

# **Update in Dementia and Alzheimer's Disease**

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- Dementia and Behavioral Neuroscience Fellowship at UCLA
- Professor of Neurology at HMS
- Director of Clinical Trials, Center for Alzheimer Research and Treatment at BWH
  - Clinical focus: Alzheimer's disease and related dementias
  - Research focus: AD clinical trials, multi-modal imaging, neuropsychiatric symptoms, and instrumental activities of daily living

# Disclosures

- Research salary support for serving as site principal investigator for trials sponsored by:
  - Eisai Inc. and Eli Lilly and Company
- Consultant for Ono Pharma USA, Inc.

# Objectives

- Discuss the current recommended diagnostic assessments of Alzheimer's disease (cognitive, imaging, and fluid markers)
- Discuss management of Alzheimer's disease (Components of management, FDA-approved treatments, lifestyle modifications, supplements)

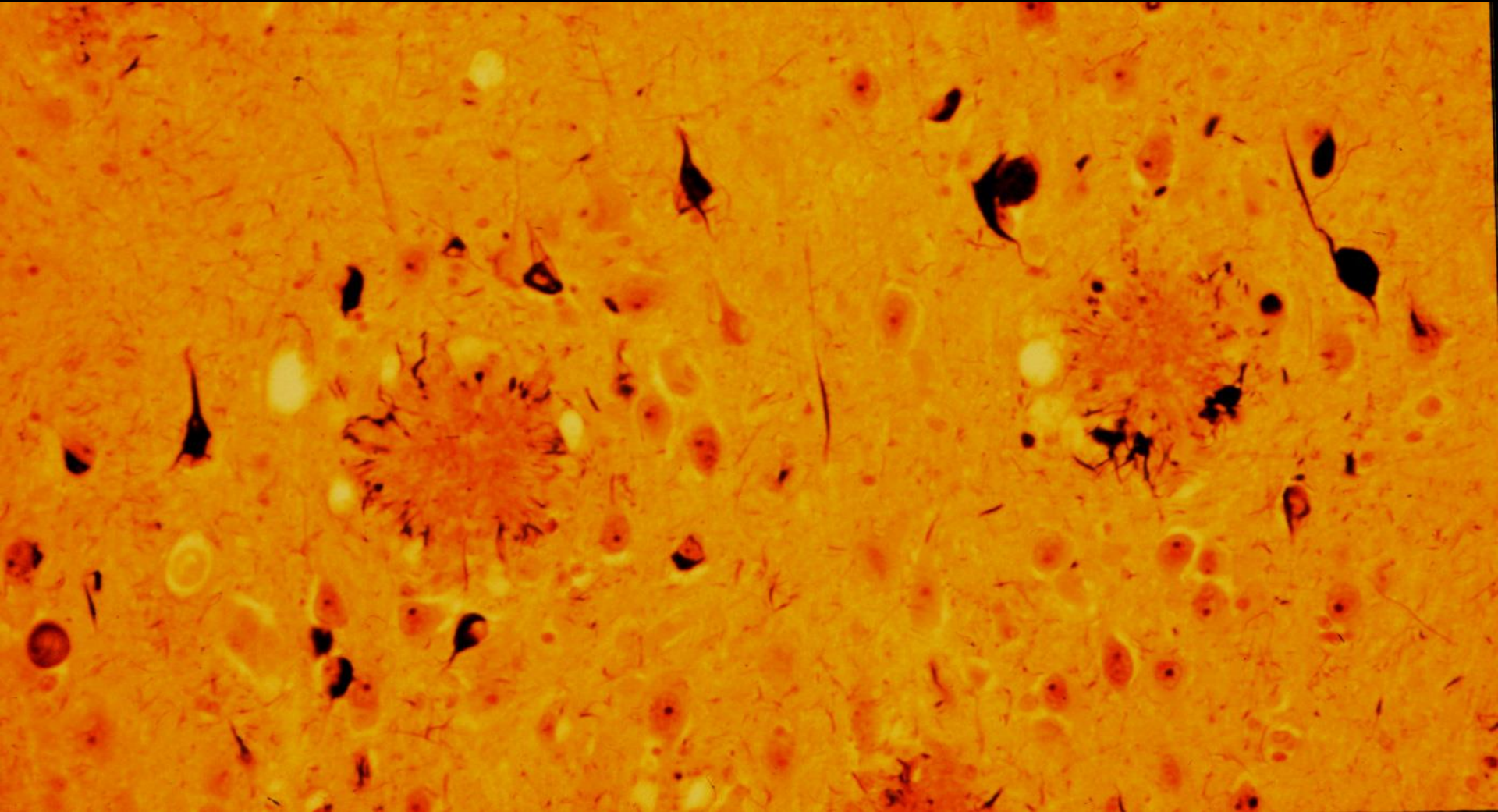
# Dementia Diagnostic Criteria

- Dementia is a chronic progressive syndrome consisting of cognitive, behavioral, and functional dysfunction
- Symptoms interfere with daily functioning
- Represents a decline from previous abilities
- Not explained by delirium or primary psychiatric condition
- Cognitive impairment is assessed by history (patient/caregiver) and exam (“bedside” or neuropsychological testing)
- Cognitive or behavioral impairment of 2 or more domains: memory, attention/executive function, visuospatial function, language, behavior

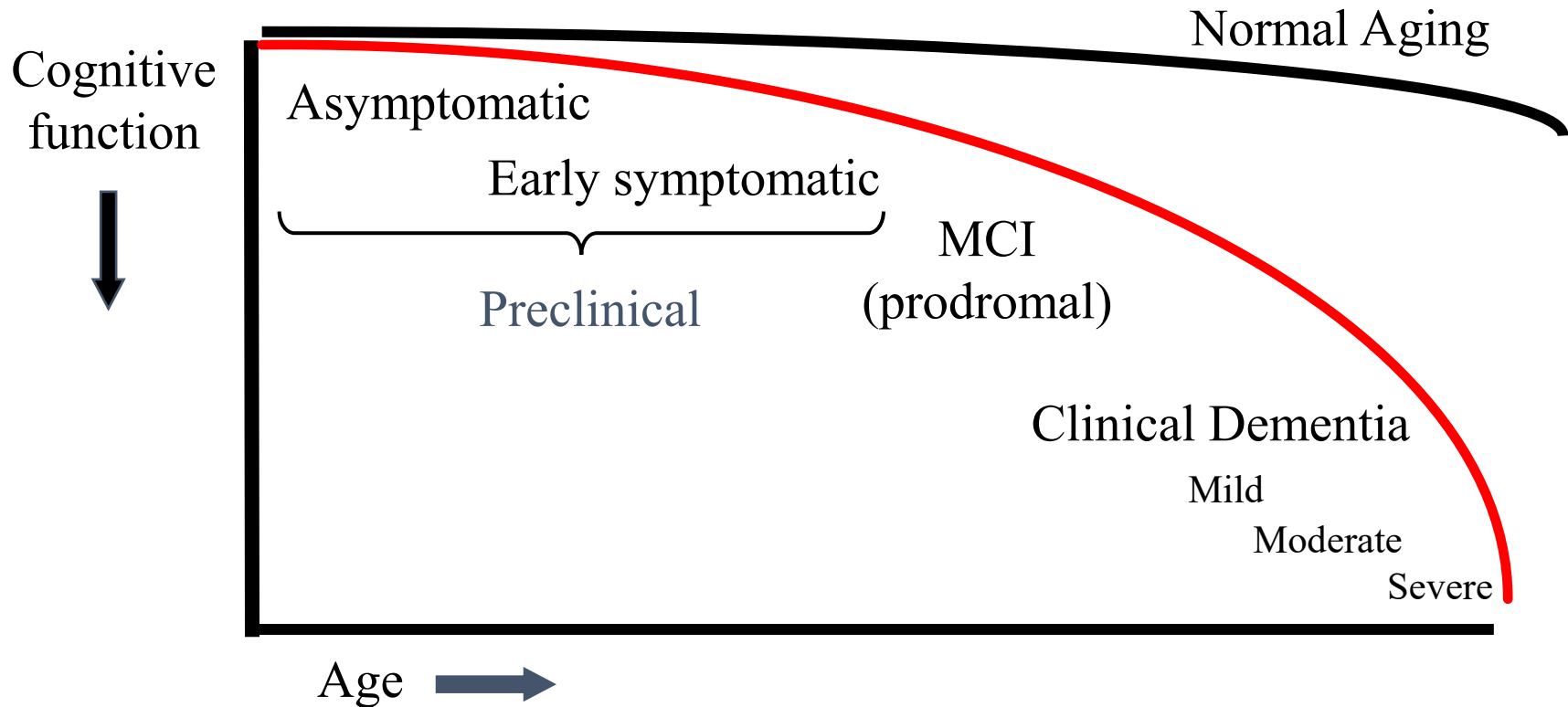
# Alzheimer's Disease

- Most common cause of dementia
- Typical onset in early 70's
- Progressive neurodegenerative disease
  - Insidious clinical progression over years
  - Typically begins with impaired short-term memory, sense of direction, and praxis
  - Eventually affects general cognition, behavior, and daily functioning
- Over 7 million people in U.S. carry a diagnosis of AD dementia (Alzheimer's Association 2025)
  - Will approach 14 million by 2060
  - Prevalence doubles every 5 years
  - Cost estimates: > \$350 billion/year
  - 1.5x more prevalent in Hispanics, 2x in African Americans

# Alzheimer's Disease Pathology



# Alzheimer's Disease Trajectory



# Case Study—Joe: Initial Evaluation

- PCP: Annual visit
- Joe is a 66-year-old man who is seen alone
- Retired special-education teacher and later information technology specialist
- Reported decline in recent memory
- No relevant past medical history or family history
- Cognitive screening
  - Mini-Cog: 3/5 (-2 recall)
  - AD8: 3
- Referred to specialist

