



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

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### Outline



- 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

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### Learning Objectives



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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## Disclosure



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

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What words come to mind  
when you think of dementia?



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## Mild Cognitive Impairment (Minor neurocognitive disorder)



1. Concern regarding a change in cognition
2. Impairment in  $\geq 1$  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)

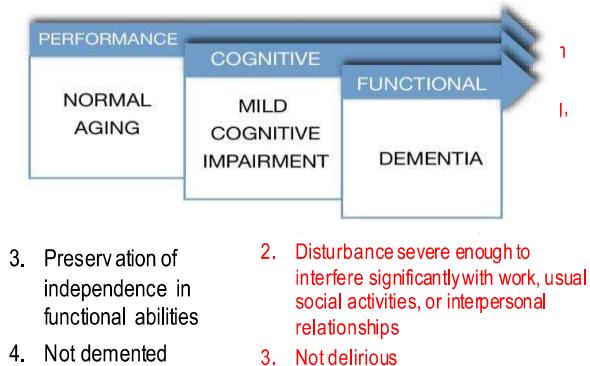
## Dementia (Major neurocognitive disorder)



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



## Diagnosing Dementia



- 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

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**The Mini-Mental State Exam**

**Montreal Cognitive Assessment (MoCA)**

**Instructions for Administration & Scoring**

**Step 1: Three Word Registration**

**Step 2: Clock Drawing**

**Step 3: Three Word Recall**

**Scoring**

**Memory**: Total score of words recalled (most repeat items). Draw a circle around the three words the person was able to recall correctly.

**Attention**: Total score of digits recited. If the person fails to repeat all digits, move on to Step 2 (clock drawing).

**Language**: Total score that takes into account both verbal and non-verbal communication.

**Abstraction**: Total score following a brief example.

**Delayed Recall**: Total score of words remembered after 30 minutes.

**Orientation**: Total score of months, date, and year.

**Word List Version**: \_\_\_\_\_ Person's Answers: \_\_\_\_\_

**www.mocatest.org**

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**Diagnostic Evaluation of Cognitive Impairment**

**Vanderbilt University**

**Laboratory serologies**

- E.g., CMP, CBC, TSH/T4, vitamin B12

**Brain imaging**

- CT head
- MRI brain

**Referral?**

- Specialty
- PT
- OT
- SLP

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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!

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# Primary progressive aphasia

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

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**Diagnostic Criteria for PPA**

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**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 visuospatial impairments
- 4 Prominent, initial behavioral disturbance

<sup>a</sup> Reprinted with permission from Gorno-Tempini ML, et al. Neurology. <sup>b</sup> © 2011 American Academy of Neurology. CONTINUUM: LIFELONG LEARNING IN 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



- Features**

- often **getting lost/disoriented**
- prominent **forgetting and repeating (amnestic)**
- Typically **anosognosic**



\*ADAM

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## PollEverywhere Question



- 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



- 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



\*ADAM

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## Logopenic PPA



### 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)

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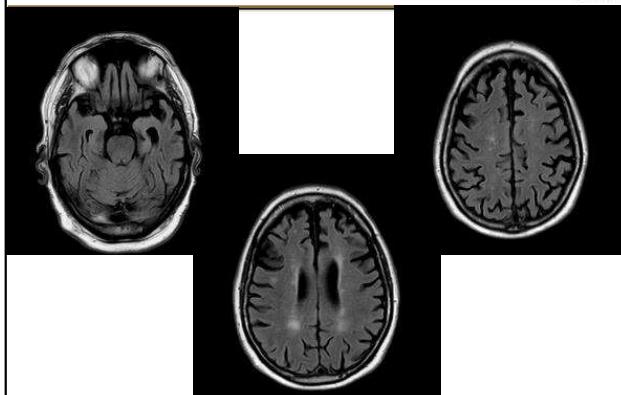
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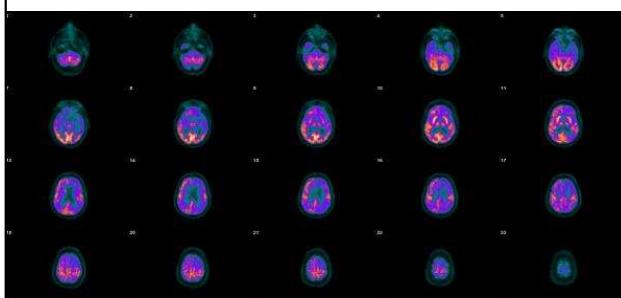
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FDG-PET brain



"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."

