Screen, Gene, and Intervene:
The Diagnostics, Genetics, and Pharmacologics of Dementia

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Speech and Language Pathology
February 23, 2024

Outline

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- Diagnostic work-up and general management of dementia
- Genetics of dementia, focusing on:
  - Alzheimer's disease
  - Frontotemporal lobar degeneration (FTD)
- Pharmacologic management of dementia
- Q&A

Learning Objectives

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1. Compare the diagnosis and management of dementia from the PCP/geriatrics, psychiatry, and neurology
2. Describe utility of genetic testing, including APOE genotyping
3. Assess utility of available pharmacologic management of dementia, with a focus on monoclonal antibodies in Alzheimer's disease

Disclosure

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- Principal investigator/study physician for ongoing and previously conducted Alzheimer's disease clinical trials at Vanderbilt, with industry sponsors including:
  - AbbVie
  - Acadia
  - Genenetch/Roche
  - Janssen
  - CND

Learning Objectives

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1. **Compare the diagnosis and management of dementia from the PCP/geriatrics, psychiatry, and neurology**
2. Describe utility of genetic testing, including APOE genotyping
3. Assess utility of available pharmacologic management of dementia, with a focus on monoclonal antibodies in Alzheimer's disease

What words come to mind when you think of dementia?

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Mild Cognitive Impairment (Minor neurocognitive disorder)

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1. Concern regarding a change in cognition
2. Impairment in ≥1 cognitive domain
   - Memory, executive function, attention, language, visuospatial skills
3. Preservation of independence in functional abilities
4. Not demented

Albert et al., *Alzheimer's and Dementia* (2011)

Dementia (Major neurocognitive disorder)

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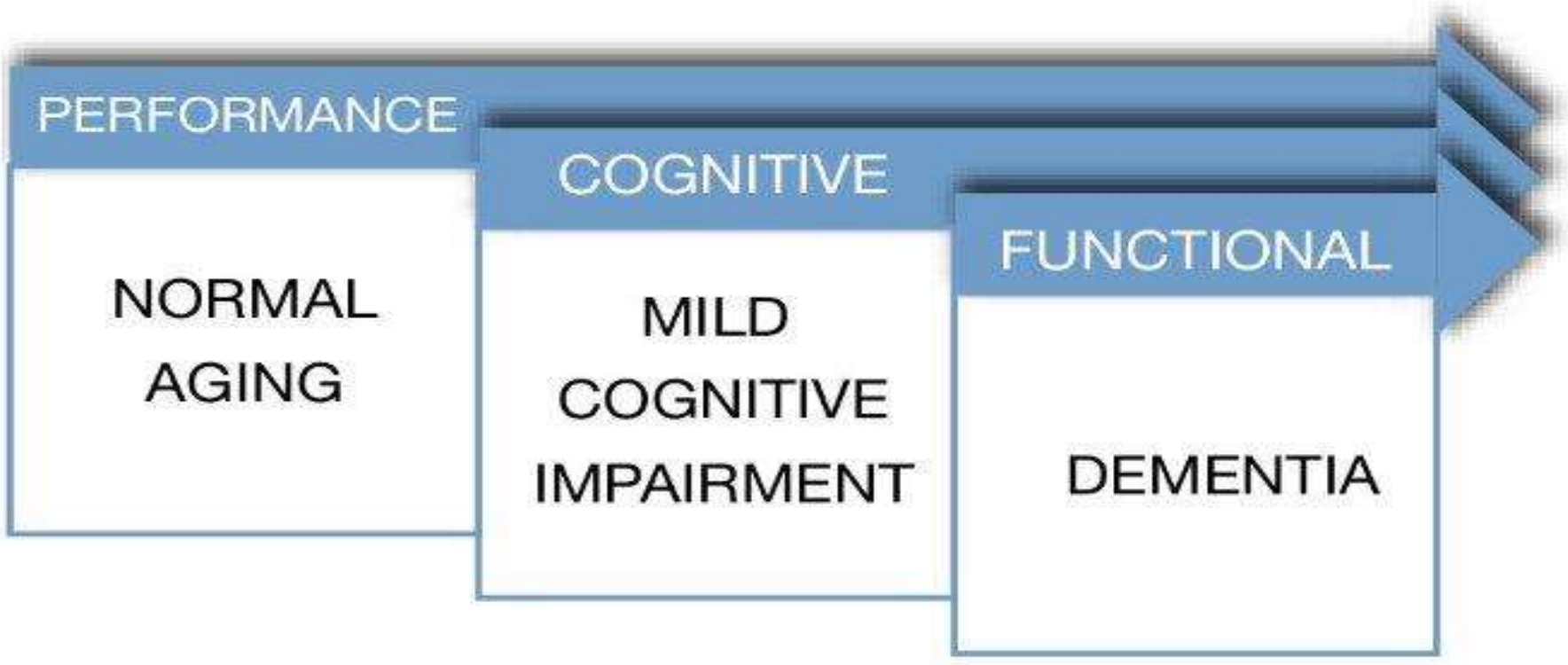
1. Impairment in short- and long-term memory associated with
   a. impairment in abstract thinking,
   b. impaired judgment,
   c. other disturbances of higher cortical function,
   d. or personality change.
2. Disturbance severe enough to interfere significantly with work, usual social activities, or interpersonal relationships
3. Not delirious

DSM-IV

MCI vs. Dementia



3. Preservation of independence in functional abilities
4. Not demented

2. Disturbance severe enough to interfere significantly with work, usual social activities, or interpersonal relationships
3. Not delirious

Diagnosing Dementia

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- Who diagnoses dementia?
  - PCP usually the first to hear about this
  - May be referred:
    - Geriatrics
    - Psychiatry
    - Neurology
- What is necessary for the diagnosis of dementia?
  - Clinical history
  - Cognitive assessment

The Mini-Mental State Exam

Patient_____

Maximum Score

5 ( )

3 ( )

5 ( )

3 ( )

2 ( )
1 ( )
3 ( )

1 ( )
1 ( )
1 ( )

_____

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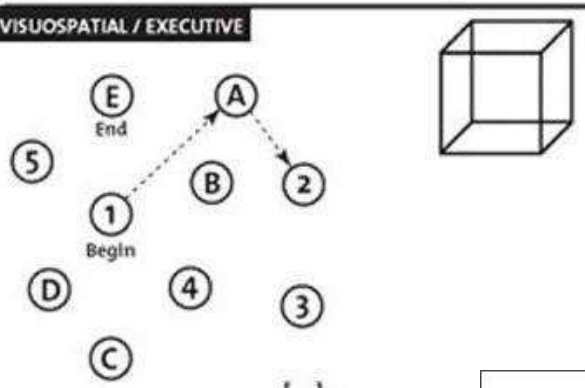
MONTREAL COGNITIVE ASSESSMENT (MOCA)

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

VISUOSPATIAL / EXECUTIVE



Copy cube

[ ]