### 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.<sup>1-3</sup> 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: \_\_\_\_\_

### Scoring

|                                   |  |
|-----------------------------------|--|
| Word Recall: _____ (0-3 points)   | 1 point for each word spontaneously recalled without cueing.   |
| Clock Draw: _____ (0 or 2 points) | Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored.<br>Inability or refusal to draw a clock (abnormal) = 0 points.                         |
| Total Score: _____ (0-5 points)   | Total score = Word Recall score + Clock Draw score.<br><br>A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status. |

# AD8 Dementia Screening Interview

Patient ID#: \_\_\_\_\_

CS ID#: \_\_\_\_\_

Date: \_\_\_\_\_

| Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems. | YES,<br>A change | NO,<br>No change | N/A,<br>Don't know |
|--|------------------|------------------|--------------------|
| 1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)                                   |                  |                  |                    |
| 2. Less interest in hobbies/activities   |                  |                  |                    |
| 3. Repeats the same things over and over (questions, stories, or statements)   |                  |                  |                    |
| 4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)                                   |                  |                  |                    |
| 5. Forgets correct month or year   |                  |                  |                    |
| 6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)                                      |                  |                  |                    |
| 7. Trouble remembering appointments  |                  |                  |                    |
| 8. Daily problems with thinking and/or memory  |                  |                  |                    |
| <b>TOTAL AD8 SCORE</b>   |                  |                  |                    |

Score  $\geq 2$  cut-off for cognitive impairment

# Case Study: Specialist History

- Neurologist evaluation
- 66-year-old right-handed man with 18 years of education, seen with wife
- 2-year history of gradual onset and progression of decline in recent memory
  - Repeating himself
  - Forgetting details of recent events
  - Forgetting his schedule for the day
  - Misplacing items
  - Mild difficulties with learning new information
- Remote memory remains intact

# Case Study: Specialist History

- Mild difficulties with sense of direction in unfamiliar environments
- Mild word-finding difficulties without paraphasic errors
- Mild difficulties with calculations
- Difficulties making connections and integrating ideas
- Mild difficulties with organization and planning, especially when multiple steps are involved
- Issues with working memory

# Case Study: Specialist History

- Recent mild situational anxiety and depressive symptoms when he thinks about his cognitive deficits
- 6-7 years of insomnia (taking diphenhydramine)
- Instrumental activities of daily living are mildly impaired
  - Not as efficient in completing tasks
  - Difficulties preparing meals due to difficulties keeping track of multiple steps
  - Mild difficulties calculating tips
  - Mild difficulties shopping even when he uses a list
- Still very intellectually active—runs a men's group, takes piano lessons, reads books
- Exercises 3/week and has a healthy diet


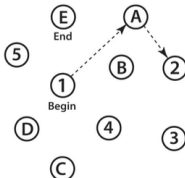



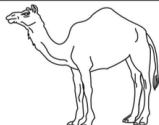
# Case Study: Specialist Exam

- General physical exam and neurological exam unremarkable
- Cognitive exam:
  - MoCA 22/30
  - -1 Trails, -1 copy of cube, -1 clock (incorrect hand placement), -1 serial 7's, -3 delayed recall (+1 with multiple choice cues), -1 orientation
- Diagnosis: Mild cognitive impairment, amnesic, multiple domain

# Screening Cognitive Assessments

- Variety of cognitive assessments typically used in primary care or specialist settings

| MoCA     | Montreal Cognitive Assessment                            |
|----------|--|
| MMSE     | Mini-Mental State Examination                            |
| AMTS     | Abbreviated Mental Test Score                            |
| MSQ      | Mental Status Questionnaire                              |
| SPMSQ    | Short Portable Mental Status Questionnaire               |
| 6CIT     | Six-item Cognitive Impairment Test                       |
| GPCOG    | General Practitioner Assessment of Cognition             |
| AD8      | Eight-item Interview to Differentiate Aging and Dementia |
| Mini-Cog | Three-item Recall Test and Clock Drawing Test            |

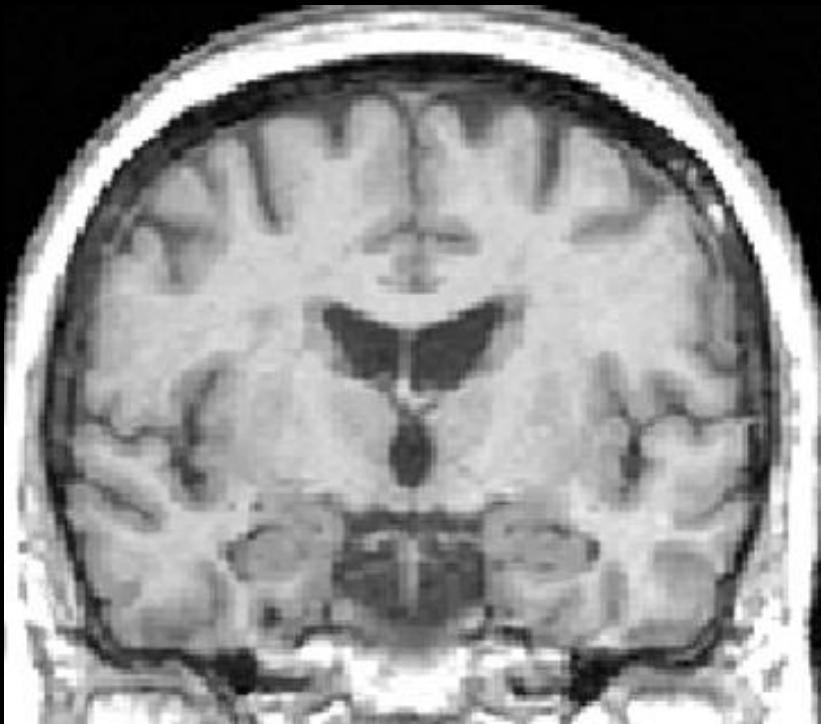
| <b>MONTREAL COGNITIVE ASSESSMENT (MOCA)</b><br><b>Version 7.1 Original Version</b>  |      |        |        |       |     |                               |  |  |  | <b>NAME:</b><br><b>Education:</b><br><b>Sex:</b>   | <b>Date of birth:</b><br><b>DATE:</b> |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
|---|------|--------|--------|-------|-----|-------------------------------|--|--|--|--|---------------------------------------|--------|--------|-------|-----|--|---------------------------------|-----|-----|-----|-----|-----|-------------------------------|--------------|--|--|--|--|--|---------------------|--|--|--|--|--|-------|--|
| <b>VISUOSPATIAL / EXECUTIVE</b>   |      |        |        |       |     |                               |  |  |  | <div style="display: flex; align-items: center;"> <div style="flex: 1;">  </div> <div style="flex: 1; padding-left: 10px;"> <b>Copy cube</b> </div> <div style="flex: 1; padding-left: 10px;"> <b>Draw CLOCK</b> (Ten past eleven)<br/>(3 points)           </div> </div> |                                       | POINTS |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  </div> <div style="text-align: center;">  </div> </div>   |      |        |        |       |     |                               |  |  |  |  | ___/5                                 |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>NAMING</b>   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <div style="display: flex; justify-content: space-around; align-items: center;">    </div>   |      |        |        |       |     |                               |  |  |  |  | ___/3                                 |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>MEMORY</b>   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful.<br>Do a recall after 4 minutes.   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;"></th> <th style="width: 15%;">FACE</th> <th style="width: 15%;">VELVET</th> <th style="width: 15%;">CHURCH</th> <th style="width: 15%;">DAISY</th> <th style="width: 15%;">RED</th> <th style="width: 20%;"></th> </tr> </thead> <tbody> <tr> <td>1st trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td rowspan="2" style="text-align: center; vertical-align: middle;">No points</td> </tr> <tr> <td>2nd trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>   |      |        |        |       |     |                               |  |  |  |  | FACE                                  | VELVET | CHURCH | DAISY | RED |  | 1st trial                       |     |     |     |     |     | No points                     | 2nd trial    |  |  |  |  |  |                     |  |  |  |  |  |       |  |
|   | FACE | VELVET | CHURCH | DAISY | RED |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| 1st trial   |      |        |        |       |     | No points                     |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| 2nd trial   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>ATTENTION</b>  |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Read list of digits (1 digit/ sec.).  |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Subject has to repeat them in the forward order [ ] 2 1 8 5 4<br>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<br>[ ] F B C A M N A A J 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<br>4 or 5 correct subtractions: <b>3 pts.</b> 2 or 3 correct: <b>2 pts.</b> 1 correct: <b>1 pt.</b> 0 correct: <b>0 pt.</b>   |      |        |        |       |     |                               |  |  |  | ___/3  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>LANGUAGE</b>   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Repeat: I only know that John is the one to help today. [ ]<br>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  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>ABSTRACTION</b>  |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler   |      |        |        |       |     |                               |  |  |  | ___/2  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>DELATED RECALL</b>   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
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|   | FACE | VELVET | CHURCH | DAISY | RED |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Has to recall words WITH NO CUE   | [ ]  | [ ]    | [ ]    | [ ]   | [ ] | Points for UNCUED recall only |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Category cue  |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| Multiple choice cue   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>Optional</b>   |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>ORIENTATION</b>  |      |        |        |       |     |                               |  |  |  |  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City  |      |        |        |       |     |                               |  |  |  | ___/6  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| © Z.Nasreddine MD<br>Administered by: _____   |      |        |        |       |     |                               |  |  |  | ___/30   |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
| <b>www.mocatest.org</b>   |      |        |        |       |     |                               |  |  |  | Normal ≥ 26 / 30<br>TOTAL  |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |
|   |      |        |        |       |     |                               |  |  |  | Add 1 point if ≤ 12 yr edu   |                                       |        |        |       |     |  |                                 |     |     |     |     |     |                               |              |  |  |  |  |  |                     |  |  |  |  |  |       |  |

