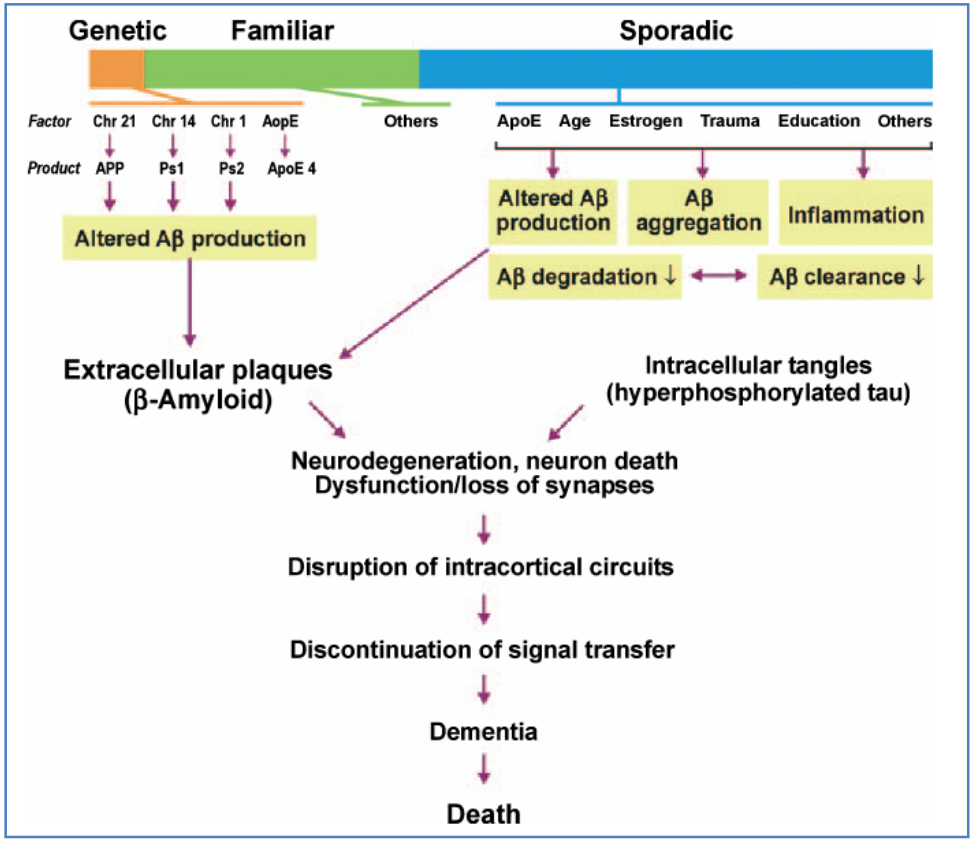
Genetics & environment?





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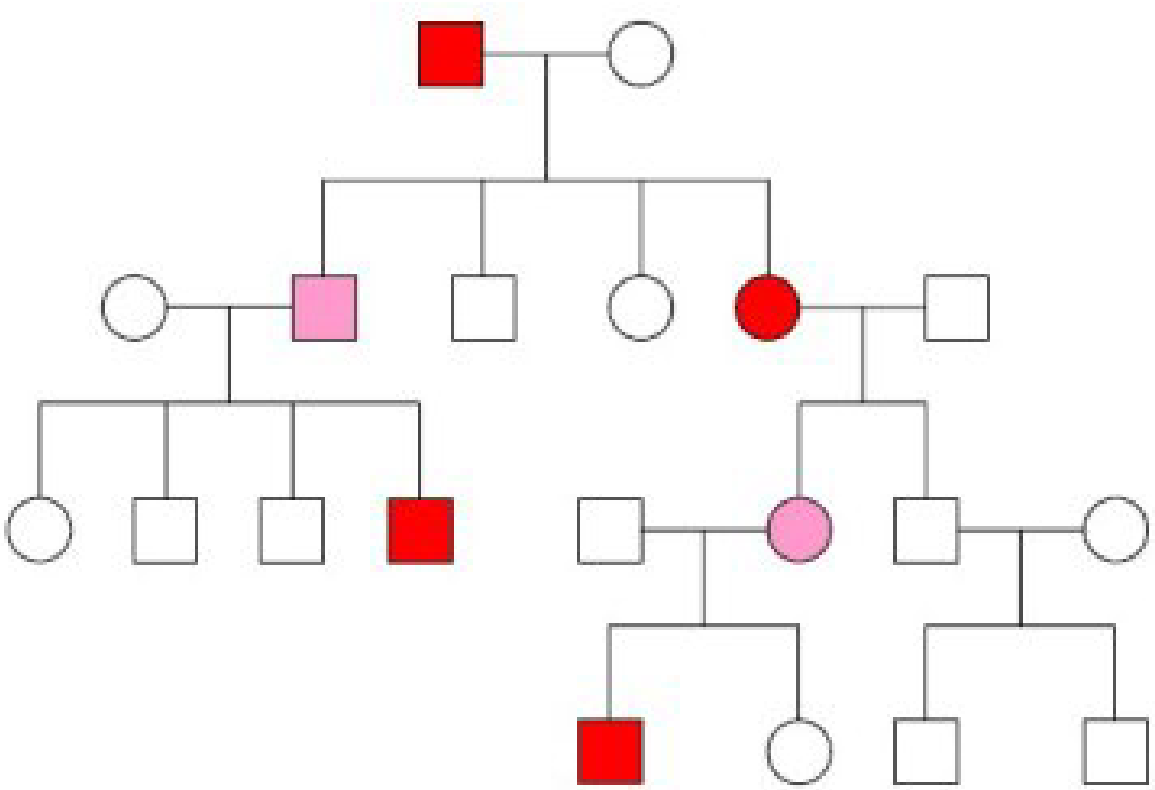
Incomplete penetrance: ApoE a "risk factor" gene



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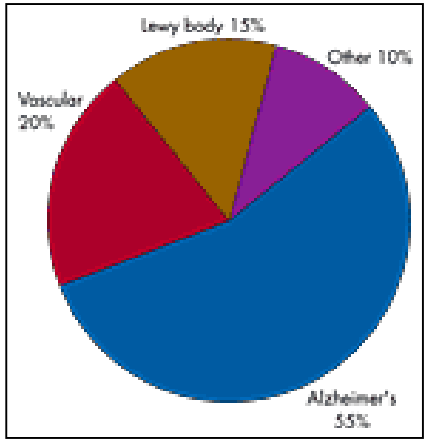
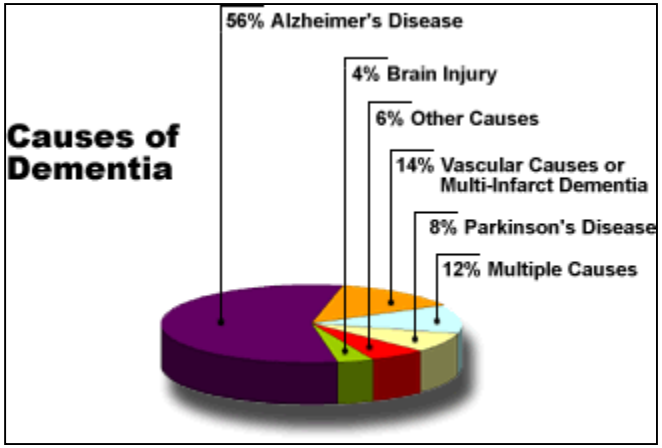
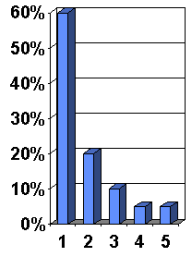
It's clear that dementia is a "mixed bag" of disorders