Draw CLOCK (Ten past eleven)
(3 points)

POINTS

NAMING

[ ]

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

1st tri
2nd tri

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

Read list of letters. The subject must tap with his hand at each le
[ ]

Serial 7 subtraction starting at 100 [ ] 93 [
4 or 5 cor

LANGUAGE Repeat : I only know that John is the one t
The cat always hid under the co

Fluency / Name maximum number of words in one minute

ABSTRACTION Similarity between e.g. banana - orange =

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VE
		[ ]	
Optional	Category cue		
	Multiple choice cue		

ORIENTATION [ ] Date [ ] Month [

www.mocatest.org

Mini-Cog™

Instructions for Administration & Scoring

ID: _____ Date: _____

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.[1-3] For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

Word List Version: ____ Person's Answers: _____ _____ _____

Diagnostic Evaluation of Cognitive Impairment

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- Laboratory serologies
  - E.g., CMP, CBC, TSH/T4, vitamin B12
- Brain imaging
    - CT head
    - MRI brain
- Referral?
  - Specialty
  - PT
  - OT
  - SLP

Dementia

http://www.alzsd.org/resources/

Types of dementia

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- Alzheimer's disease
- Frontotemporal lobar degeneration
- Dementia with Lewy bodies
- Vascular dementia
- Normal pressure hydrocephalus
- Progressive Supranuclear Palsy
- Corticobasal Syndrome
- Parkinson's disease dementia
- … and many, many more!

Primary progressive aphasia

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- Neurodegenerative diseases characterized by early and prominent language impairment occurring in the relative absence of cognitive impairment, behavioral disturbance, or motor symptoms.

Diagnostic Criteria for PPA

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- Primary Progressive Aphasias and Apraxia of Speech
- Botha, Hugo; Josephs, Keith A.
- CONTINUUM: Lifelong Learning in Neurology25(1):101-127, February 2019.
- doi: 10.1212/CON.0000000000000699

Inclusion: Criteria 1–3 Must Be Answered Positively

1 Most prominent clinical feature is difficulty with language

2 These deficits are the principal cause of impaired daily living activities

3 Aphasia should be the most prominent deficit at symptom onset and for the initial phase of the disease

Exclusion: Criteria 1–4 Must Be Answered Negatively for a Primary Progressive Aphasia Diagnosis

1 Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders

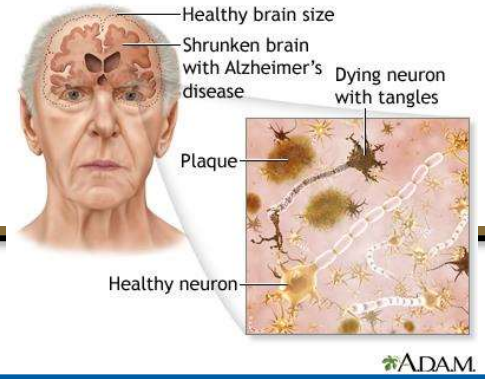
2 Cognitive disturbance is better accounted for by a psychiatric diagnosis

3 Prominent initial episodic memory, visual memory, and visuoperceptual impairments

4 Prominent, initial behavioral disturbance

[a] Reprinted with permission from Gorno-Tempini ML, et al, Neurology.[1] © 2011 American Academy of Neurology.

Alzheimer's Disease



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Alzheimer's Disease	Progressive disorder of recent episodic memory, language, visuospatial function, and executive function associated with high frequency of neurobehavioral abnormalities at some point in the course
Clinical Features	**Amnestic** **Non-Amnestic** (Language, Visuospatial, Executive dysfunction) Insidious; Progressive; No disturbance of consciousness; Onset between 40-90 yo; Absence of other dz Trisomy 21
Pathology	**Beta-amyloid and tau**
Neurological Exam	**Other than impaired cognition, physically non-focal usually**
Diagnostic work-up	CSF (increased tau, decreased amyloid)
Imaging	MRI (hippocampal atrophy) or FDG-PET brain (temporoparietal hypometabolism)
Treatment	**AChE inhibitors**; NMDA receptor antagonists

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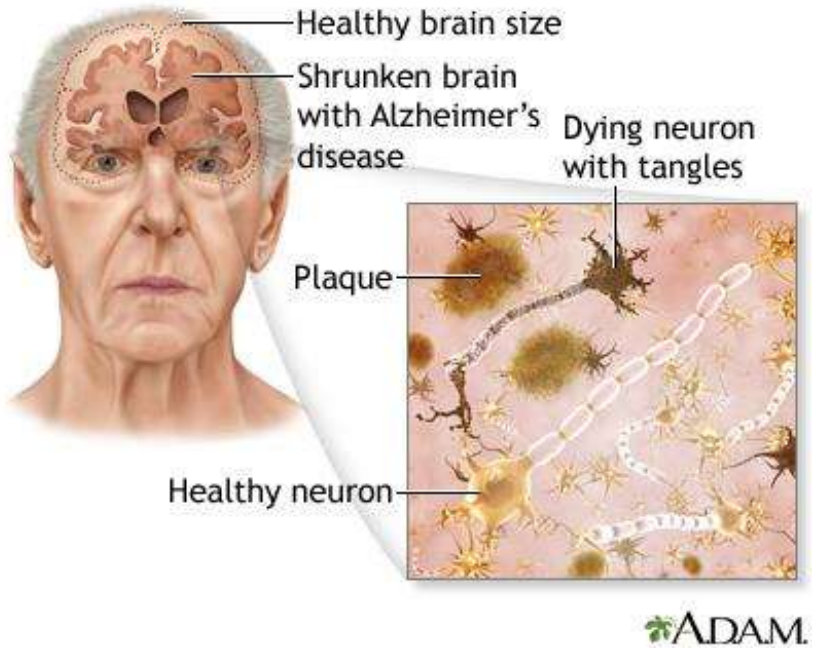

Alzheimer's Disease

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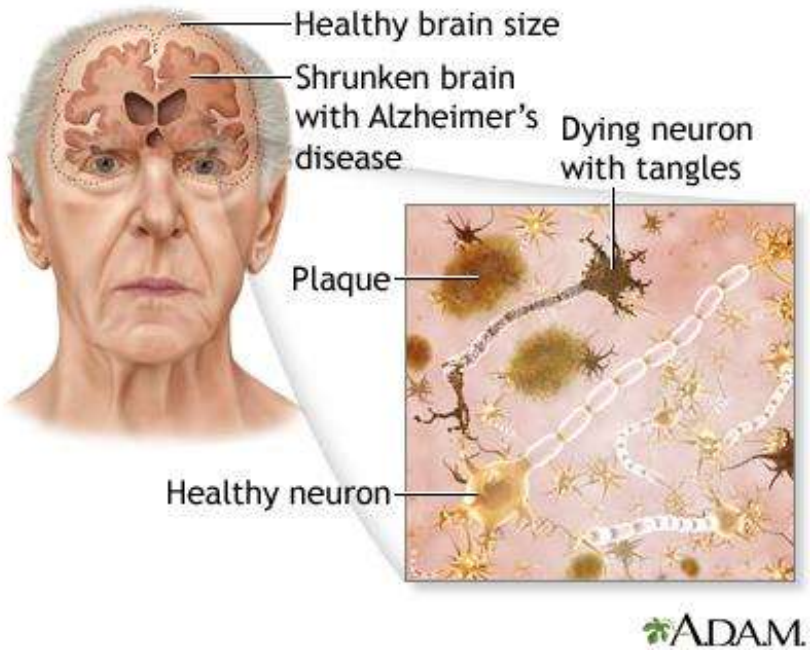
- **Features**
  - often **getting lost/disoriented**
  - prominent **forgetting** and **repeating (amnestic)**
  - Typically **anosognosic**
- **Deposition of amyloid and tau**