Ghadiri-Sani et al. *Clin Pract.* 2014; Janssen et al. *BMC Fam Pract.* 2017; Smith et al. *Can J Psychiatry* 2007

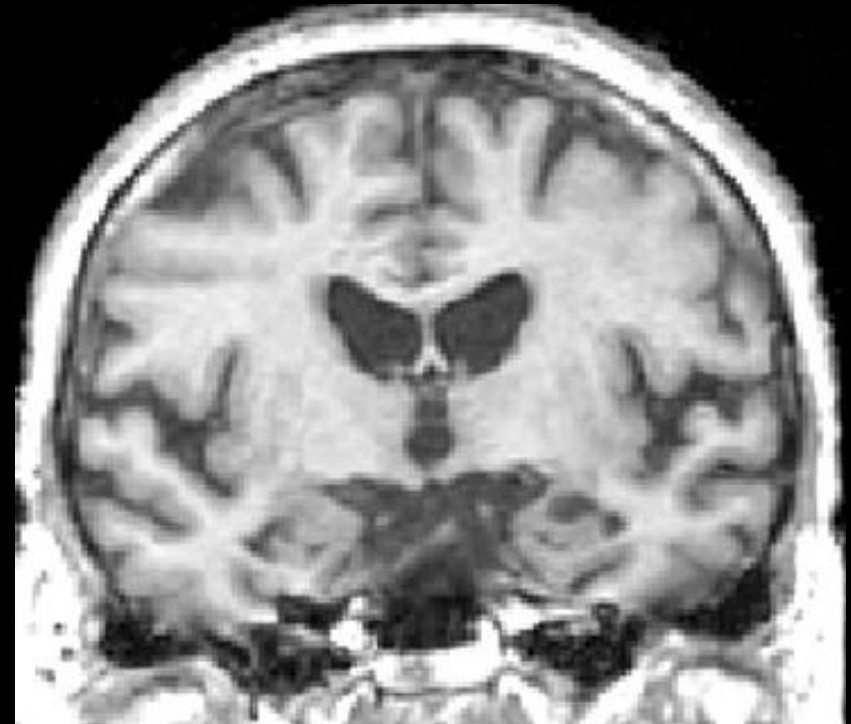
# Case Study: Specialist Diagnostic Assessments

- Laboratory assessment for reversible causes of cognitive impairment: Normal vitamin B12, TSH (lipids, CBC, electrolytes)
- MRI of the brain: Mild-moderate bilateral parietal atrophy, minimal bilateral frontal atrophy, mild bilateral hippocampal atrophy, and mild-moderate small vessel ischemic disease. No strokes, hemorrhages, or masses

# Structural Magnetic Resonance Imaging (MRI) in AD: Atrophy

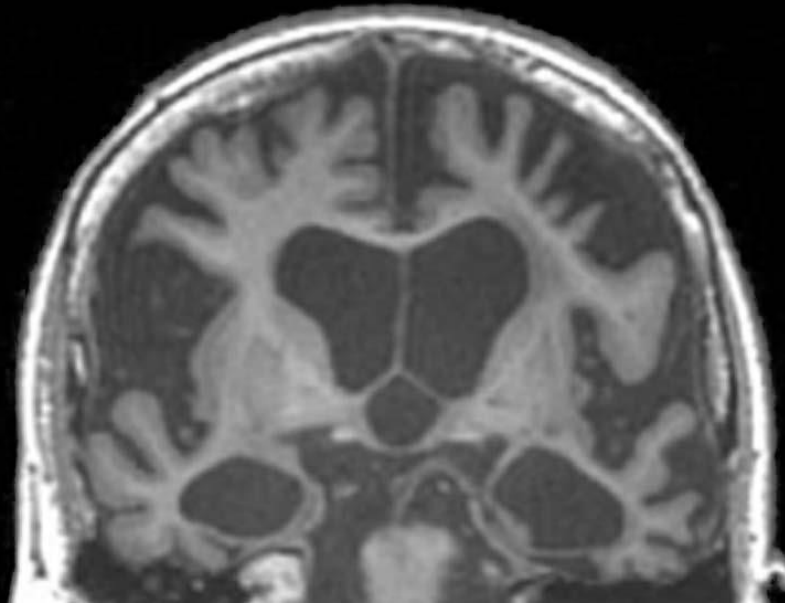


Normal older individual  
(age = 77)



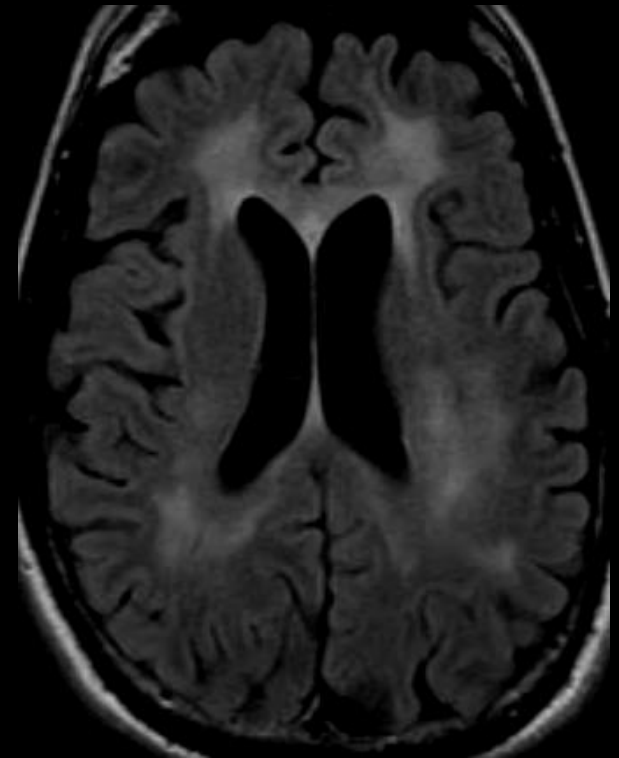
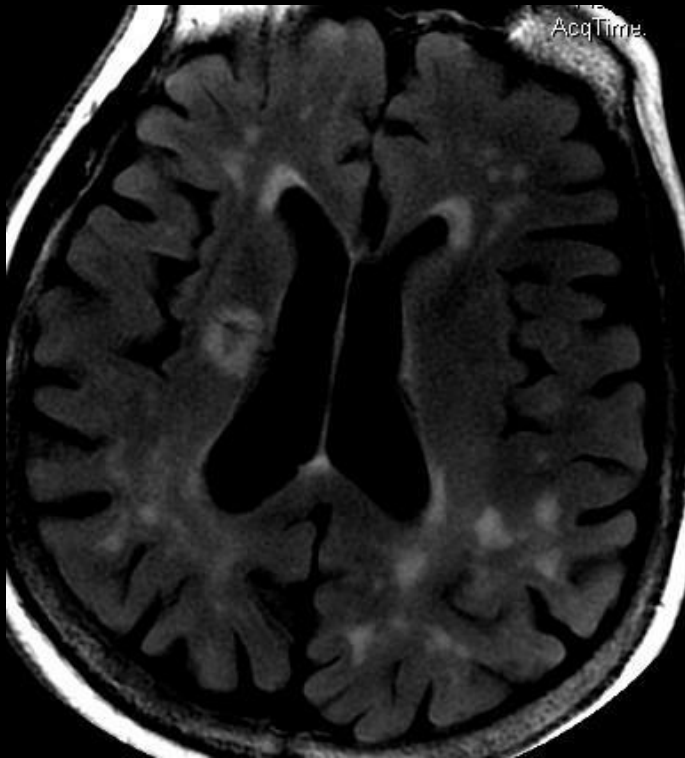
Patient with mild AD dementia  
(age = 77)

# Structural MRI in AD: Atrophy



Patient with severe AD dementia  
(age = 86)

# Structural MRI: Cerebrovascular disease



# Case Study: Additional Diagnostic Assessments

- Neuropsychological testing:
  - Premorbid intelligence in the superior range
  - MMSE 26/30, Blessed Dementia Scale 3, CDR global 0.5, sum of boxes 2.5
  - Attention average to impaired
  - Executive function average to impaired (average to impaired working memory, average phonemic verbal fluency, impaired semantic verbal fluency, impaired divided attention, average abstract reasoning, and impaired visual planning)
  - Non-contextual verbal memory impaired for encoding and retrieval and low average to impaired for storage
  - Naming average
  - Visuospatial function average to impaired
  - Questionnaires of mood: no significant depression or anxiety
- Underlying pathology: Likely a combination of Alzheimer's disease and cerebrovascular disease

# Assessing Global Functioning and ADL

- Clinical Dementia Rating (CDR)
  - Interview caregiver and patient
  - 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care
- Weintraub ADL
  - Interview caregiver
  - 7 domains: self-care activities, household care, employment and recreation, shopping and money, travel, communication, social responsibilities
- Lawton and Brody scale, Functional Activities Questionnaire (FAQ)
  - Interview caregiver to assess IADL

Morris *Neurology* 1993; Weintraub *J Am Geriatr Soc* 2004; Lawton et al. *Gerontologist*. 1969; Pfeffer et al. *J Gerontol*. 1982