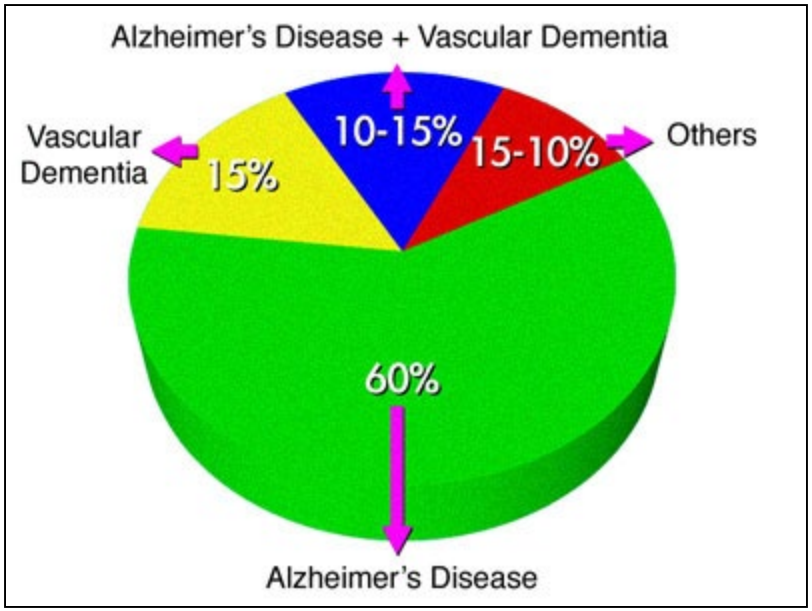


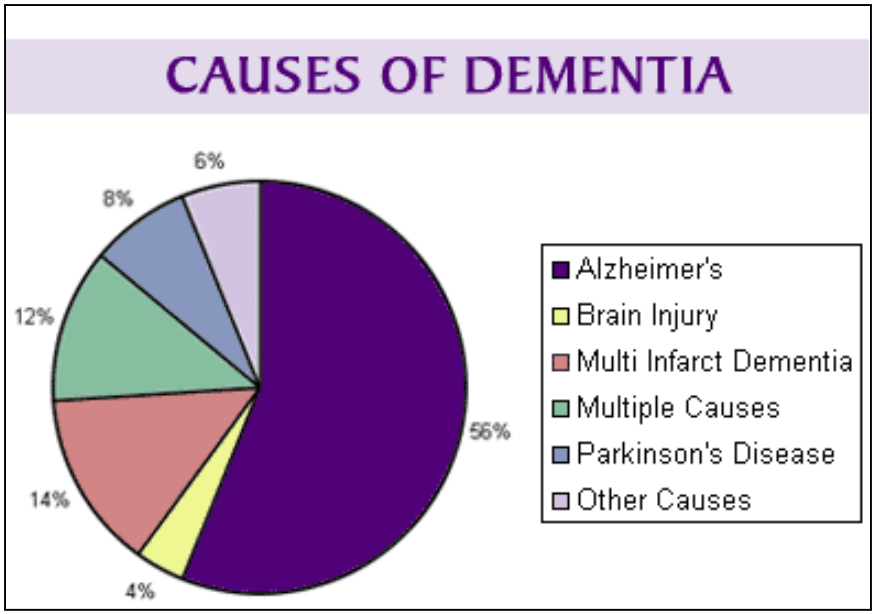


CAUSES OF DEMENTIA IN THE UNITED STATES

- #1-Dementia of Alzheimer's type.
- #2- Vascular/multi-infarct dementia.
- #3-Lewy Body dementia.
- #4-Mixed dementia (AD/VAS).
- #5-Other.







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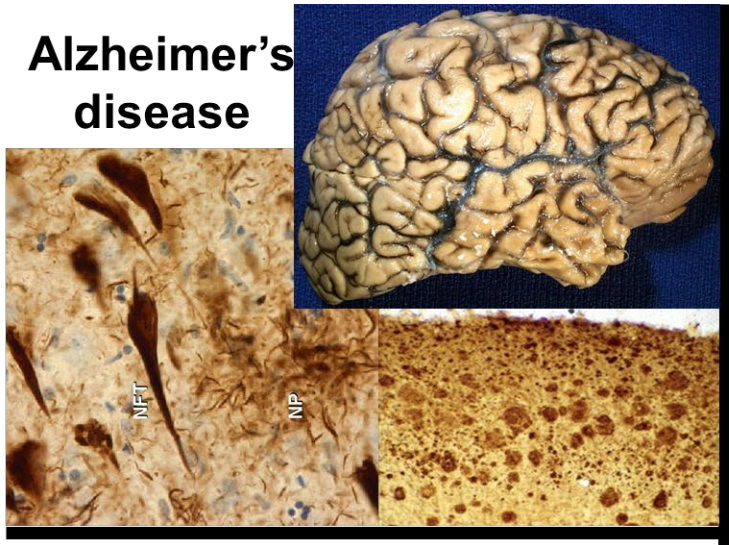
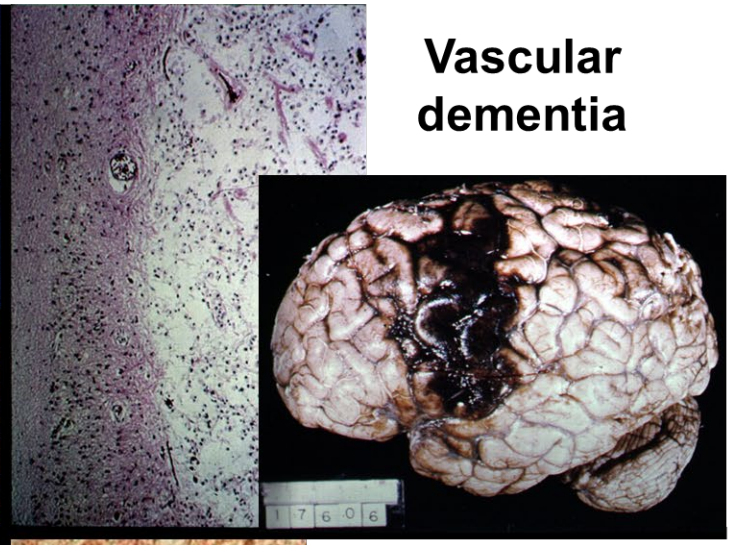
The big 4…