PollEverywhere Question

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- What variant(s) of primary progressive aphasia (PPA) is/are most often associated with Alzheimer's as the underlying pathology?
- A. Logopenic aphasia
- B. Semantic aphasia
- C. Agrammatic/nonfluent aphasia
- D. Primary progressive apraxia of speech

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Alzheimer's Disease

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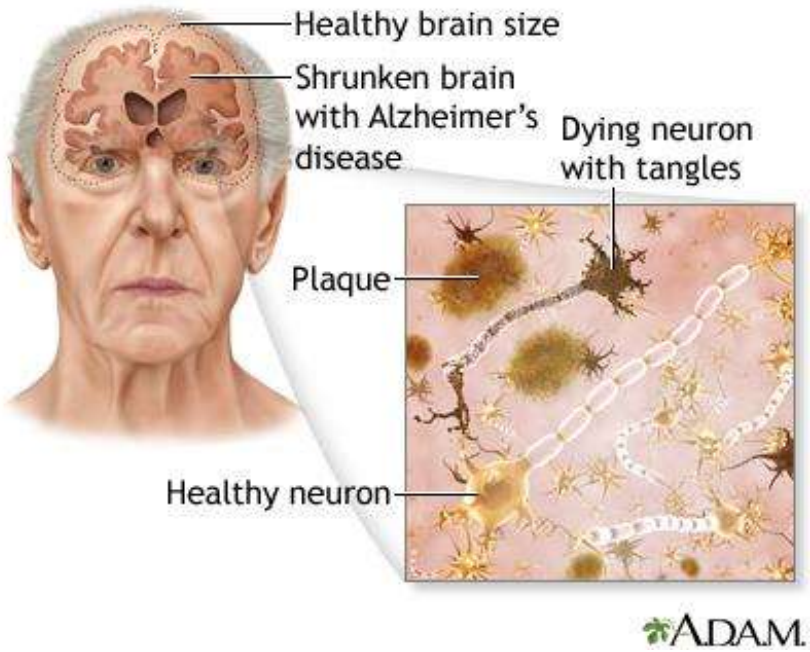
- **Features**
  - often **getting lost/disoriented**
  - prominent **forgetting** and **repeating (amnestic)**
  - Typically **anosognosic**
- Deposition of amyloid and tau
- PPA variant: **logopenic**
  - Impaired sentence repetition
  - Word-finding difficulty



Logopenic PPA

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Symptoms

- Decreased spontaneous language: “fewer words”
- Anomia
- Impaired repetition and pseudoword reading
- Comprehension relatively intact

Imaging

- Left hemisphere posterior temporal and inferior parietal lobes

Pathology: Alzheimer’s > FTD

Gorno-Tempini et al *Neurology* (2011)
Kirshner *Neuropsychiatr Dis Treat* (2014)
Migliaccio et al *Neurology* (2009)