# Assessing Mood and Neuropsychiatric Symptoms

- Depression
  - Patient Health Questionnaire 9 (PHQ-9)
  - Geriatric Depression Scale (GDS)
- Anxiety
  - Geriatric Anxiety Inventory (GAI)
  - Generalized Anxiety Disorder 7 (GAD-7)
- Multiple neuropsychiatric symptoms
  - Neuropsychiatric Inventory Questionnaire (NPI-Q)
  - Mild Behavioral Impairment Checklist (MBI-C)

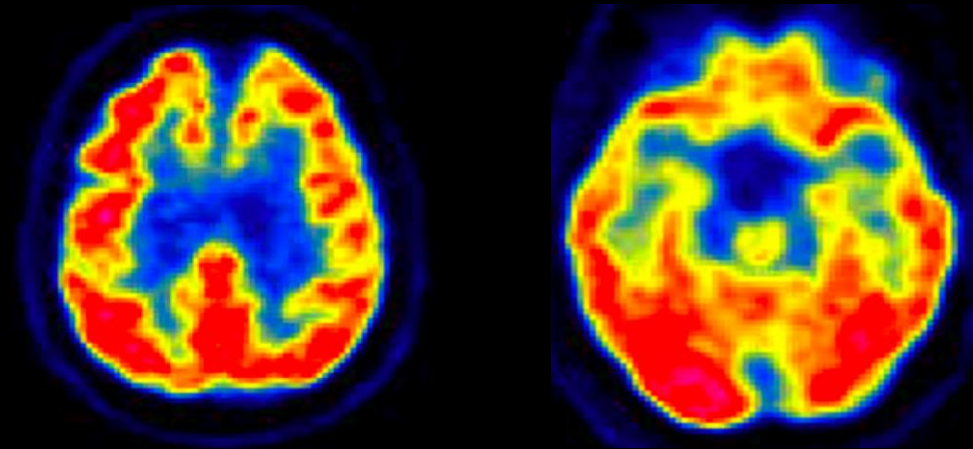
Kroenke et al. *J Gen Intern Med* 2001; Yesavage et al. *J Psychiatr Res* 1982; Pachana et al. *Int Psychogeriatr* 2007; Spitzer et al. *Arch Intern Med* 2006; Kaufer et al. *J Neuropsychiatry Clin Neurosci* 2000; Ismail *J Alzheimers Dis* 2017

# Case Study: Additional Diagnostic Assessments

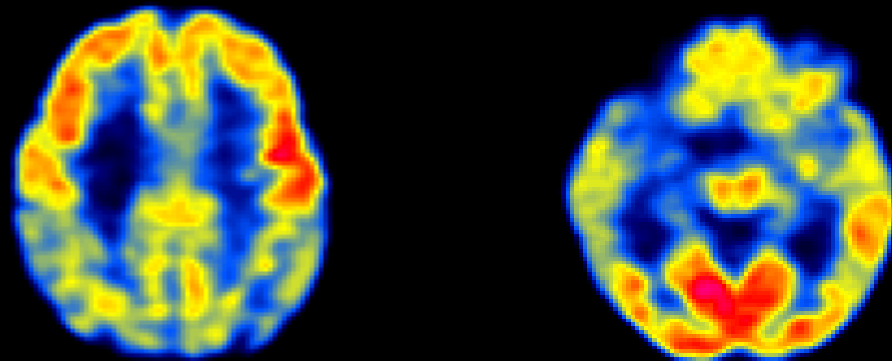
- Considered obtaining FDG PET
  - Declined by patient and wife
- Considered performing lumbar puncture or obtaining amyloid PET
  - Florbetapir PET: elevated amyloid across 4 cortical regions with a centiloid value of 75
  - Consistent with underlying Alzheimer's disease pathology

# **$^{18}\text{F}$ -Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in AD**

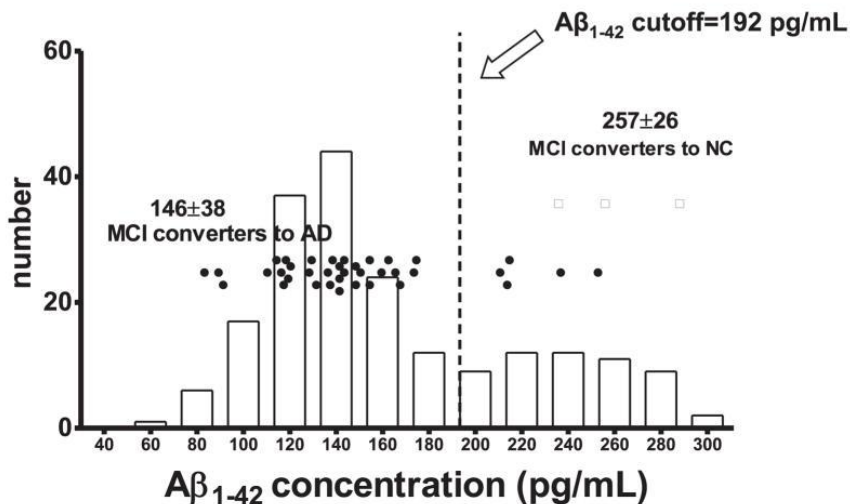
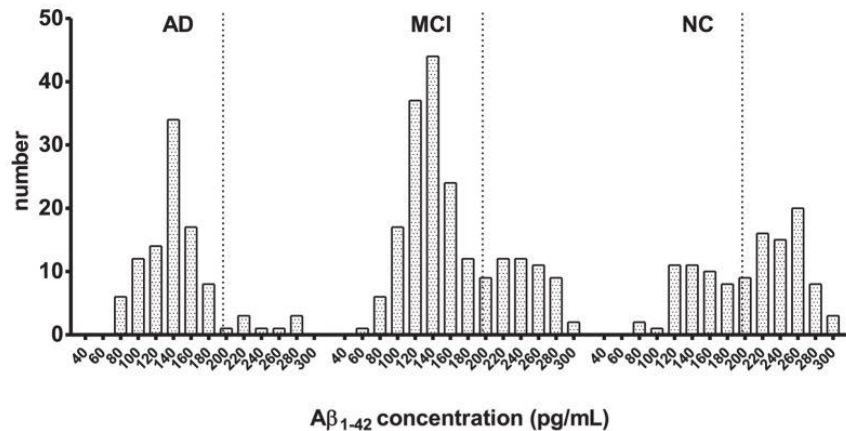
Normal older  
individual



AD dementia



# CSF Biomarker Signature of AD

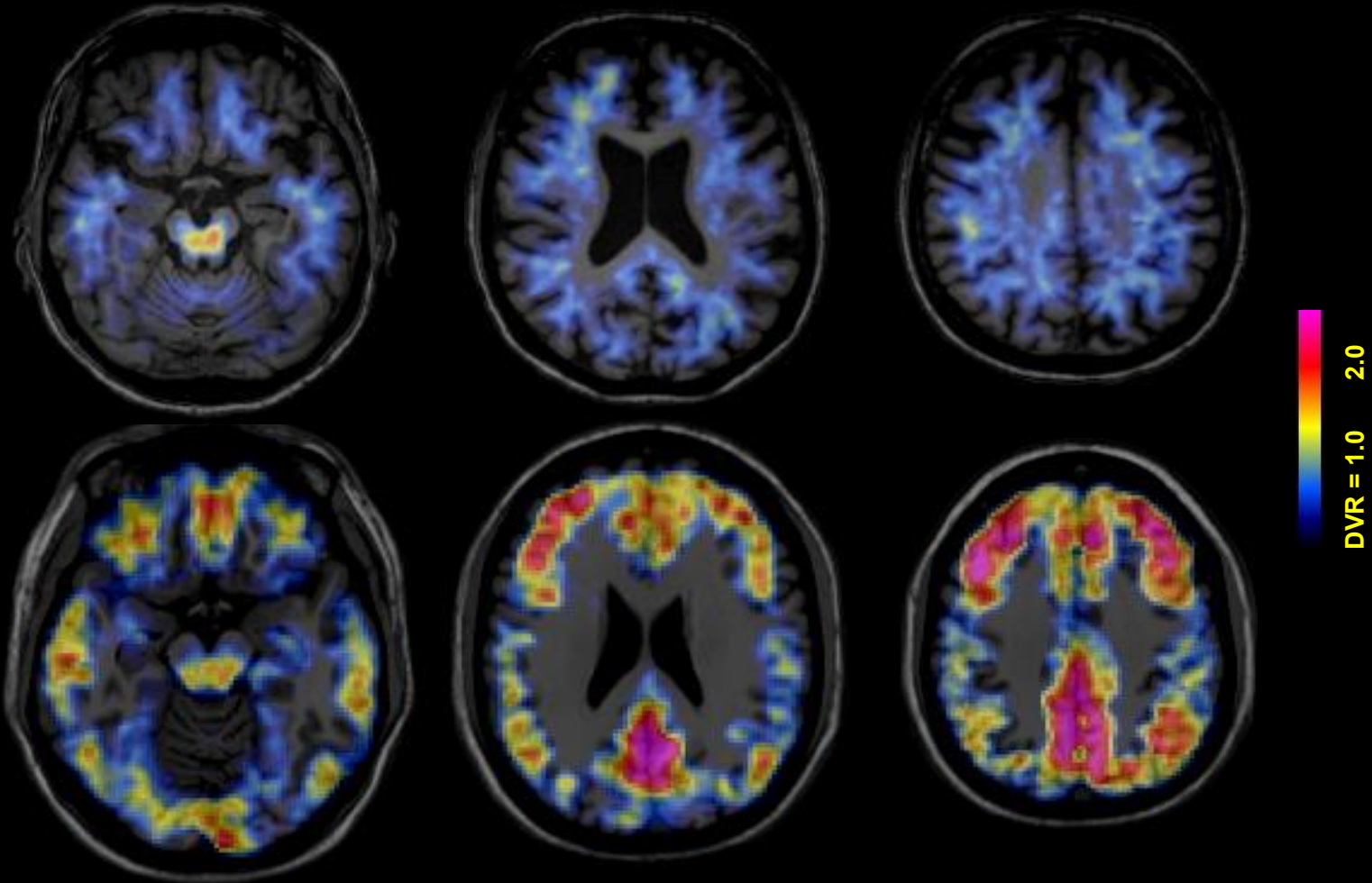


- $A\beta_{1-42} < 192$  pg/ml  
(sensitivity 96%, specificity 77%)
- Total tau > 93 pg/ml  
(sensitivity 70%, specificity 92%)
- Phospho-tau > 23 pg/ml  
(sensitivity 68%, specificity 73%)
- Total tau /  $A\beta_{1-42} > 0.39$   
(sensitivity 86%, specificity 85%)
- Phospho-tau /  $A\beta_{1-42} > 0.10$   
(sensitivity 91%, specificity 71%)
- CSF  $A\beta_{1-42} / A\beta_{1-40}$  FDA approved May 2022
  - Covered by Medicare and private insurance