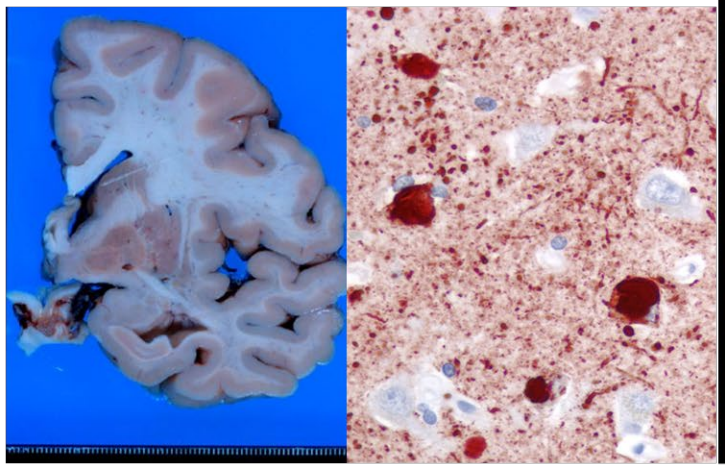
Alzheimer's disease



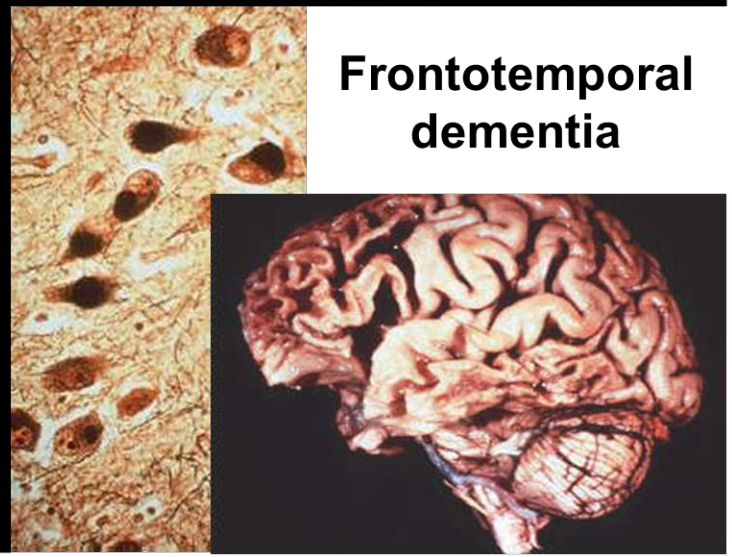
Vascular dementia



Dementia with Lewy bodies



Frontotemporal dementia



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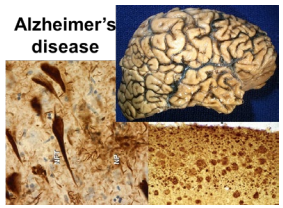
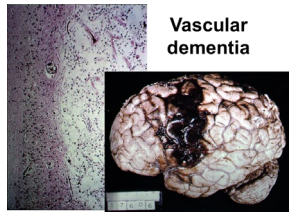
4 Major Forms of Dementia



Alzheimer's disease (NINDS-ADRDA)

<u>Dementia by DSM-V criteria</u>

- Deficits in two or more areas of cognition
- Progressive worsening of memory and cognitive dysfunction
- Functional impairment
- Absence of other systemic/brain disorders
- Not c/w another type of dementia



Vascular dementia (NINDS-AIREN)

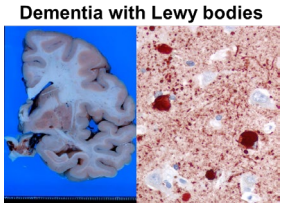
<u>Dementia by DSM-V criteria</u>

- Cerebrovascular disease present:

a) focal neurologic signs (stroke)
    - history of stroke not necessary

b) CT or MRI evidence of stroke

- Onset of dementia ≤ 3 months of stroke, abrupt deterioration or stepwise course



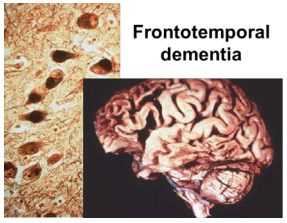
Dementia with Lewy bodies (3rd IWG on DLB)

<u>Dementia by DSM-III-R/V criteria</u>

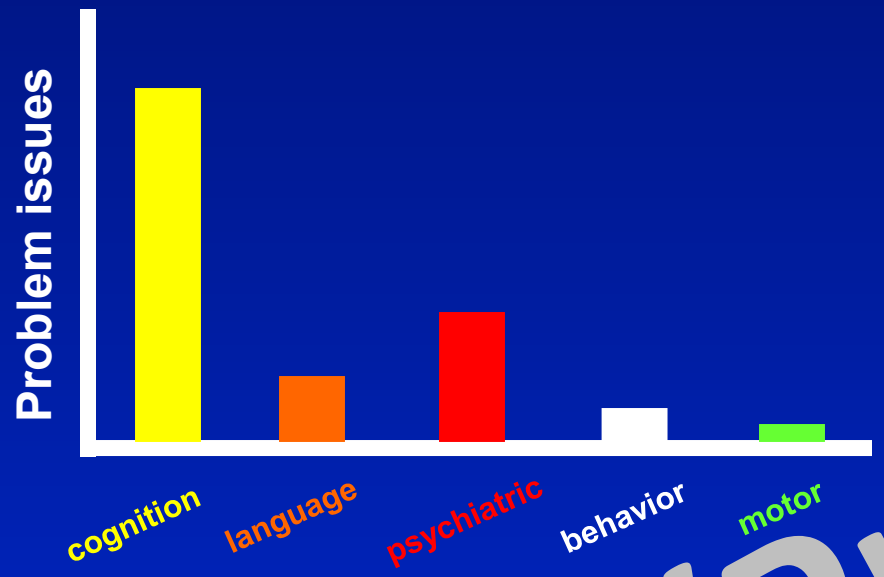
- Deficits in cognition may not be memory (usually attention/spatial)
- Parkinsonism
- Early hallucinations
- Fluctuations
- Supportive:
    - Depression
    - RBD

Frontotemporal dementia (NIH work group on FTD)

- Prominent behavioral disorder
    - Loss of interpersonal skills
    - Emotional blunting
    - Perseveration/impersistance
    - or
- Language involvement
    - Comprehension or fluency
- Cognition typically preserved
- Can be assoc with MND/ALS