MRI

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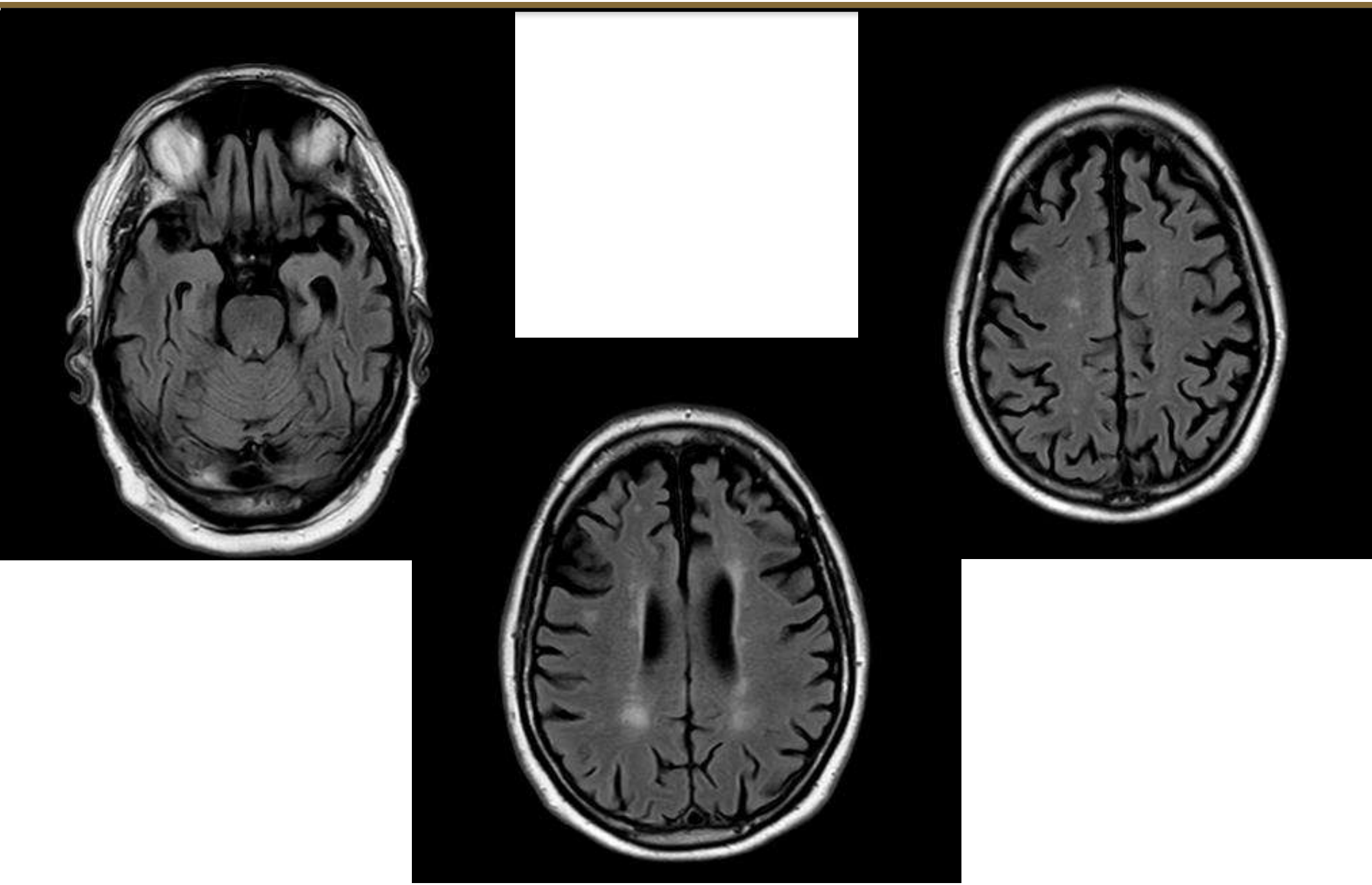
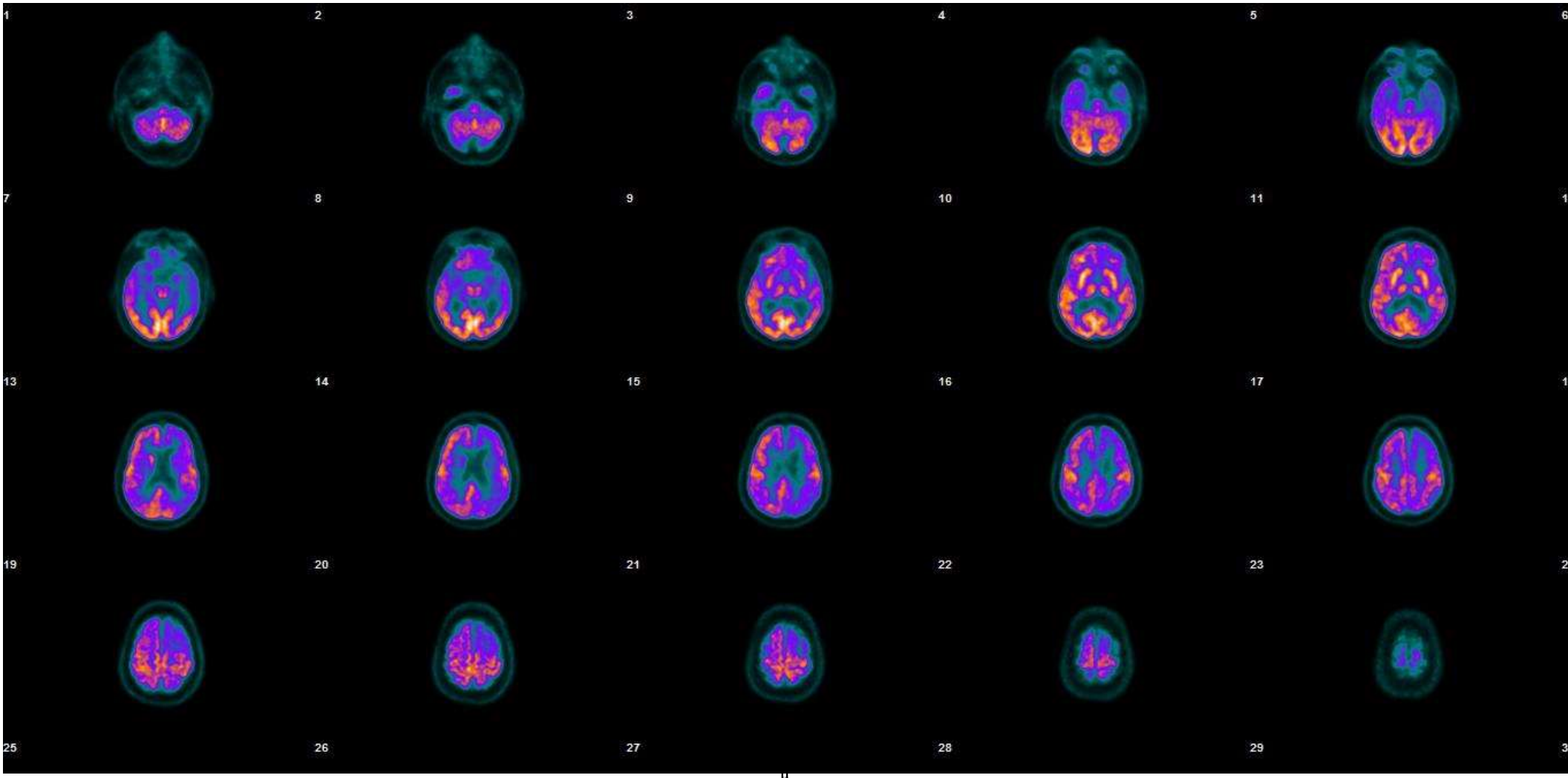
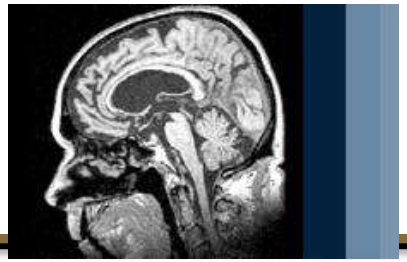


FDG-PET brain



“Severely decreased FDG update in bilateral frontal and temporal lobes with mild to moderate decreased uptake in bilateral parietal lobes. These findings most likely represent frontal temporal dementia but a more intense form of Alzheimer's cannot be excluded.”

FTLD



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Frontotemporal lobar degeneration	Neurodegenerative disease process with "focal" symptoms of progressive language dysfunction or behavioral changes
Clinical Features	**1. Behavioral variant** ***Personality change/alterations in social conduct (disinhibition)*** ***Appetite*** ***Abulia/apathy*** ***Decline in hygiene*** *Language variants* 2. Semantic dementia 3. Progressive non-fluent aphasia
Pathology	**Tau (Pick bodies)**
Neurological Exam	Disinhibited behavior or personality change Frontal release signs, hyperreflexia, fasciculations, etc. Bulbar symptoms
Diagnostic work-up	Genetic variants
Imaging	MRI (fronto-temporal atrophy) or FDG-PET brain (fronto-temporal hypometabolism)
Treatment	Supportive; behavioral rx with SSRIs

FTLD: Diagnosis

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- Personality change and alterations in social conduct
  - Disinhibition
  - "witzelsucht"
- Appetite
- Abulia/apathy
- Decline in hygiene
- Anosognosic
- Memory loss usually not prevalent

Kirshner HS (2014). Frontotemporal dementia and primary progressive aphasia, a review. *Neuropsychiatr Dis Treat.*10:1045-55. doi: 10.2147/NDT.S38821.