# Amyloid Imaging

## $^{11}\text{C}$ PiB-PET (Pittsburgh compound B)

Normal older  
individual

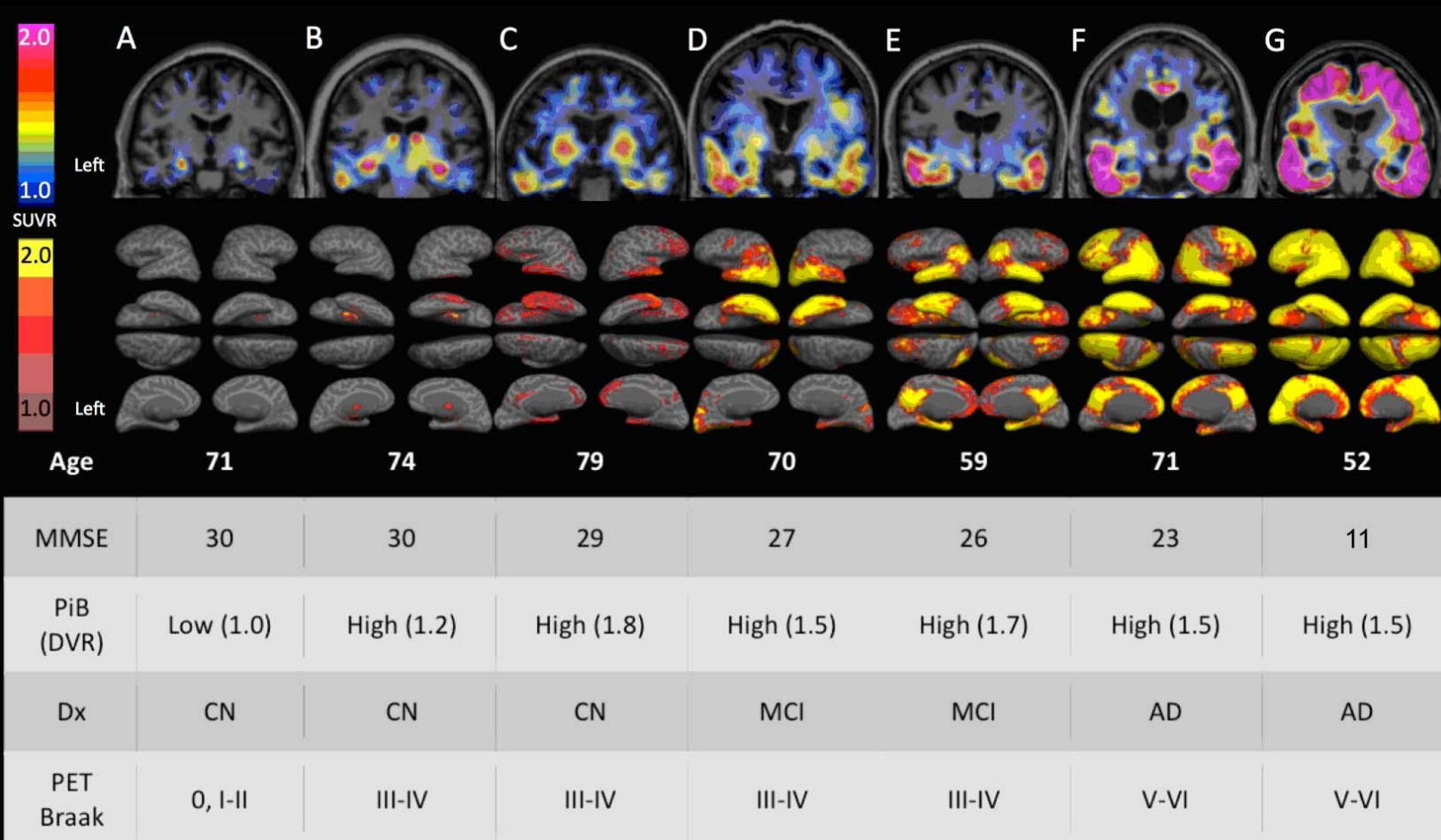


AD dementia

# Amyloid imaging: F-18 agents

- Longer half-life than PiB (~2 hrs vs. 20 min)
  - More practical for clinical use
- Florbetapir (Amyvid™,  $^{18}\text{F}$ -AV-45)
  - Widely used in clinical trials
  - Approved by FDA for detecting amyloid *in vivo* in symptomatic patients in April, 2012
  - Visual rating training for radiologists available
- Flutemetamol (Vizamyl™,  $^{18}\text{F}$ -GE067)
  - Approved by FDA October, 2013
- Florbetaben (Neuroceq™,  $^{18}\text{F}$ -BAY94-9172)
  - Approved by FDA March, 2014
- IDEAS (Imaging Dementia—Evidence for Amyloid Scanning) (Rabinovici 2019)
  - Improved diagnostic accuracy, management
  - Covered by Medicare as of October 2023

# Flortaucipir PET Tau imaging



- Flortaucipir (Tauvid™) approved by FDA May 2020;  
not covered by Medicare

Johnson et al. *Ann Neurol* 2016

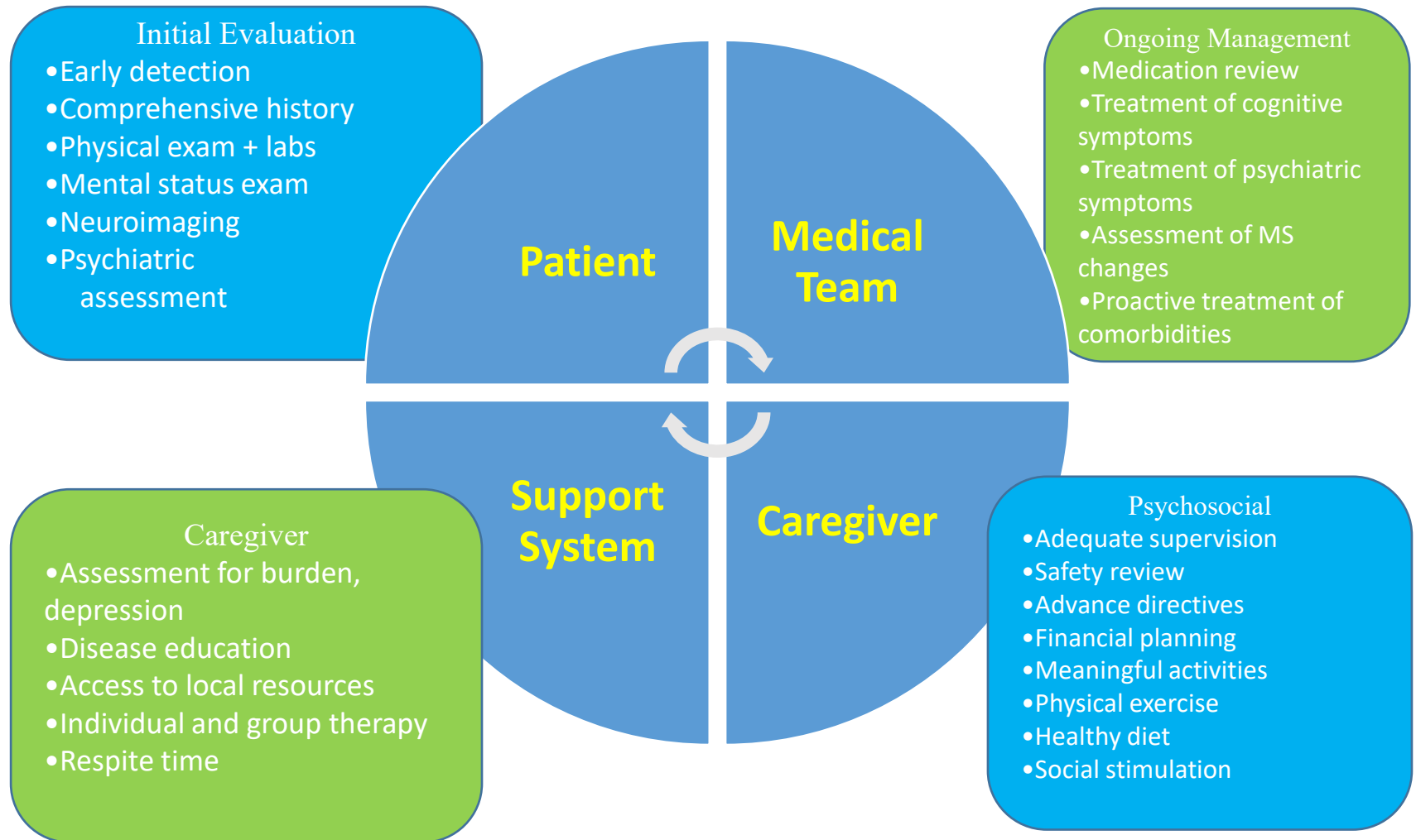
# Dementia Diagnostic Assessments: Summary