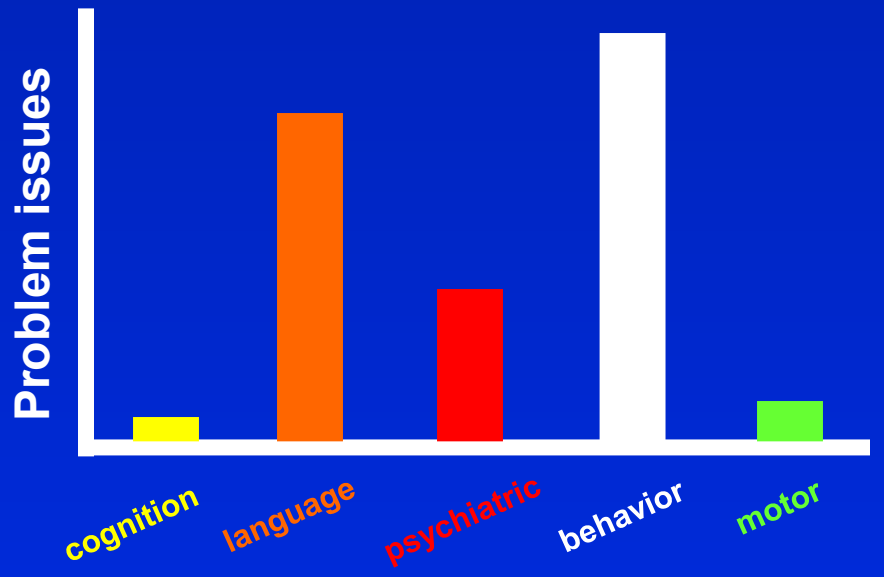
Alzheimer's disease



Vascular dementia

Dementia with Lewy bodies

Frontotemporal dementia



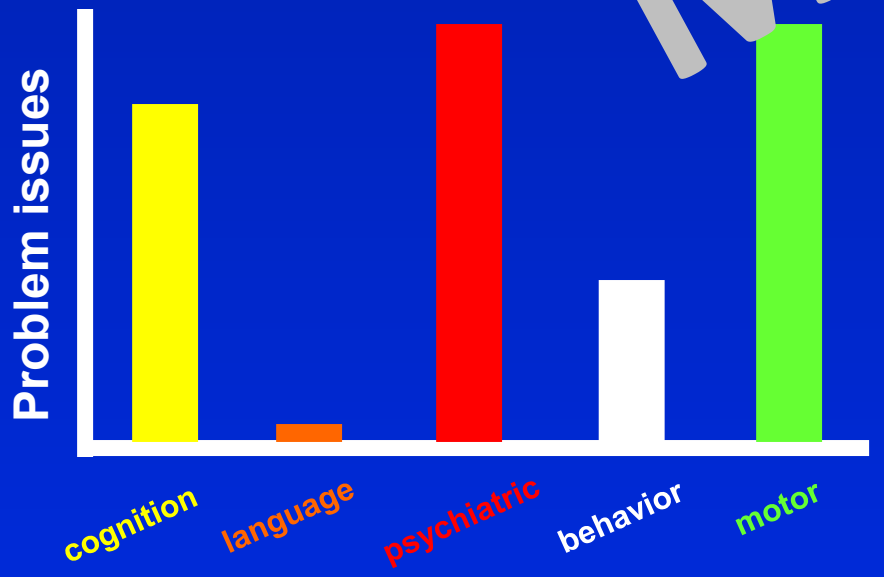
Early/Prodromal

Alzheimer's disease

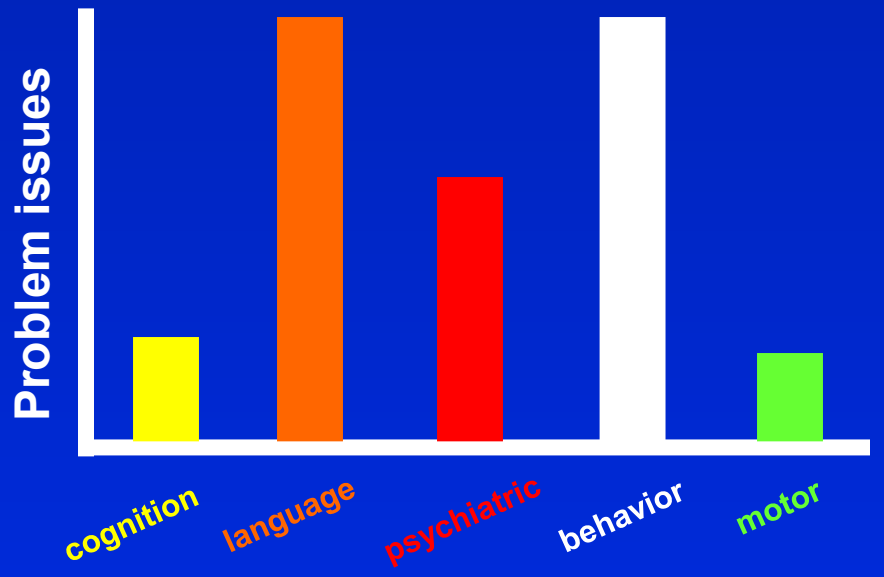
Vascular dementia

MILD

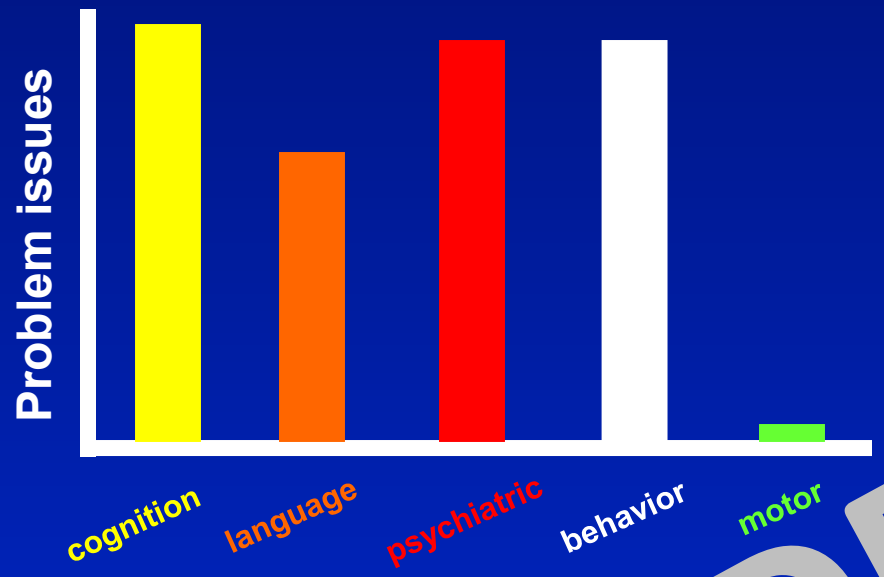
Dementia with Lewy bodies



Frontotemporal dementia



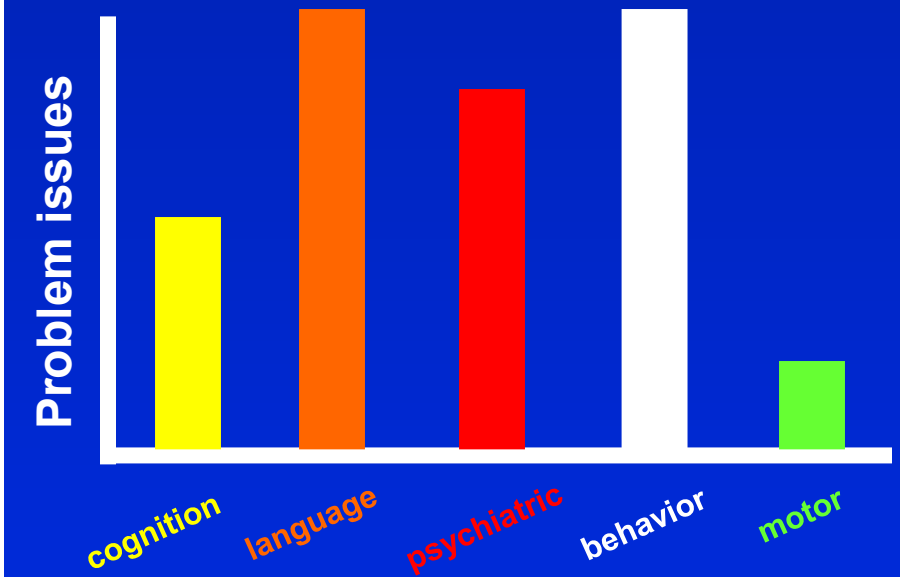
Alzheimer's disease



Vascular dementia

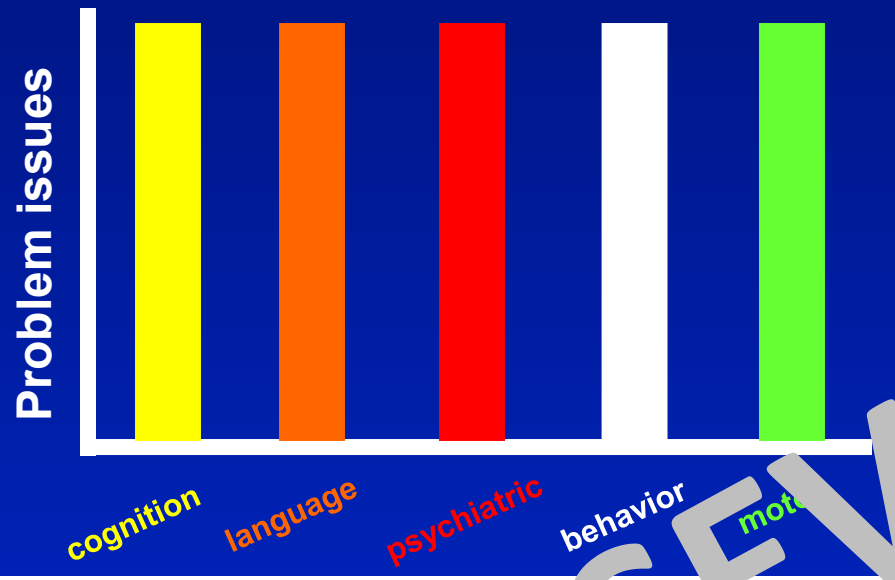
Dementia with Lewy bodies

Frontotemporal dementia

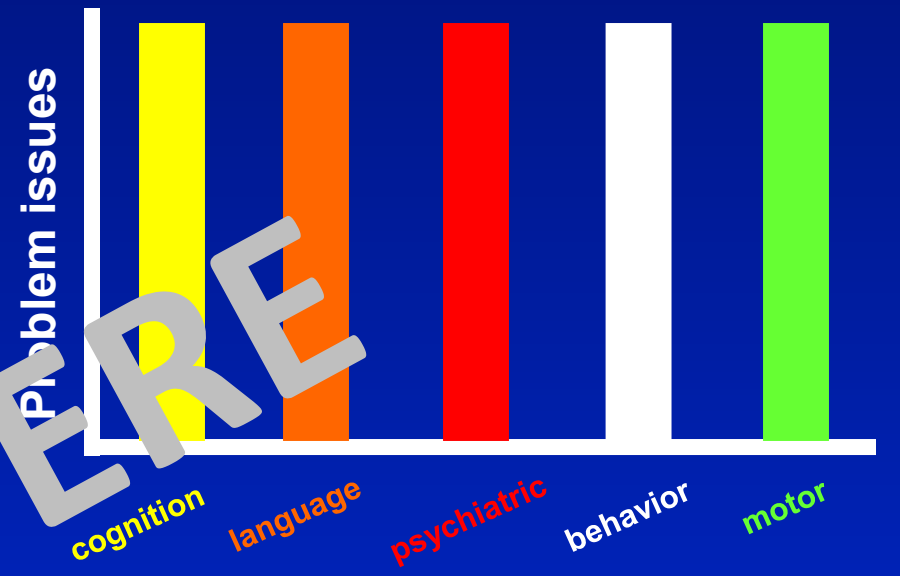


MODERATE