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- C. Agrammatic/nonfluent aphasia
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FTLD Language Variants

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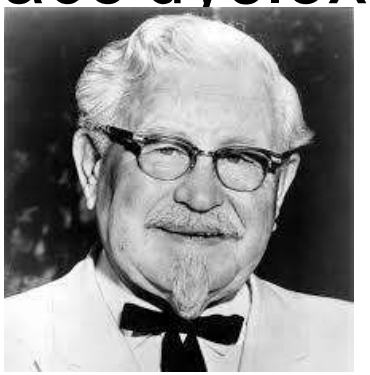
Non-fluent/Agrammatic PPA

- Effortful, halting speech
  - "Broca-like"
- Simplified, "agrammatic"
- Comprehension relatively preserved
  - word
  - sentence

Semantic PPA

- Fluent aphasia
- Anomia
- Impaired word meaning
- Repetition intact
- Surface dyslexia

"yacht"



"colonel"

Kirshner *Neuropsychiatr Dis Treat* (2014)

FTLD Language Variants

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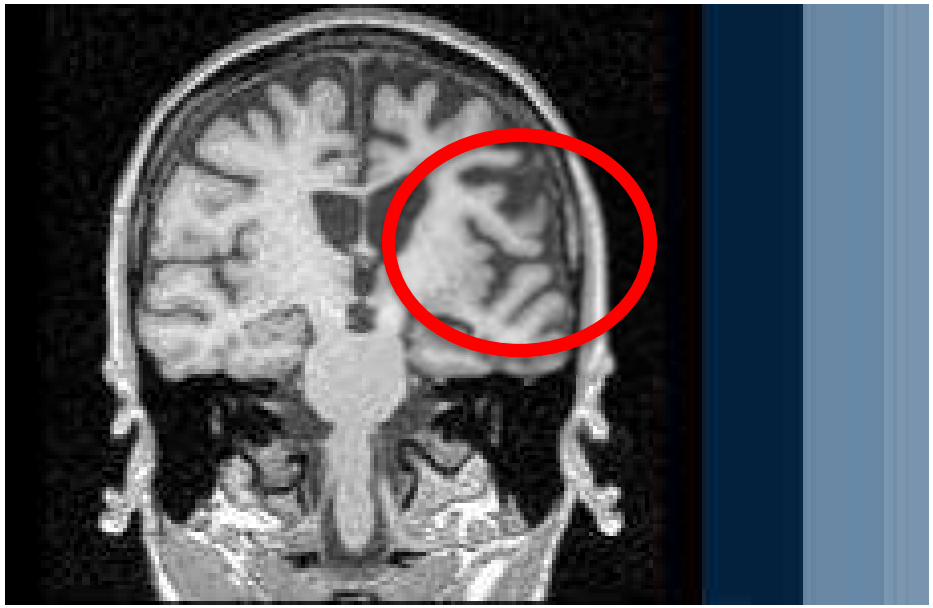
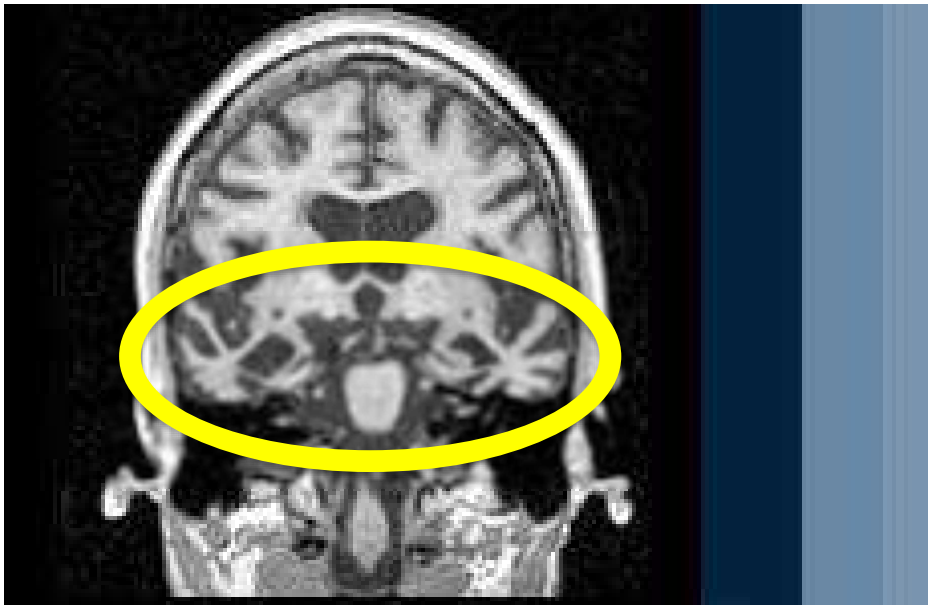
Non-fluent/ Agrammatic Aphasia



- Peri-Sylvian atrophy

• Semantic Aphasia



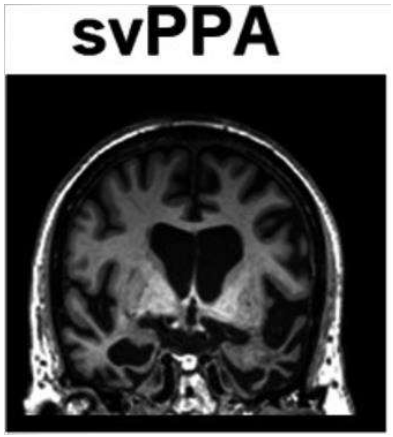
- Anterior temporal lobe atrophy

UCSF, http://memory.ucsf.edu/ftd/overview/ftd/forms/multiple/sd

FTLD

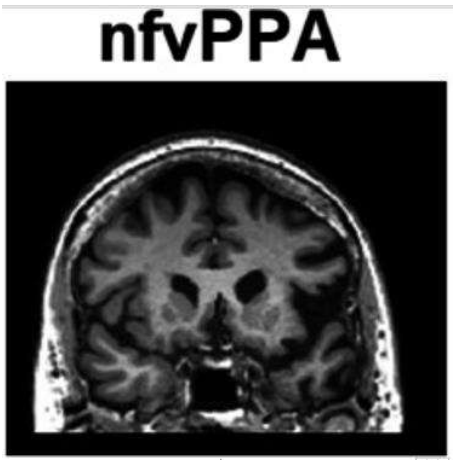
Semantic

- Fluent aphasia
- Anomia
- Impaired word meaning
- Repetition intact
- Surface dyslexia
- Radiology: anterior temporal atrophy



Non-Fluent/ Agrammatic

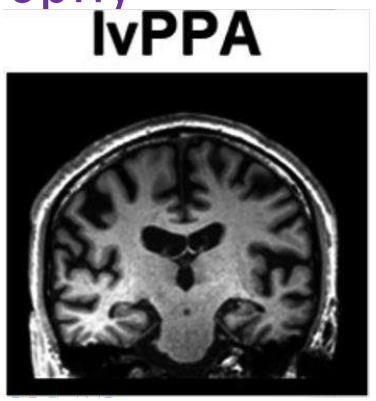
- "Broca-like"
- Simplified, "agrammatic"
- Comprehension relatively preserved
- Radiology: peri-Sylvian atrophy



