The Latest Buzz in Diagnosis and Treatment of Cognitive Disorders

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1/21/23

The Ohio State University
Wexner Medical Center

Disclosures

Grants:

Avanir
Biohaven
BioVie
Cassava
Cerevel Therapeutics
Cognition Therapeutics
Eisai
Genetech
InSightec
Janssen
Precision Medicine
Roche
UCB Biopharma
uniQure
Vivoryon Therapeutics

Consultant:

Acadia
Biogen
Brain Test
Eisai
Medscape/WebMD
Vascular Scientific

Learning Objectives

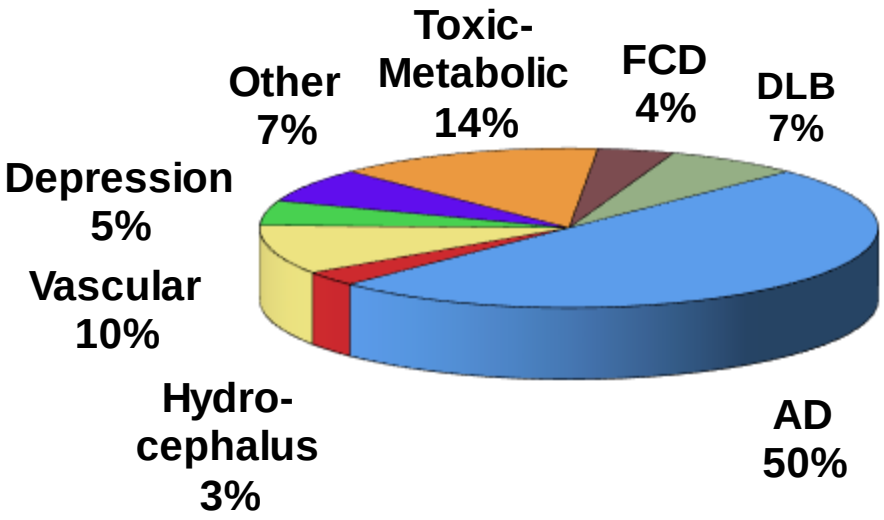
- Discuss diagnosis of common dementia conditions
- Learn about management approaches for the patient with cognitive disorders
- Review new treatments for Alzheimer's and Lewy body disorders

Normal

Mild Cognitive Impairment

Dementia

Prevalence of Dementia Syndromes



AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; FCD = Focal cortical degeneration

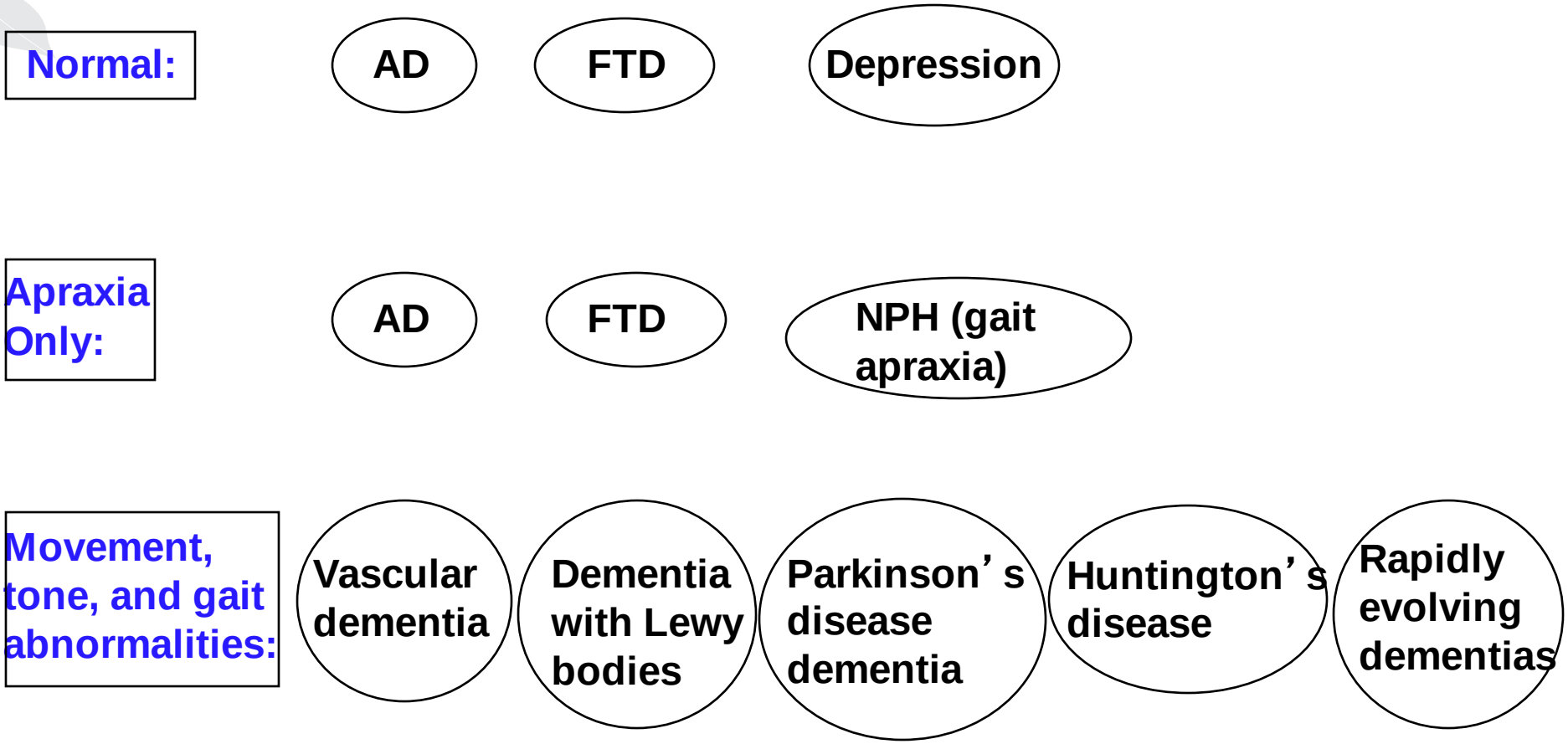
Steps in Differential Diagnosis

- History
- Physical Exam
- Mental Status Exam
- Behavioral and Psychiatric symptoms
- Laboratory Evaluations
- Neuroimaging