Alzheimer's disease

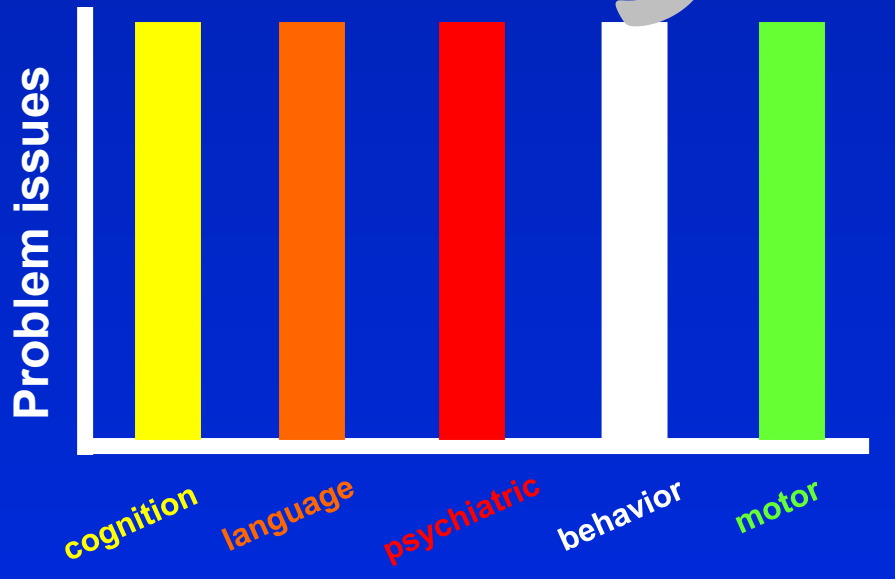


Vascular dementia

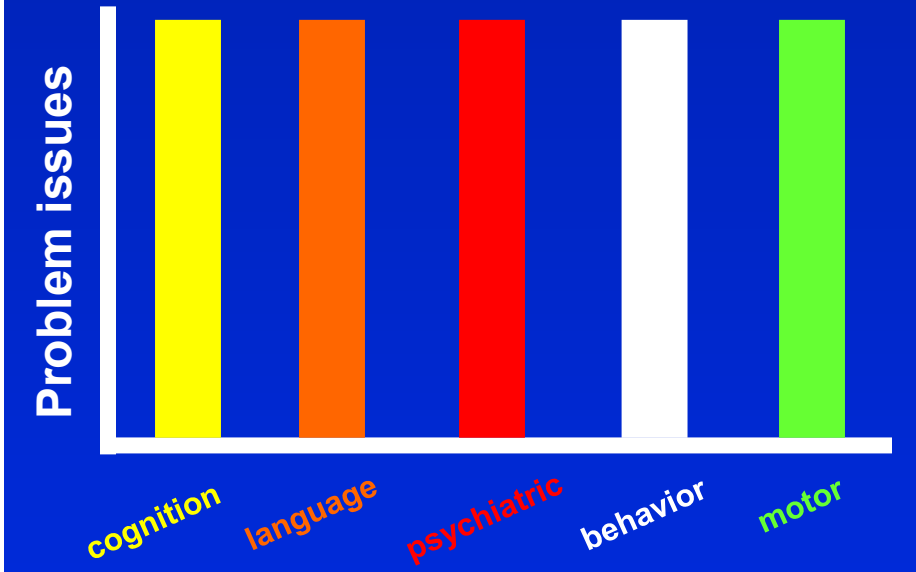


SEVERE

Dementia with Lewy bodies



Frontotemporal dementia



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Final Stage Clinical Manifestations

- Seizures (also can occur in mid stage)
- Urinary and fecal incontinence
- Rigidity, gegenhalten, or spasticity
- Loss of ability to walk
- Contractures
- Bedridden
- Eventually fetal-like posture
- Mute

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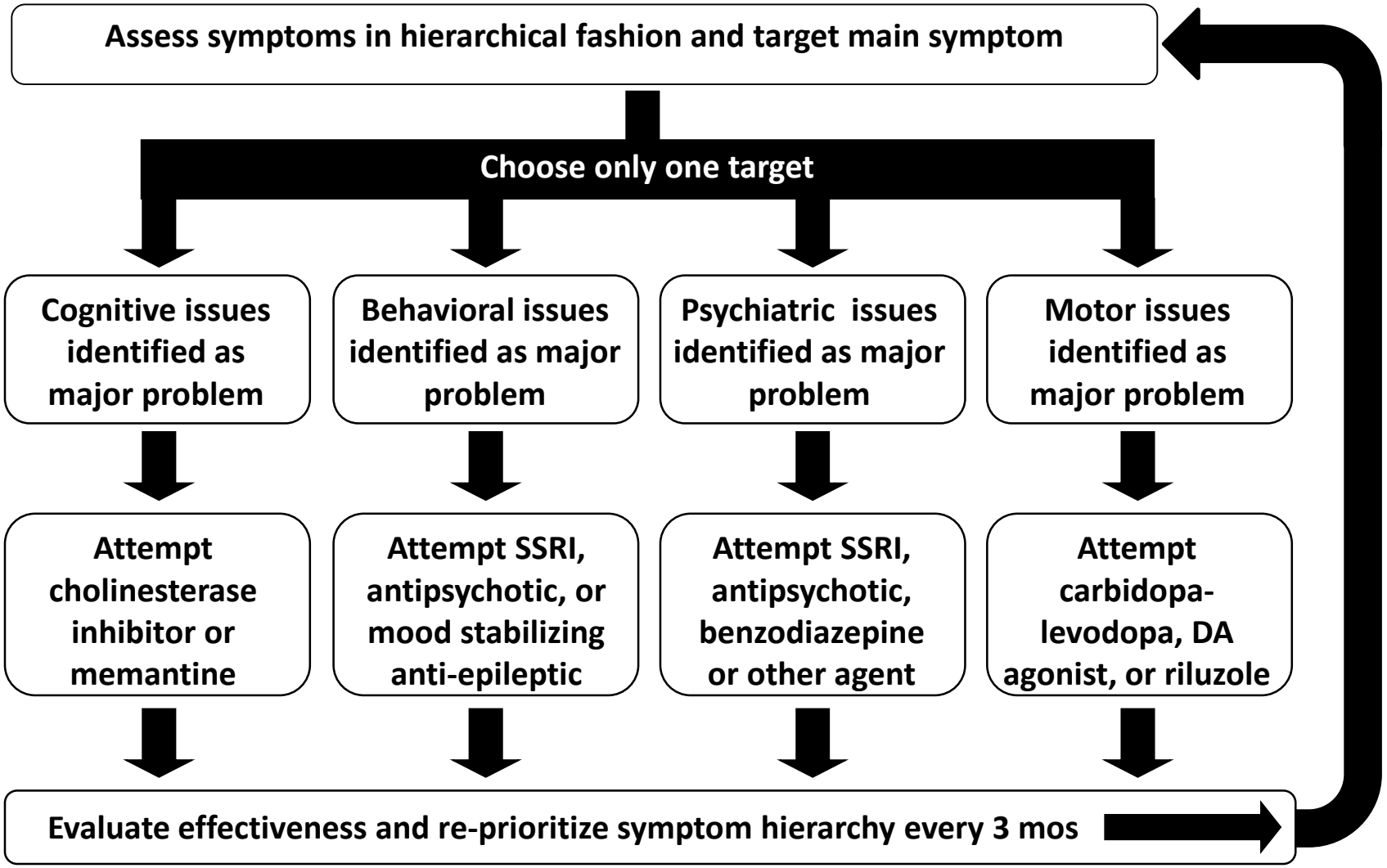
Let's talk about treatment