AD

Logopenic

- ↓spontaneous language production ("fewer words")
- Anomia
- Impaired repetition
- Comprehension relatively intact
- Radiology: temporoparietal atrophy



PPA Clinical Features

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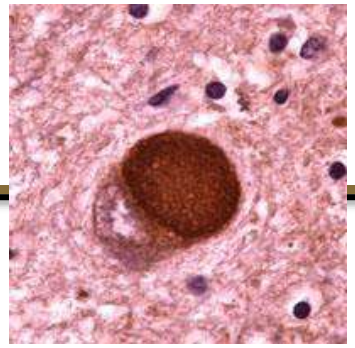
Characteristic	Non-fluent/ agrammatic	Semantic	Logopenic
Fluency	**Non-fluent**	Fluent	Fluent
Naming	Some anomia	Some anomia	Anomia
Repetition	Non-fluent	Fluent	**Impaired**
Comprehension	Intact for simple items	Impaired, even at single-word level	Intact for simple items
Reading	Intact for short items	**Surface alexia**	Intact for simple items
Nonsense words	Normal	Impaired for irregular words	Impaired

Modified from: Kirshner *Neuropsychiatr Dis Treat* (2014)

Lewy Body Dementia (DLB)



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DLB	Dementia secondary to Lewy bodies (alpha-synuclein) with fluctuating cognition, hallucinations, and parkinsonism
Clinical Features: **CORE**	**Dementia:** Attention, dyexecutive, visuospatial, memory loss **Fluctuating cognition** **Visual hallucinations** **Parkinsonism** **REM disorder** **Parkinsonism (>1 cardinal feature)**
Pathology	**Lewy bodies (alpha-synuclein protein)**
Neurological Exam	Parkinsonism
Diagnostic work-up	Sleep study if concern for REM disorder Neuropsychological testing
Imaging	CT/MRI nonspecific; FDG-PET brain (occipital hypometabolism)
Treatment	AChE inhibitors for memory; dopaminergic therapy for parkinsonism

Vascular Dementia

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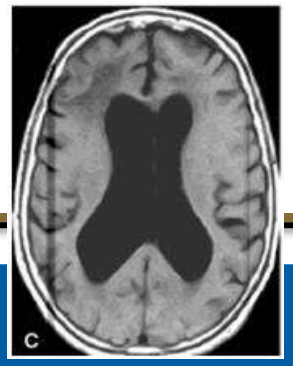
Vascular dementia	**NINDS-AIREN criteria** • Onset or worsening of dementia is w/in 3 months s/p clinical stroke • Imaging shows evidence of bilateral infarcts in cortical regions, basal ganglia, thalamus, or white matter • Can also be secondary to accumulation of "silent" infarcts • Focal deficits on neurological exam
Clinical Features	"**stepwise**" decline cognitively, with accompanying focal neurological deficits
Pathology	Stroke
Neurological Exam	Focal neurological deficits (cognitively, often aphasia)
Diagnostic work-up	Arrhythmias, lipids, hemoglobin A1c
Imaging	NCHCT (hemorrhagic stroke) MRI brain (acute ischemic stroke: DWI and ADC changes)
Treatment	Managing stroke risk factors Symptomatic treatment (e.g., depression)

Normal Pressure Hydrocephalus (NPH)



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Normal pressure hydrocephalus	Chronic communicating hydrocephalus
Clinical Features	Mental impairment, gait disturbance, and incontinence **"weird, wet, and wobbly"**
Pathology	n/a
Neurological Exam	Cognitive changes, **magnetic gait**
Diagnostic work-up	CT or MRI brain **Lumbar puncture** (NORMAL opening pressure) with **high volume tap** (>30 cc) → yields symptomatic improvement CSF typically without abnormalities
Imaging	**Ventriculomegaly**
Treatment	**Ventriculoperitoneal shunt**

Diagnosing Dementia: inpatient?

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- Need to rule out alternative causes
- Can't diagnose when somebody is delirious
  - Outpatient > inpatient

Learning Objectives

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2. **Describe utility of genetic testing, including APOE genotyping**
3. Assess utility of available pharmacologic management of dementia, with a focus on monoclonal antibodies in Alzheimer's disease

Genetics

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- Most dementias do not have a genetic cause
- A minority of patients with neurodegenerative dementia get referred to genetic counseling

Genetics: Alzheimer's dsiease

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- Most dementias do not have a genetic cause
- Alzheimer's disease (AD)
  - Early onset AD, <65 yo
    - Presenilin, APP
  - APOE genotype

Genetics: Frontotemporal lobar degeneration

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- Most dementias do not have a genetic cause
- Frontotemporal lobar degeneration
  - C9orf72
  - MAPT
  - Progranulin

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Pharmacologic Therapies

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- Major categories of pharmacological interventions for dementia
  - **Cholinesterase inhibitors**
  - **NMDA receptor antagonists**
  - Monoclonal antibodies
  - Antidepressants and anxiolytics
  - Antipsychotics
  - Hypnotics

Pharmacologic Therapies

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Drug category	Drug names	AD	FTLD	DLB	PSP/CBS	PDD	VD
Cholinesterase inhibitors	Donepezil Rivastigmine Galantamine	✓ ✓ ✓	X X X	✓ ✓ ?	X X X	✓ ✓ ✓	✓ ✓ ✓
NMDA r. ant.	Memantine	✓	X	✓	X	?	✓
Antidepressants	SSRIs, SNRIs	✓	✓	✓	✓	✓	✓
Anxiolytics	Buspirone, SNRIs	✓; avoid benzodiazepines in general					
Hypnotics, REM disorder	Melatonin, trazodone, Mirtazapine, suvorexant Clonazepam	✓ ✓ ✓ X	✓ ✓ ✓ X	✓ ✓ ✓ ✓			
Antipsychotics	Pimavanserin, Quetiapine, Clozapine risperidone	✓, with caution	~~Risperidone~~ o/w?/✓	~~Risperidone~~ o/w?/✓	~~Risperidone~~ o/w?/✓	~~Risperidone~~ o/w?/✓	✓, with caution
Parkinsonism	Carbidopa-levodopa Dopamine agonists Amantadine			✓ X ?	✓ X ✓	✓ ✓ ✓	
Dystonia	Baclofen Clonazepam ~~Trihexyphenidyl~~ Botulinum toxin				✓ ✓ X ✓		