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FTLD



Frontotemporal lobar degeneration	Neurodegenerative disease process with “focal” symptoms of progressive language dysfunction or behavioral changes
Clinical Features	<p>1. Behavioral variant  <i>Personality change/alterations in social conduct (disinhibition)</i>  <i>Appetite</i>  <i>Abulia/apathy</i>  <i>Decline in hygiene</i>  <i>Language variants</i>          2. Semantic dementia          3. Progressive non-fluent aphasia</p>
Pathology	Tau ( <b>Pick bodies</b> )
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



- 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.

## PollEverywhere Question



- What variant(s) of primary progressive aphasia (PPA) is/are most often associated with FTLD as the underlying pathology?
    - A. Logopenic aphasia
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## FTLD Language Variants



### Non-fluent/Agrammatic PPA

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



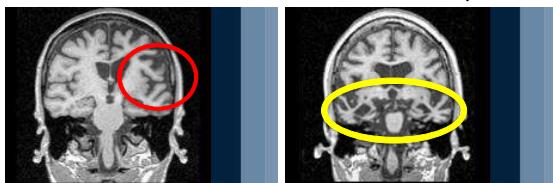
### Semantic PPA

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

## FTLD Language Variants



### Non-fluent/ Agrammatic Aphasia



### Semantic Aphasia

- Peri-Sylvian atrophy
- Anterior temporal lobe atrophy

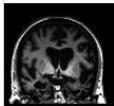
[UCSF http://memory.ucsf.edu/fld/overview/fldforms/multipleisd](http://memory.ucsf.edu/fld/overview/fldforms/multipleisd)

## FTLD

### Semantic

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

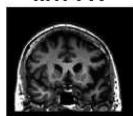
### svPPA



### Non-Fluent/ Agrammatic

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

### nfvPPA



### AD

- Logopenic**
- ↓spontaneous language production (“fewer words”)
  - Anomia
  - Impaired repetition
  - Comprehension relatively intact
  - Radiology: temporoparietal atrophy

### lvPPA



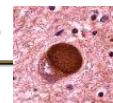
## PPA Clinical Features



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)



DLB	Dementia secondary to Lewy bodies (alpha-synuclein) with fluctuating cognition, hallucinations, and parkinsonism
Clinical Features: CORE	Dementia: Attention, dysexecutive, 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



Vascular dementia	<b>NINDS-AIREN criteria</b> <ul style="list-style-type: none"> <li>Onset or worsening of dementia is w/in 3 months s/p clinical stroke</li> <li>Imaging shows evidence of bilateral infarcts in cortical regions, basal ganglia, thalamus, or white matter           <ul style="list-style-type: none"> <li>Can also be secondary to accumulation of "silent" infarcts</li> <li>Focal deficits on neurological exam</li> </ul> </li> </ul>
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)	
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, <b>magnetic gait</b>
Diagnostic work-up	CT or MRI brain <b>Lumbar puncture</b> (NORMAL opening pressure) with <b>high volume tap</b> (>30 cc) → yields symptomatic improvement CSF typically without abnormalities
Imaging	<b>Ventriculomegaly</b>
Treatment	<b>Ventriculoperitoneal shunt</b>

Diagnosing Dementia: inpatient?
<ul style="list-style-type: none"> <li>• Need to rule out alternative causes</li> <li>• Can't diagnose when somebody is delirious           <ul style="list-style-type: none"> <li>– Outpatient &gt; inpatient</li> </ul> </li> </ul>

Learning Objectives
<ol style="list-style-type: none"> <li>1. Compare the diagnosis and management of dementia from the PCP/geriatrics, psychiatry, and neurology</li> <li>2. <b>Describe utility of genetic testing, including APOE genotyping</b></li> <li>3. Assess utility of available pharmacologic management of dementia, with a focus on monoclonal antibodies in Alzheimer's disease</li> </ol>

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## Genetics



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

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## Genetics: Alzheimer's disease



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

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## Genetics: Frontotemporal lobar degeneration