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Cholinesterase Inhibitors

- **FDA has approved 3 AChEI's for Alzheimer's Disease**
  - *Aricept (donepezil)*
  - *Exelon (rivastigmine)*
  - *Razadyne (galantamine)*
- **All show similar efficacy**
  - Cognition, Behavior, ADL's
- **Side effects**
  - Mostly overactivation of the GI system (nausea or diarrhea)
  - Rivastigmine patch may have less GI side effects
  - Can cause vivid disturbing dreams if taken at night
- **Benefit is sustained with long-term therapy when compared to no treatment**
- **All available in generic currently!**

AchEI	BuChEI	ACh+
+	-	-
+	+	-
+	-	+

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Memantine *(Namenda)*

- **Improvement or less decline in:**
  - Cognition
  - Behavior
  - ADL's
  - Global functioning
- **Reduced caregiver time**
- **Reduced cost of care**
- **Approved for mod-severe Alzheimer's Dz.**
- **New XR is not generic, but may help if once daily medication oversight is all we have**

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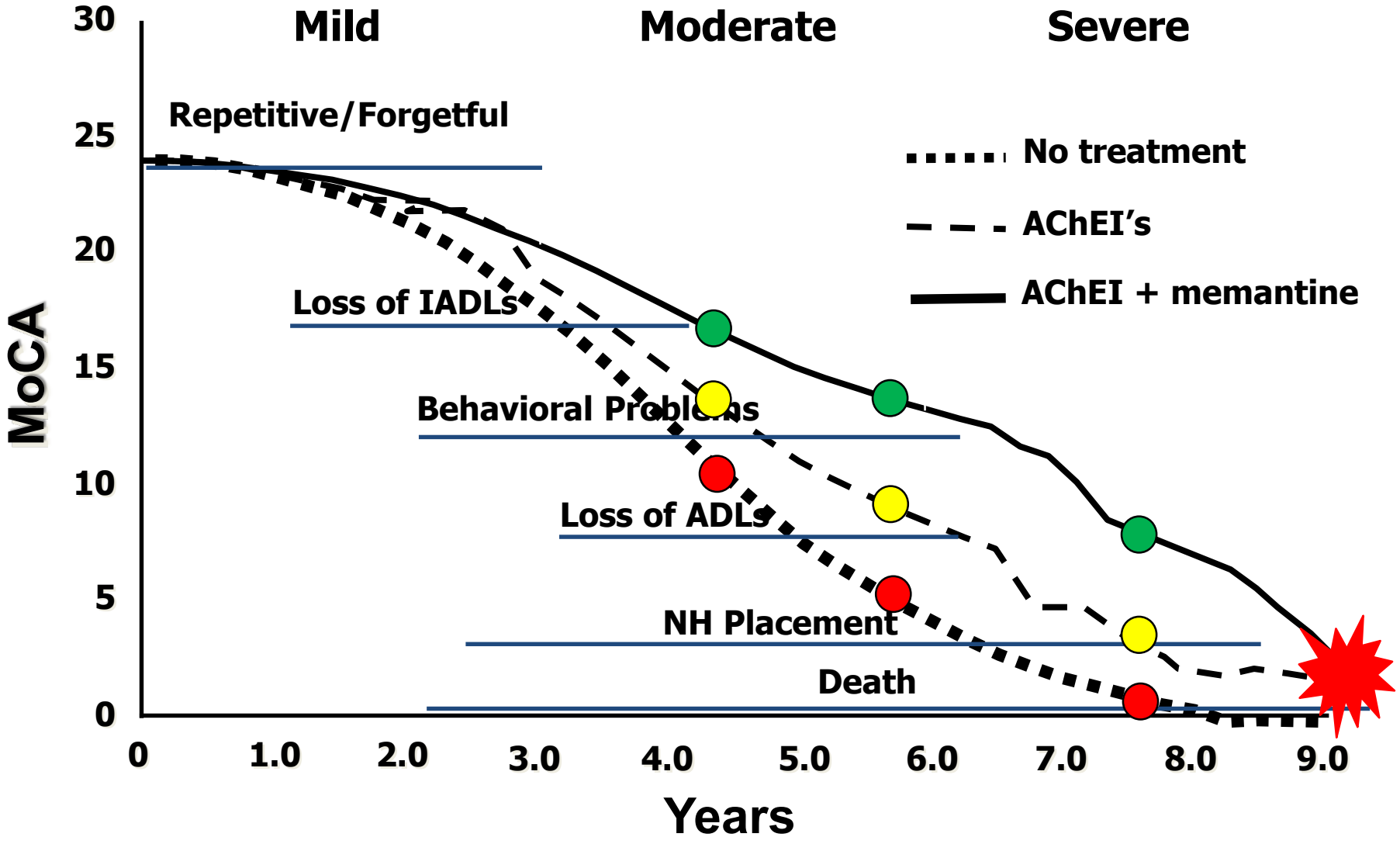
Treatment effects over the lifetime course of Alzheimer's Disease



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Lifestyle modifications for slowing or preventing dementia?

- **National Academies of Science, Medicine, & Engineering consensus panel recommendations from 2018**

- **Three interventions were supported by encouraging evidence**
  - Cognitive training
  - Blood pressure management for those with hypertension
  - Increased physical activity

- **All have minimal risk of harm, and two are known to be beneficial for other conditions**

- Diet & social activity are also important, but we don't yet know how much. More work is needed in these areas…