Dementia Treatment

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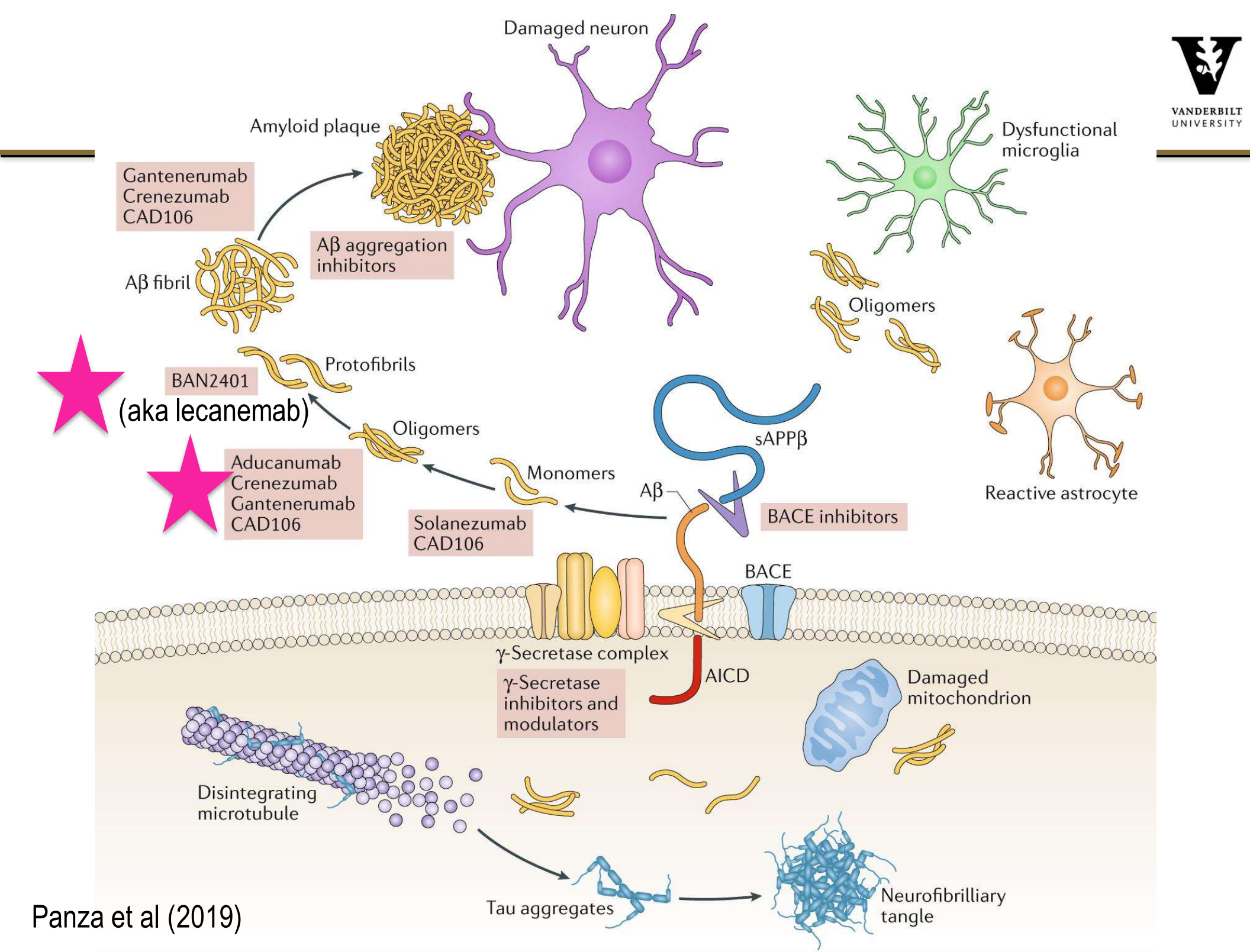
- Drugs used depend on the disease: cannot be used across all dementias
- E.g., cholinesterase inhibitors can make behaviors worse in FTLD
- E.g., certain antipsychotics can make symptoms of dementia with Lewy bodies worse

Feldman et al. *Lancet Neurol* (2007)
Lu et al *Neurology* (2009)
McShane et al *Cochrane Rev* (2006)
Salloway et al *Neurology* (2004)



Panza et al (2019)

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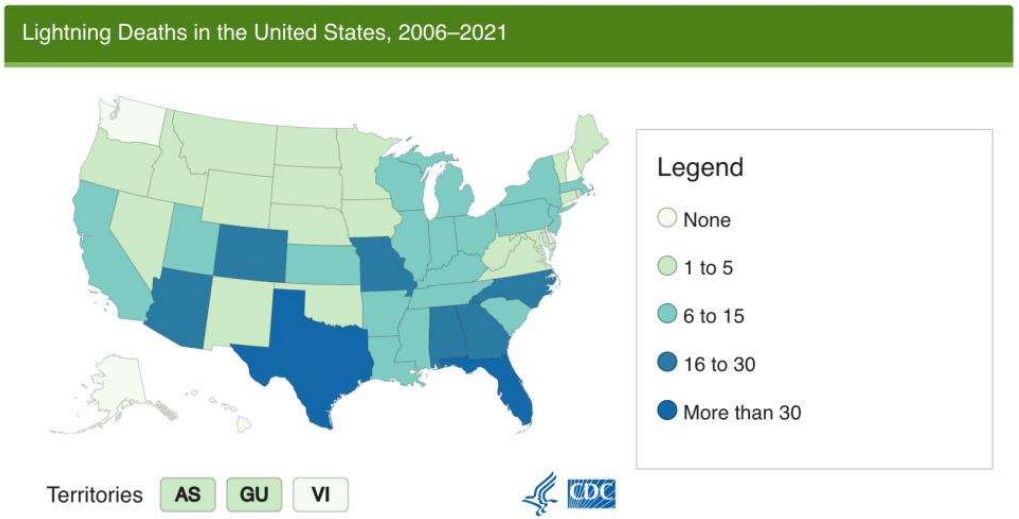

Table 3.4. Adverse Events

Harms		
Any Adverse Event, n/N (%)		
Serious Adverse Event, n/N (%)	126/898 (14.0%)	101/897 (11.3%)
Discontinuation Due to Adverse Event, n/N (%)	62/898 (6.9%)*	26/897 (2.9%)*
Any ARIA-H, n/N (%)	155/898 (17.3%)	81/897 (9.0%)
Any ARIA-E, n/N (%)	113/898 (12.6%)	15/897 (1.7%)
Symptomatic ARIA-E, n/N (%)	25/898 (2.8%)	0/897 (0%)

ARIA-E: amy… …es du… …l: amyloid-related imaging abnormalitie… …ial si… …n: number of participants *Per the pro… …scon… …: AE, lost to follow-up, subject choice, with… …udy t… …other.

https://icer.org/news-insights/press-releases/icer-publishes-final-evidence-report-on-lecanemab-for-alzheimers-disease/