- “Bedside” assessment
  - Brief: Mini-Cog, AD8
  - Intermediate: MoCA, MMSE, SLUMS, Blessed
  - Long: ACE, CERAD, CDR
  - Physical exam: Parkinsonism, localizing features, motor neuron disease features
- Neuropsychological testing
- Fluid: CSF (routine,  $A\beta_{1-42}$ , tau, 14-3-3), plasma (p-tau217,  $A\beta_{42/40}$ ), blood (B12, TSH, CBC, electrolytes, LFTs), urinalysis
- Brain imaging
  - Brain Structure: MRI (CT)
  - Brain Function: FDG-PET (SPECT)
  - Molecular imaging of pathology: Amyloid and tau PET imaging
- Genetic testing (family history suggestive of autosomal dominant inheritance: PS1, PS2, APP)
- EEG, EMG/NCS

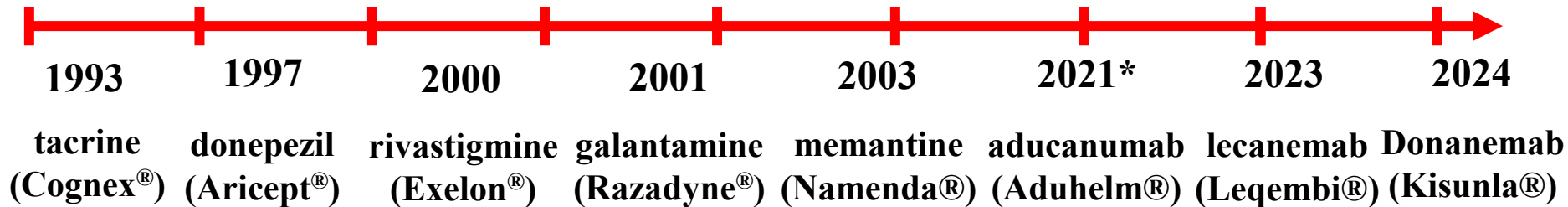
# Case Study: Management

- Recommended discontinuing diphenhydramine
- Discussed medication options
  - Patient and wife elected to hold off on a cholinesterase inhibitor
  - Considered lecanemab or donanemab, which received traditional/full approval by the FDA for MCI and mild AD dementia in 2023 and 2024
- Recommended aggressive control of vascular risk factors
- Recommended designating healthcare proxy and durable power of attorney
- Counseled about observational research studies and clinical trials
  - Patient and wife expressed interest

# Multiple Components of Dementia Management



# FDA Approved Medications for Alzheimer's Disease



- **Cholinesterase-inhibitors (ChE-I's):** donepezil, rivastigmine, galantamine, tacrine (no longer clinically used)
  - All FDA approved for treatment of mild to moderate AD dementia
  - Donepezil also FDA approved for treatment of severe AD dementia (2006)
  - Galantamine available as a generic since 2009; donepezil, rivastigmine since 2010
- **NMDA (glutamate) receptor antagonist:** memantine
  - FDA approved for treatment of moderate to severe AD dementia (generic 2015)

\* Accelerated approval (not traditional/full approval); withdrawn from market 2024

# AD Dementia Medications: Symptomatic Benefit

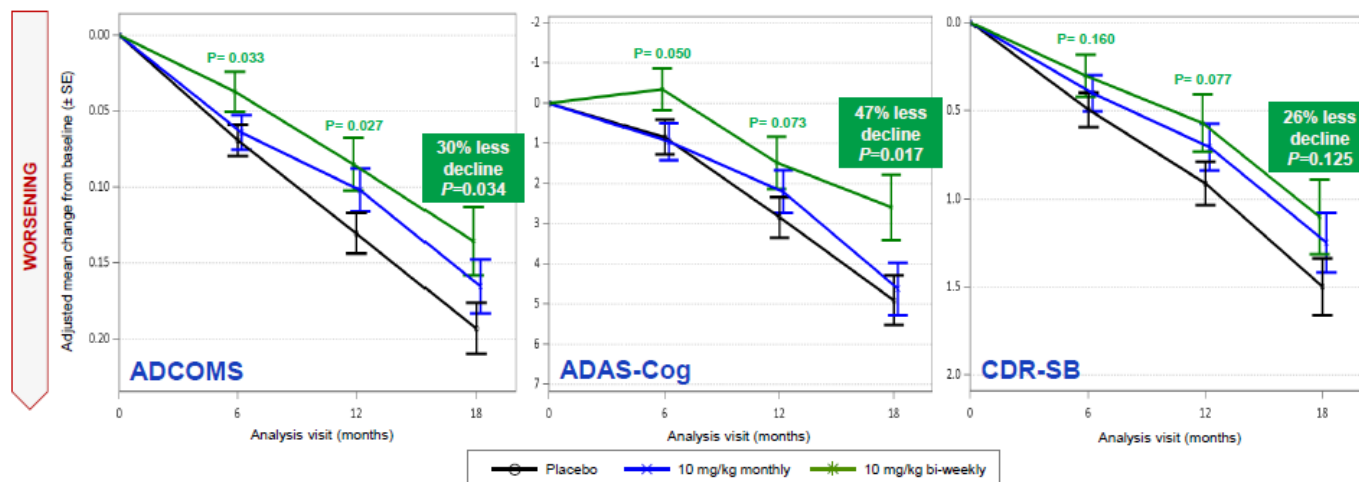
- ChE-I's and Memantine: shown in multiple randomized, double-blind, placebo-controlled trials of AD dementia to provide *modest* but *clinically significant* improvements for *groups* of participants
  - Daily functioning, cognition, neuropsychiatric symptoms, caregiver burden (and potentially saving money)
- Individual results vary
  - Highly variable effects across time between and *within* individuals

# Treatment of other dementias

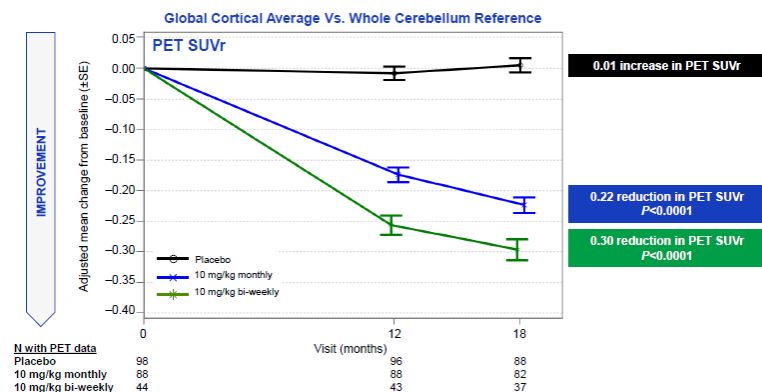
- Rivastigmine FDA approved for treatment of Parkinson's disease with dementia (PDD) since 2007
  - Off-label use of all ChE-I's for PDD and dementia with Lewy bodies (DLB)
- There is no FDA approved drug for treatment of vascular dementia (VaD)
  - ChE-I's are used off label for VaD or mixed AD/VaD dementia based on a positive donepezil trial (Roman 2005) and a positive and a partially positive galantamine trial (Erkinjuntti 2002, Auchus 2007)
- There is no FDA approved drug for frontotemporal dementia (FTD)

# Lecanemab (BAN2401) phase 2b

Anti-amyloid monoclonal antibody, MCI / mild AD dementia



| N with data        | 0 mo. | 6 mo. | 12 mo. | 18 mo. |
|--------------------|-------|-------|--------|--------|
| Placebo            | 238   | 216   | 187    | 160    |
| 10 mg/kg monthly   | 246   | 208   | 165    | 146    |
| 10 mg/kg bi-weekly | 152   | 130   | 93     | 79     |