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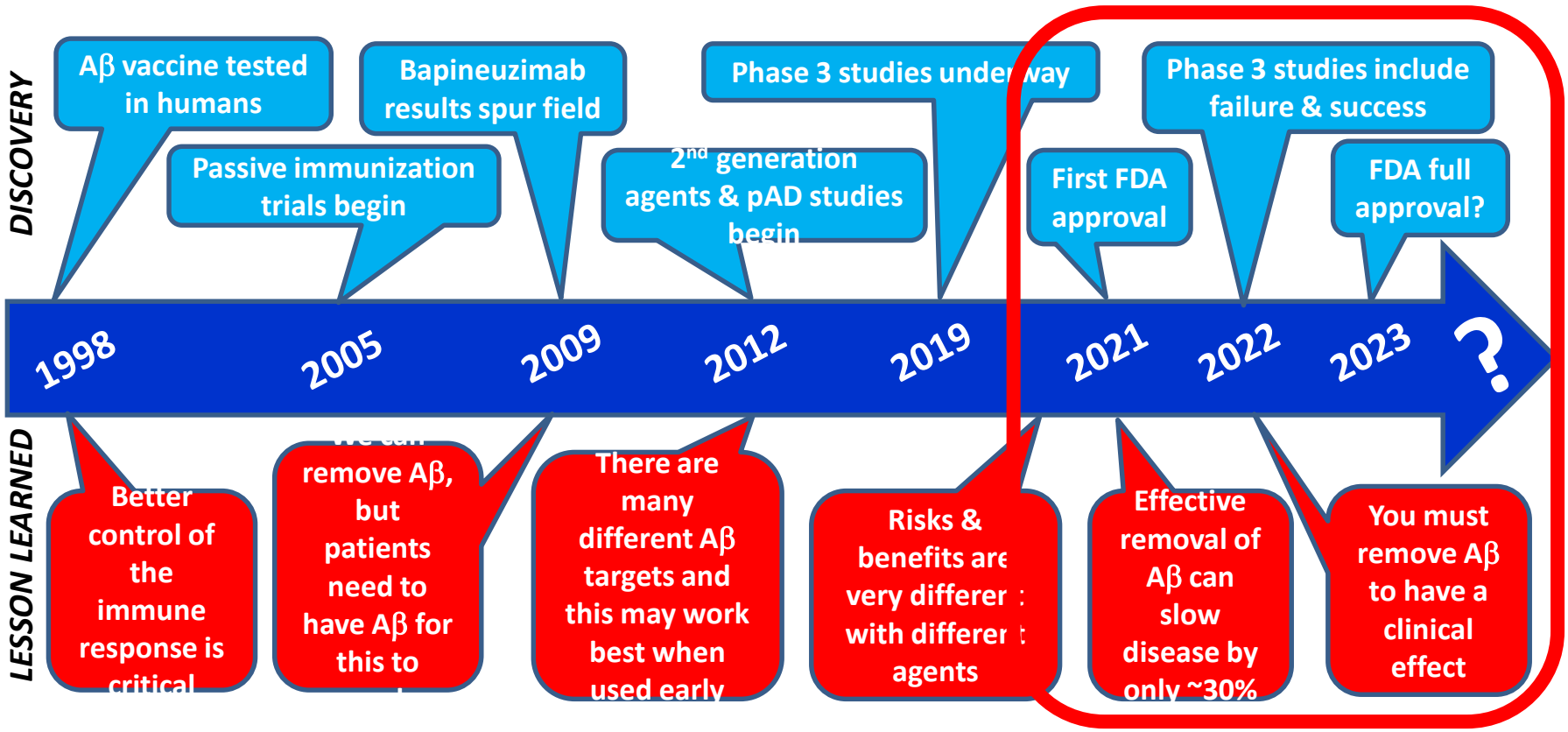
Timeline of anti-Aβ therapeutic discoveries & advances



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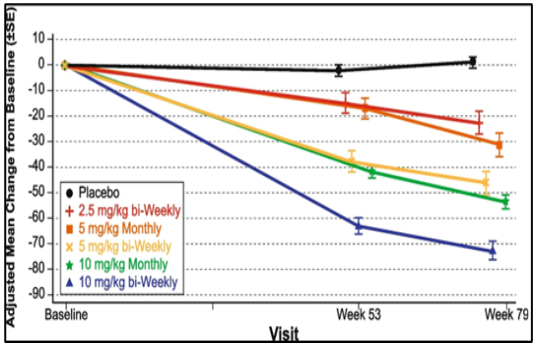
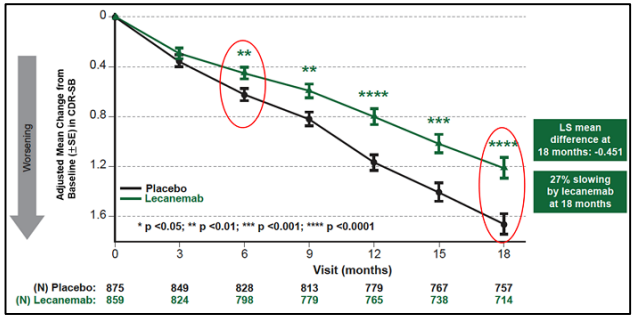
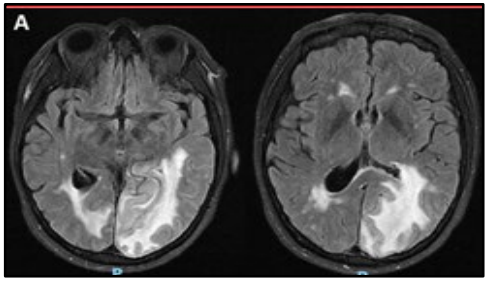
Lecanemab Lessons Learned 2022-2023

- **The Phase 3 CLARITY data is considered by most in the field to be definitive evidence of clinical benefit in addition to the previously accepted demonstration of Aβ removal**
  - The Phase 2b/3 data led to FDA accelerated approval on January 6, 2023 based solely on Aβ removal, and full FDA approval July 6, 2023 based on the clinical benefit
- **Clinical benefit ranges from 27% to 40% based on outcomes similar to the many other studies with other agents**
  - Eisai immediately filed for full approval based on the Phase 3 CLARITY data
- **ARIA rates appear low despite full clearance of Aβ but risks do still exist**







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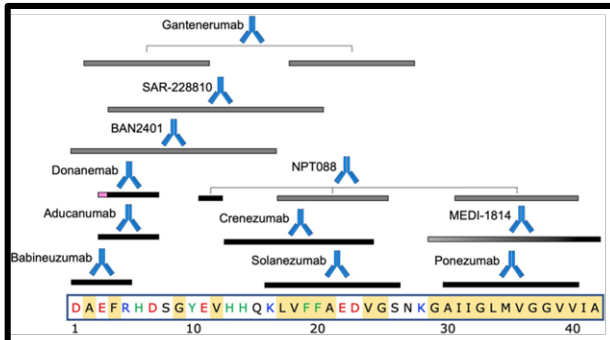
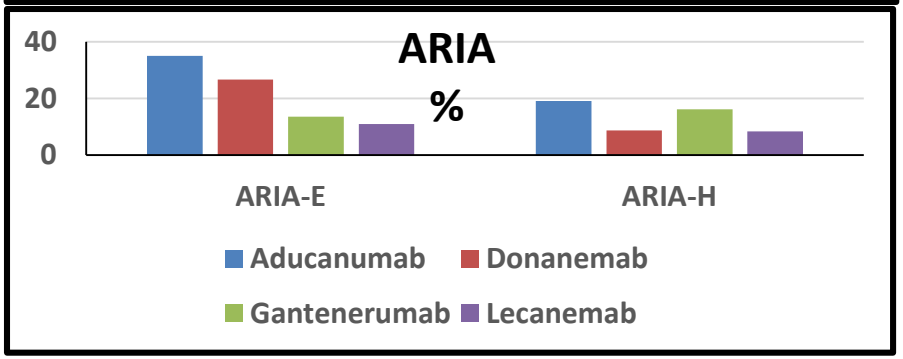
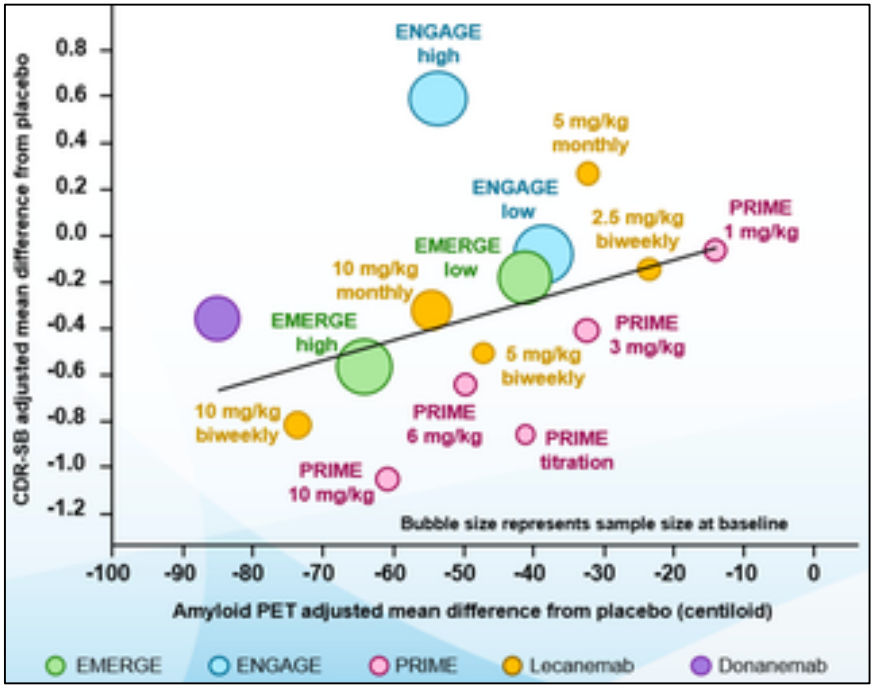
Donanemab just a week ago presented final phase 3 results that were positive