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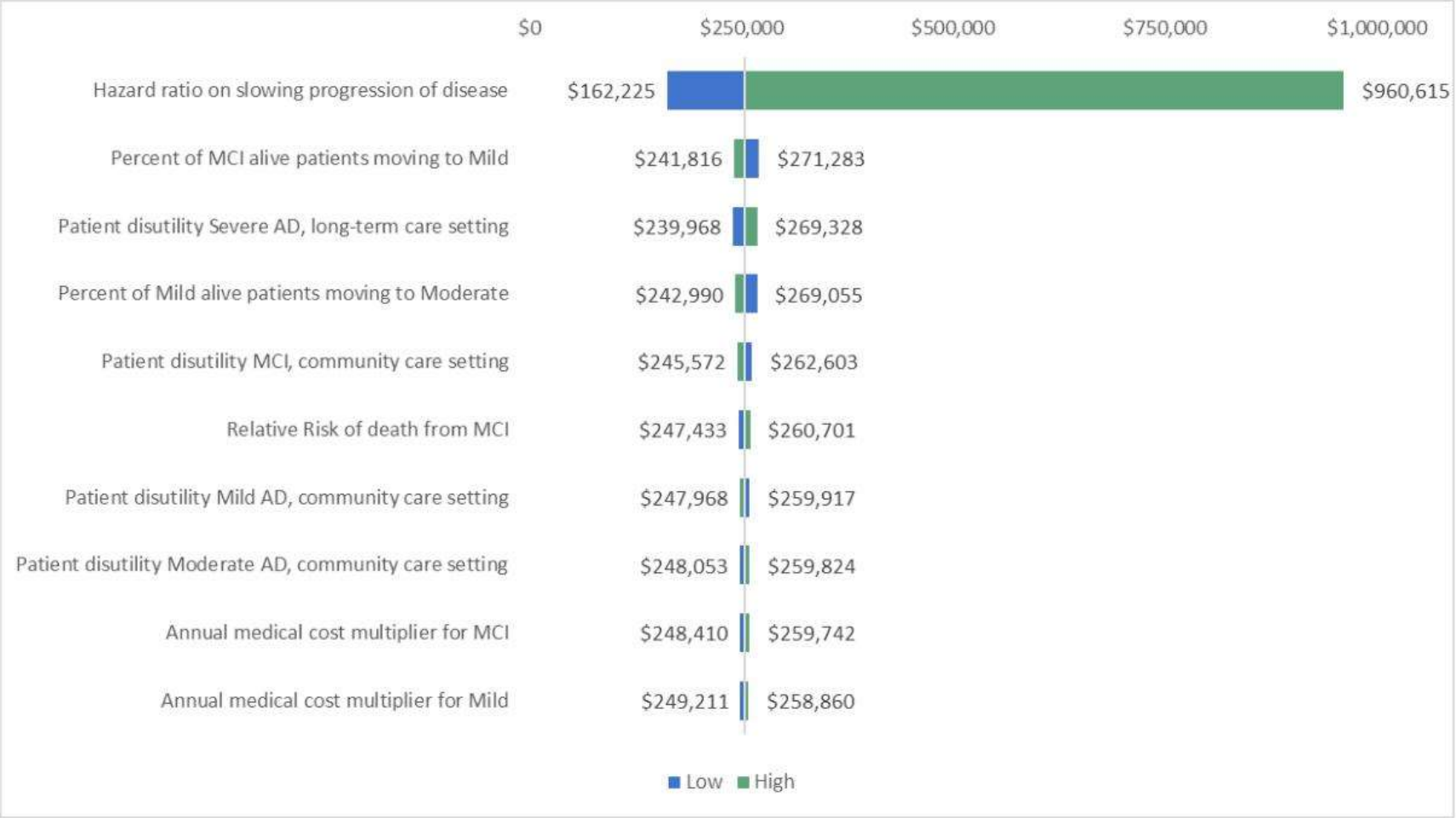
Figure 4.2. One-Way Sensitivity Analysis Results: Lecanemab versus Supportive Care Alone, Health Care Sector Perspective



AD: Alzheimer's disease, MCI: mild cognitive impairment

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Learning Objectives

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1. Compare the diagnosis and management of dementia from the PCP/geriatrics, psychiatry, and neurology
2. Describe utility of genetic testing, including APOE genotyping
3. Assess utility of available pharmacologic management of dementia, with a focus on monoclonal antibodies in Alzheimer's disease

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Thank you for your attention!

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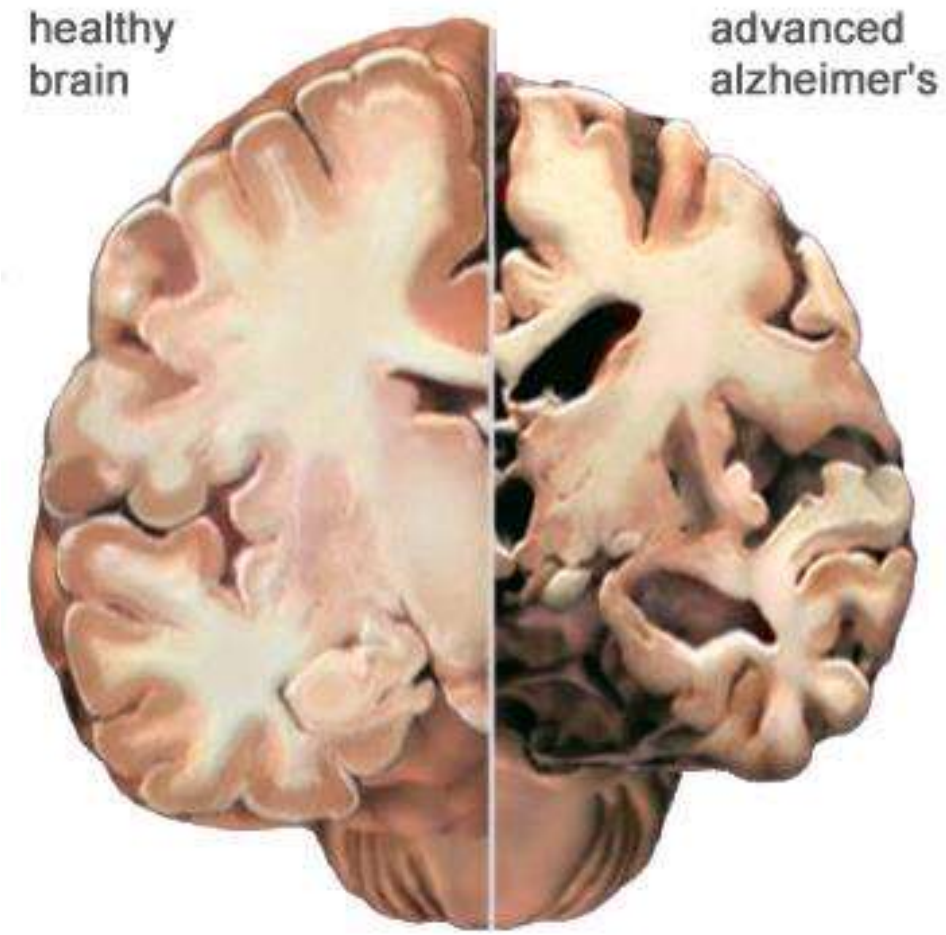
Questions?



https://www.alz.org/braintour/healthy_vs_alzheimers.asp