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

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## Learning Objectives



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## Pharmacologic Therapies



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

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## Pharmacologic Therapies



Drug category	Drug names	AD	FTLD	DLB	PSP/CBS	PDD	VD
Cholinesterase inhibitors	Donepezil, Rivastigmine Galantamine	✓ ✓ ✓	X X ?	✓ ✓ ✓	X X X	✓ ✓ ✓	✓ ✓ ✓
NMDA r. ant.	Memantine	✓	X	✓	X	?	✓
Antidepressants	SSRIs, SNRIs	✓	✓	✓	✓	✓	✓
Anxiolytics	Buspirone, SNRIs	✓; avoid benzodiazepines in general					
Hypnotics, RT-Mild sed	Melatonin, Zolpidem, Mirtazapine, suvorexant Clonazepam	✓ ✓ ✓ X	✓ ✓ ✓ X	✓ ✓ ✓ ✓			
Antipsychotics	Pimavanserin, Quetiapine, Clozapine risperidone	✓, with caution	Dependence dose?/✓	Dependence dose?/✓	Dependence dose?/✓	Dependence dose?/✓	✓, with caution
Parkinsonism	Cabergole/Levodopa Dopamine agonists Amantadine			✓ X ?	✓ X ✓	✓ ✓ ✓	
Dystonia	Baclofen Clonazepam <del>Tetrazepam</del> Botulinum toxin			✓ ✓ ✓			

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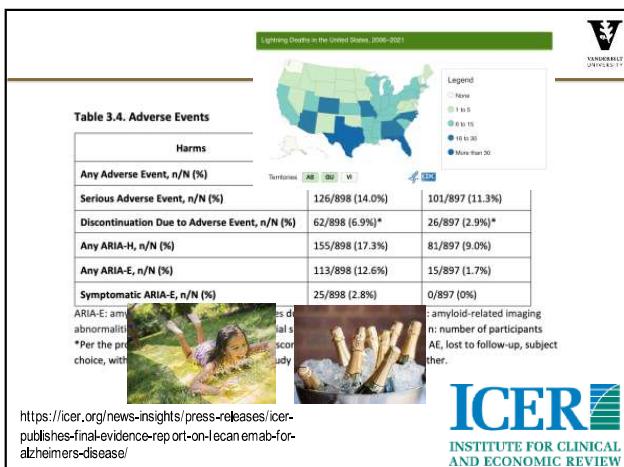
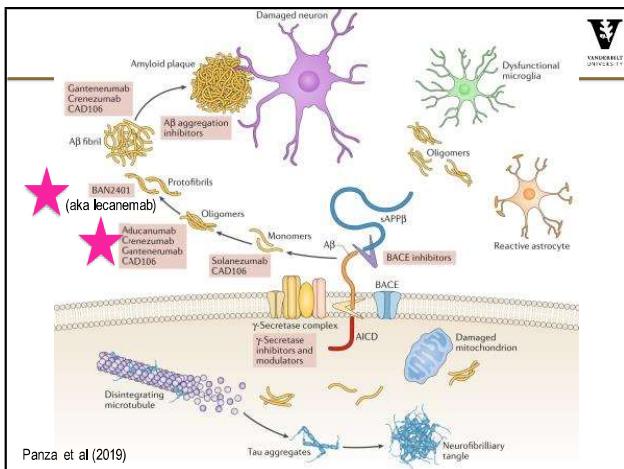
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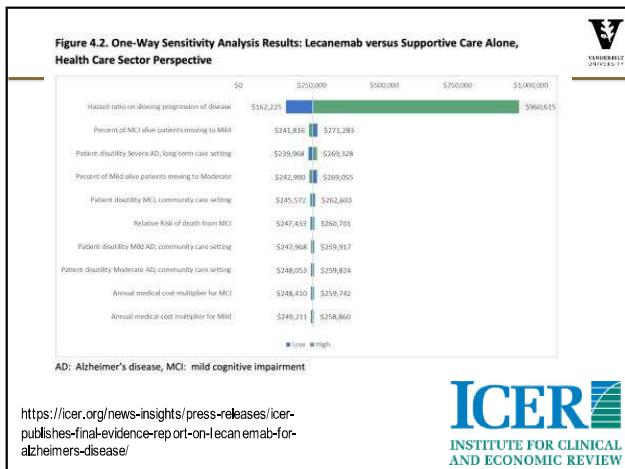
## Dementia Treatment



- 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)





## Learning Objectives

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## References

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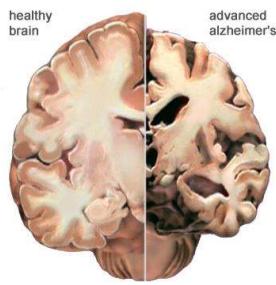


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Thank you for your attention!



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