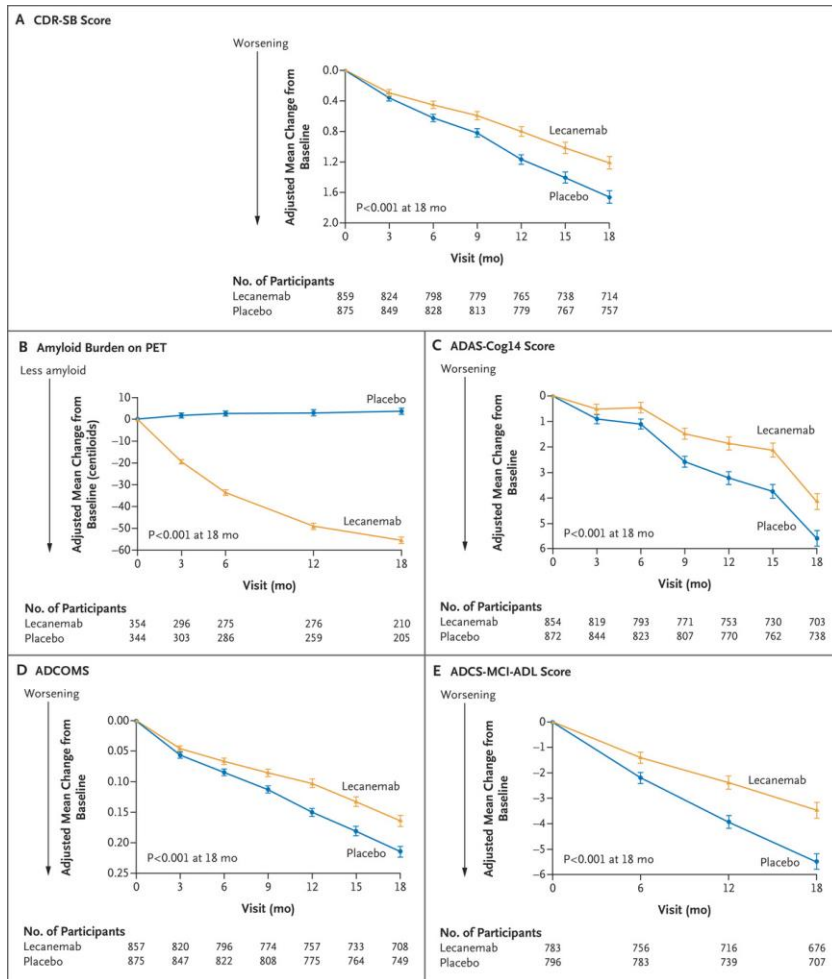


\* FDA granted accelerated approval based on phase 2b on 1/6/23

# Clarity AD: Lecanemab Phase 3 Trial

- MCI or mild AD dementia
- 1795 participants recruited across 245 sites
- MMSE 22-30
- CDR global 0.5-1
- Impaired memory (age-adjusted score on Logical Memory delayed recall)
- Positive biomarker for amyloid: amyloid PET or t-tau/A $\beta$  CSF
- MRI exclusions: >4 microhemorrhages; single macrohemorrhage ( $\geq 1$  cm); area of superficial siderosis
- Allowed anticoagulation (about 5% of participants)
- Lecanemab vs. placebo 1:1, 18-month treatment
- Infusions of 10 mg/kg every 2 weeks

# Clarity AD: Main Results

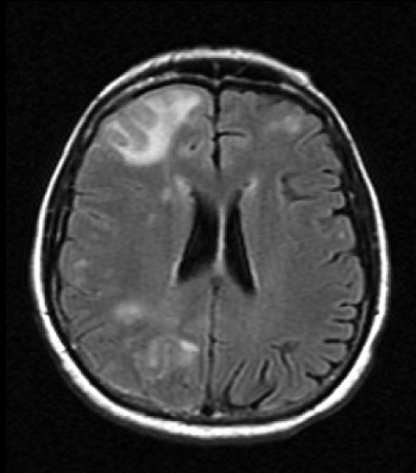


## Adverse Events:

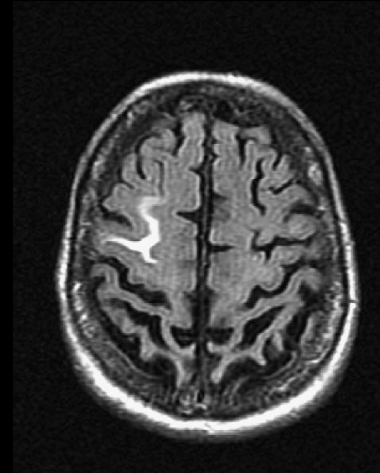
- Infusion reaction in 26.4% on Lecanemab vs. 7.4% on placebo
- ARIA-E in 12.6% on Lecanemab (higher in ApoE  $\epsilon$ 4 carriers) vs. 1.7% on placebo
- ARIA-H (mostly microhemorrhages) in 17.3% on Lecanemab vs. 9.0 on placebo (isolated ARIA-H without ARIA-E 8.9% on Lecanemab vs. 7.8% on placebo)
- Macrohemorrhages in 0.6% on Lecanemab vs. 0.1% on placebo (when anticoagulated 2.4% vs. 0%)
- Higher ARIA rate in APOE4 carriers
- FDA granted full/traditional approval on 7/6/23

# Amyloid-Related Imaging Abnormalities (ARIA)

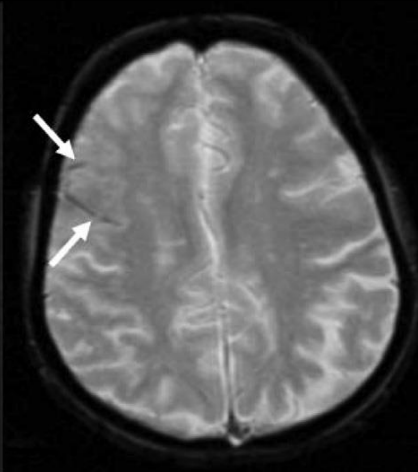
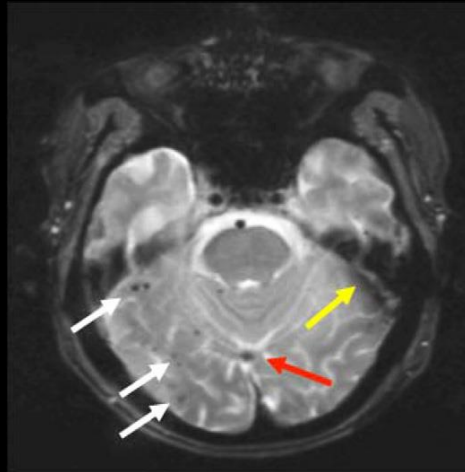
**Vasogenic Edema**



**Sulcal Effusion**



**Microhemorrhages and Superficial Siderosis**



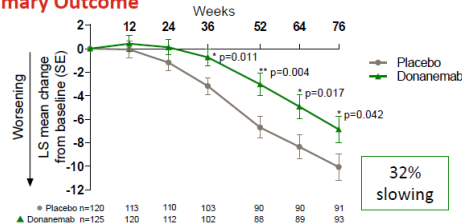
# Societal Impact of lecanemab (Leqembi)

- The first disease modifying therapy for AD to receive FDA full/traditional approval
- Cost (drug only): \$26,500/year
- Medicare is covering the drug in the clinical setting (80%)
  - Requires a registry with minimal dataset but not participation in a clinical trial
- Arguably, our healthcare system is not ready to cope with the challenges and demands of a drug like lecanemab
  - Equitable access
  - Determination of amyloid status for eligibility
  - APOE testing for risk stratification
  - Infusions every 2 weeks
  - Multiple MRI scans to monitor for ARIA
  - Specialists to determine eligibility, administer drug, and monitor for adverse events

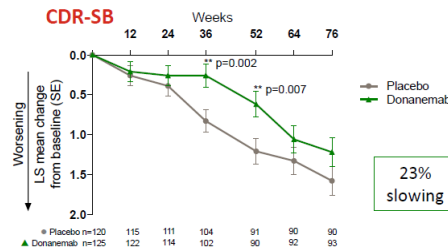
# Trailblazer (Donanemab) Phase 2 Trial Results: Clinical Outcomes

Anti-amyloid monoclonal antibody, MCI / mild AD dementia

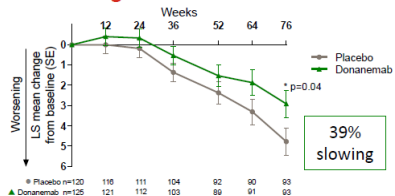
iADRS – Primary Outcome



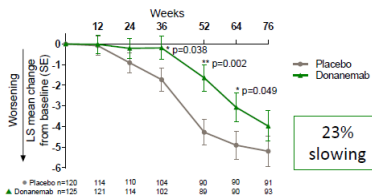
CDR-SB



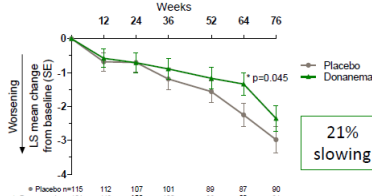
ADAS-Cog13



ADCS-iADL

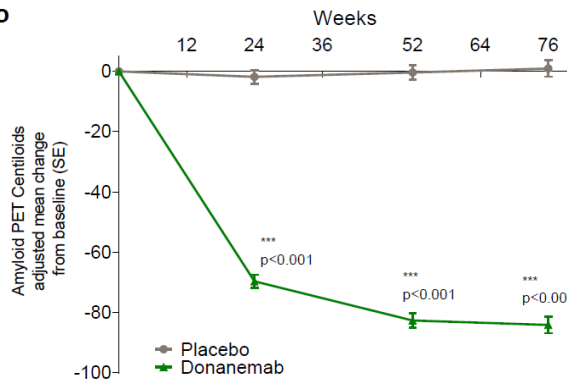


MMSE



\* Inclusion of participants based on both elevated amyloid and intermediate tau

Treatment with donanemab reduced amyloid plaque by 85 Centiloids at 76 weeks compared with placebo