There are other medicines like this, some have failed to remove amyloid or have great risks



These drugs all target Aβ differently, leading to different effects on Aβ removal and risk for ARIA





Haass & Selkoe (2022) PLoS Biol 20(7): e3001694.

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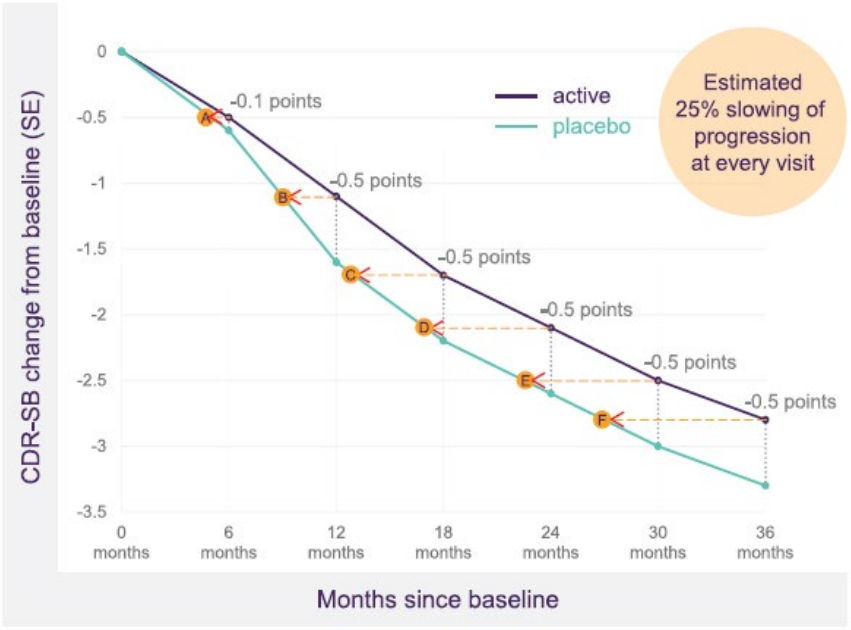
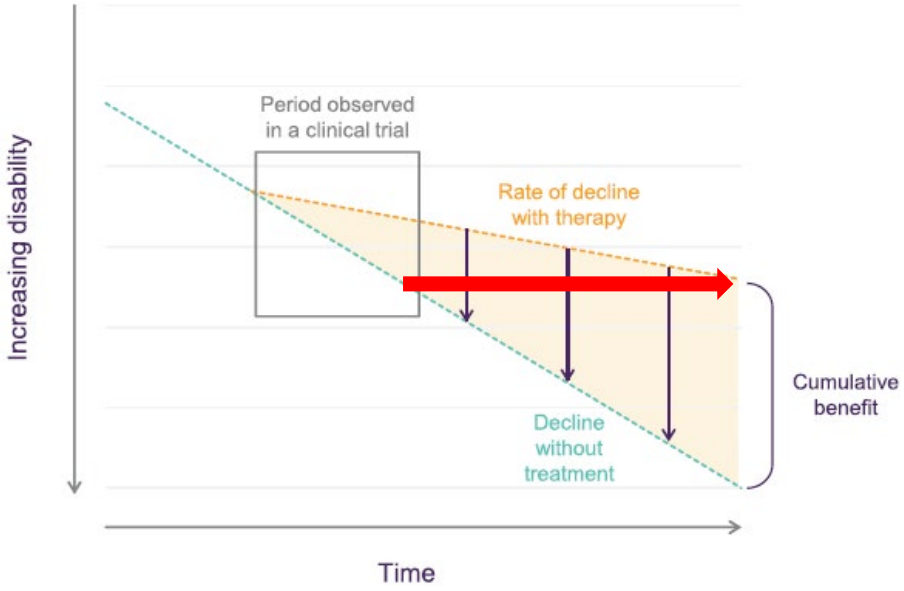
How much time will this buy us? Is it clinically meaningful?



	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 RC, Aisen PS, Andrews JS, Atri A, Matthews BR, Rentz DM, Siemers ER, Weber CJ, Carrillo MC. Expectations and clinical meaningfulness of randomized controlled trials. Alzheimers Dement. 2023 Feb 7. doi: 10.1002/alz.12959. Epub ahead of print. PMID: 36748826.

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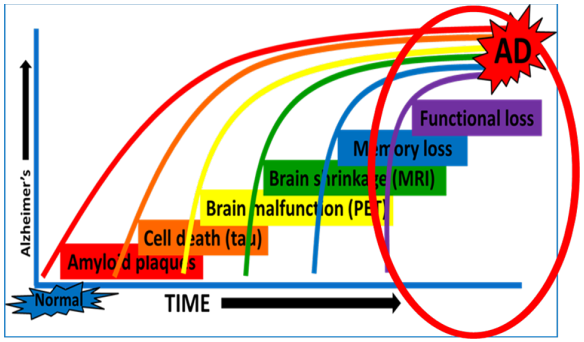
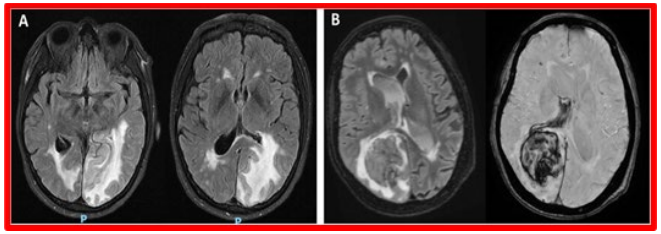
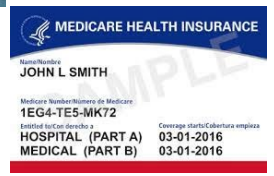
Imminent practical issues moving forward that we should all know…

Lecanemab (and potentially donanemab) is unfortunately not for everyone…

- *It is only for those with MCI and mild dementia, not for more advanced dementia*
- *Have to have positive amyloid CSF or PET scan*
- *Patients must be able to have an MRI scan for safety monitoring*
- *Patients cannot have significant past microhemorrhages or other bleeding in the brain*
- *Caution should be used for those on blood thinners (no concerns for anti-platelet blood thinners)*
- *Providing this medication may still be dependent on the uncertainty of FDA full approval & a decision by Medicare and other 3rd party payors to cover costs*







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Experimental therapies?

- There are also over 120 potential new treatments including possible cures being investigated
- The UK ADC is at the leading edge of this research
- Right here! Right now!
- The time to get involved is now!