LS Mean Change  $\Delta$  (SE)  
Donanemab vs.  
Placebo

|     |               |
|-----|---------------|
| W24 | -67.83 (3.16) |
| W52 | -82.30 (3.41) |
| W76 | -85.06 (3.87) |

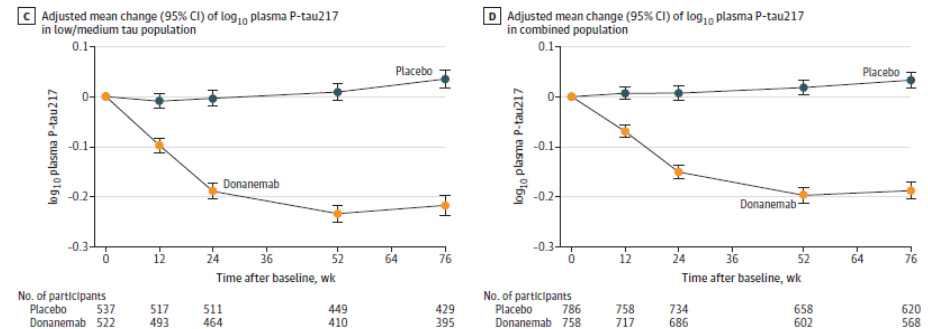
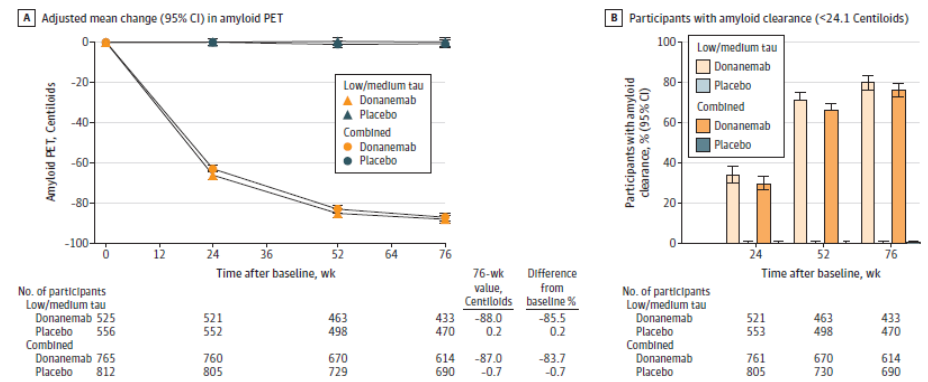
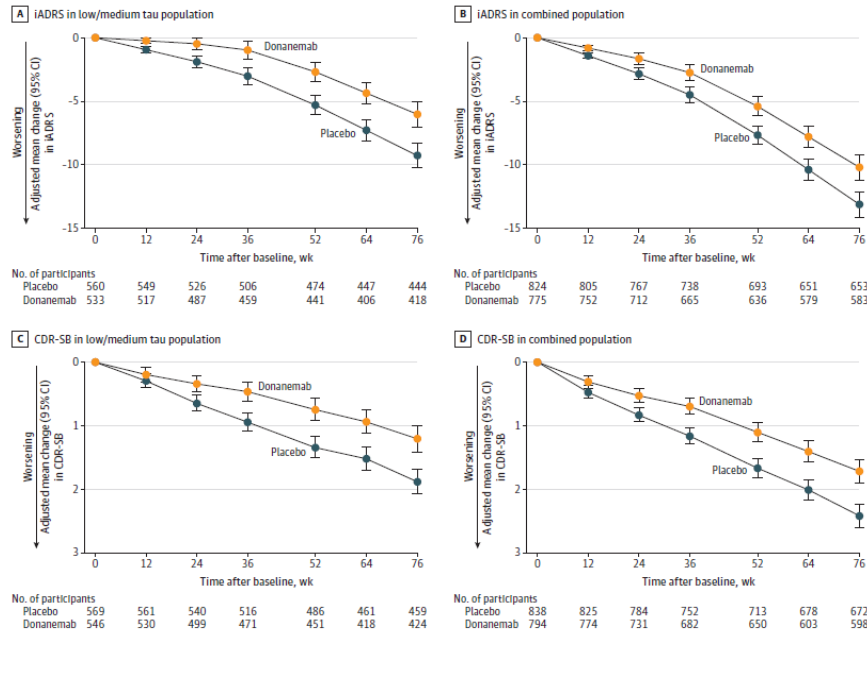
40% of donanemab-treated participants reached amyloid negative levels by 24 weeks

|  |          |          |          |
|--|----------|----------|----------|
| Placebo n=112                                | 111      | 91       | 91       |
| Donanemab n=121                              | 115      | 92       | 90       |
| Donanemab 'amyloid negative' <24.1 CL, n (%) | 46 (40%) | 55 (60%) | 61 (68%) |

# Trailblazer-ALZ 2 (Donanemab) Phase 3 Trial Results

- MCI / mild AD dementia, elevated amyloid (primary analyses in participants with low/medium tau, n=1182)
- Completed April 2023, results reported 5/3/23
- Significant slowing of clinical decline over 18 months
  - 35% slowing on iADRS
  - 37% CDR-SB, 40% ADCS-IADL, 32% ADAS-Cog 13
- Results were attenuated but still significant when including participants with high (combined) tau (n=1736)
- 34% amyloid negative by 6 months, 80% by 18 months
- Adverse events:
  - ARIA-E 24% (symptomatic in 6.1%, serious in 1.6%)
  - ARIA-H (mostly microhemorrhages or superficial siderosis) 31.4% on drug vs. 13.6% on placebo (isolated ARIA-H without ARIA-E 12.7% on drug vs. 12.4% on placebo)
  - Macrohemorrhages in 0.4% on Donanemab vs. 0.2% on placebo
  - Infusion reactions in 8.7% (most mild-moderate) on drug vs. 0.5 on placebo

# Trailblazer-ALZ 2: Clinical and Biomarker Outcomes



\* FDA granted full/traditional approval on 7/2/24

- Trailblazer-ALZ 6 (Wang 2025): modified titration reduced ARIA-E rate from 24% to 14%

# Lifestyle Modifications

- Mediterranean diet (Scarmeas 2006, Féart 2009)
  - High in vegetables, legumes, fruits, nuts, cereals, fish, olive oil
  - Low in saturated fats
  - Reduces risk of developing AD dementia and slows cognitive decline
- Physical exercise (Larson 2006, Scarmeas 2009)
  - Aerobic exercise 3 or more times per week or vigorous exercise 1 hour per week reduces risk of progressing from MCI to AD dementia
- Cognitive training (ACTIVE, Ball 2002, Willis 2006, Rebok 2014)
  - Reduced decline in reasoning, processing speed, IADL

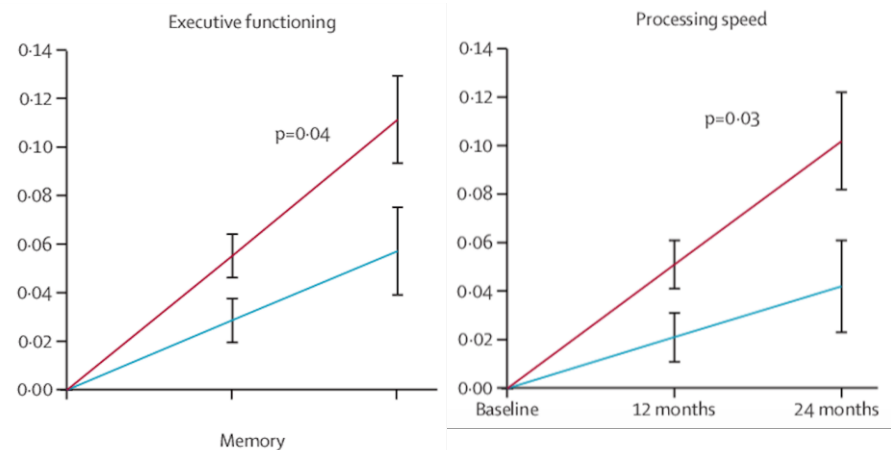
# Lifestyle Modifications: Hypertension Treatment

- SPRINT MIND trial (Williamson 2019)
- RCT in cognitively normal older adults (age 68)
  - Intensive control: SBP <120 (n=4,278)
  - Standard control: SBP <140 (n=4,285)
  - Median intervention period: 3.3 years
  - Median f/u period: 5.1 years
- Primary Outcome: progression to dementia
  - HR 0.83 (95% CI, 0.67-1.04)
- Secondary Outcome: progression to MCI
  - HR 0.81 (95% CI, 0.69-0.95)

# Lifestyle Modifications: Multi-domain

- Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER study) (Ngandu 2015)
  - 2-year multidomain lifestyle intervention trial
  - 1260 individuals aged 60-77 years and at risk for dementia
  - Randomized 1:1 to receive extra intervention

| Interventions                       |
|-------------------------------------|
| Nutrition                           |
| Exercise                            |
| Cognitive training                  |
| Management of vascular risk factors |



Findings from this large, long-term, randomized controlled trial suggest that a multidomain intervention could modestly improve or maintain cognitive functioning in at-risk elderly people from the general population

- US Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (US POINTER) (Baker 2025)
  - 2111 participants aged 60-79 years, sedentary lifestyle, suboptimal diet, plus 2 other RFs
  - Completed 2025; replicated results of FINGER study

# Nutraceuticals / Supplements

- Antioxidants (Sano 1997, Petersen 2005, Galasko 2012, Dysken 2014)
  - Vitamin E (high doses) modest benefit in treating mild to severe AD dementia (not in MCI); prevention trial ongoing
  - Vitamin C, Alpha lipoic acid, Coenzyme-Q10 ineffective in biomarker trial in AD dementia
- Cocoa extract / Multivitamin (Baker 2022)
  - Multivitamin modestly effective; cocoa ineffective in cognitively normal older adults
- Ginkgo biloba (DeKosky 2008, Vellas 2012)
  - Ineffective in preventing dementia (in cognitively normal older adults, subjective cognitive decline, and MCI)
- Omega 3 fatty acids / fish oil (DHA) (Quinn 2010, Sydenham 2012)
  - Multiple studies: ineffective in preventing cognitive decline or dementia or treating AD dementia
- Folic acid/vitamin B6/vitamin B12 (Aisen 2008)
  - Ineffective in treating AD dementia
- Huperzine, a naturally occurring ChE-I (Rafii 2011)
  - Ineffective in treating AD dementia

# Dementia Management: Summary

- Dementia management consists of medications, psychosocial support, and caregiver support
- There is a limited number of FDA approved medications for AD at the stage of dementia and more recently MCI
- Lifestyle modifications can help prevent or slow existing symptoms
- Supplements have been mostly unhelpful

# Participating in AD research

- Two major types of research studies
  - Randomized clinical trials (drug trials)
  - Observational (natural history) studies
- Research is an option that allows participants to be proactive, take some control of their future, and contribute to finding a cure for AD
- Observational studies are a nice way to engage in research and contribute for individuals who are not ready to jump into a clinical trial

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# Questions?

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