History

- Onset
- Clinical course
- Past medical history
- Psychiatric illness
- Medications
- Social and family history

Physical Exam



AD = Alzheimer's disease; FTD = Frontotemporal dementia; NPH = Normal pressure hydrocephalus

Mental Status Exam

- Attention
- Language
- Memory
- Visuospatial skills
- Abstraction and calculations
- Judgment and executive fxn
- Personality and emotional state

Cortical vs Subcortical

Speech

- Cortical: Normal, Stereotypy
- Subcortical: Hypophonic, dysarthric

Language

- Cortical: Anomia, aphasia
- Subcortical: Normal

Cortical vs Subcortical

Memory

- Cortical: Amnesia
- Subcortical: Retrieval deficit (forgetful)

Cognition

- Cortical: Acalculia, impaired attention
- Subcortical: Slow processing speed, distraction

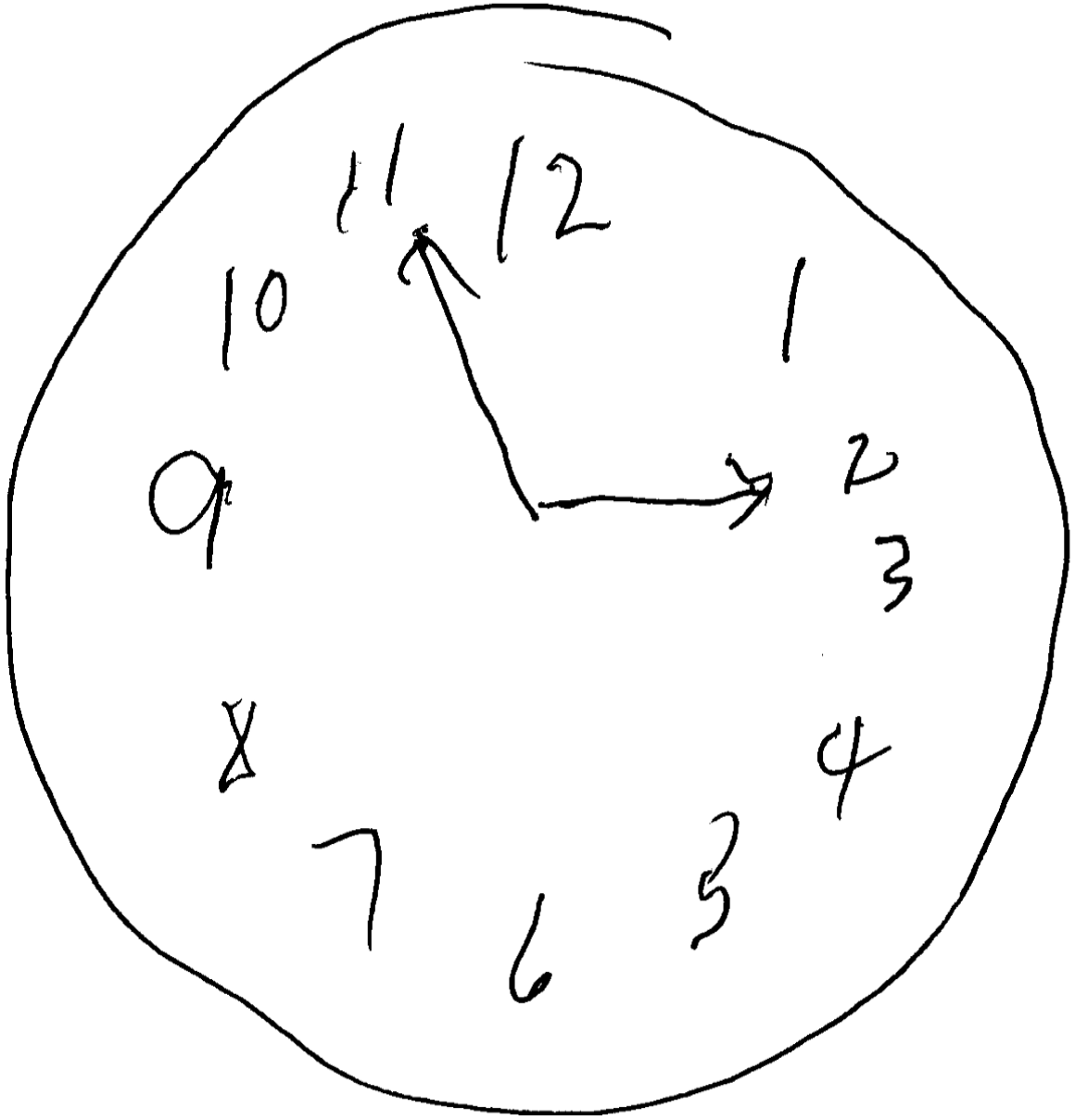
Cortical vs Subcortical

Executive

- Cortical: Impaired sequencing, apraxia, poor judgment & insight, ↓ verbal fluency
- Subcortical: Similar only if frontal-subcortical nuclei circuits involved

Visuospatial

- Cortical: Abnormal orientation and constructions
- Subcortical: Abnormal constructions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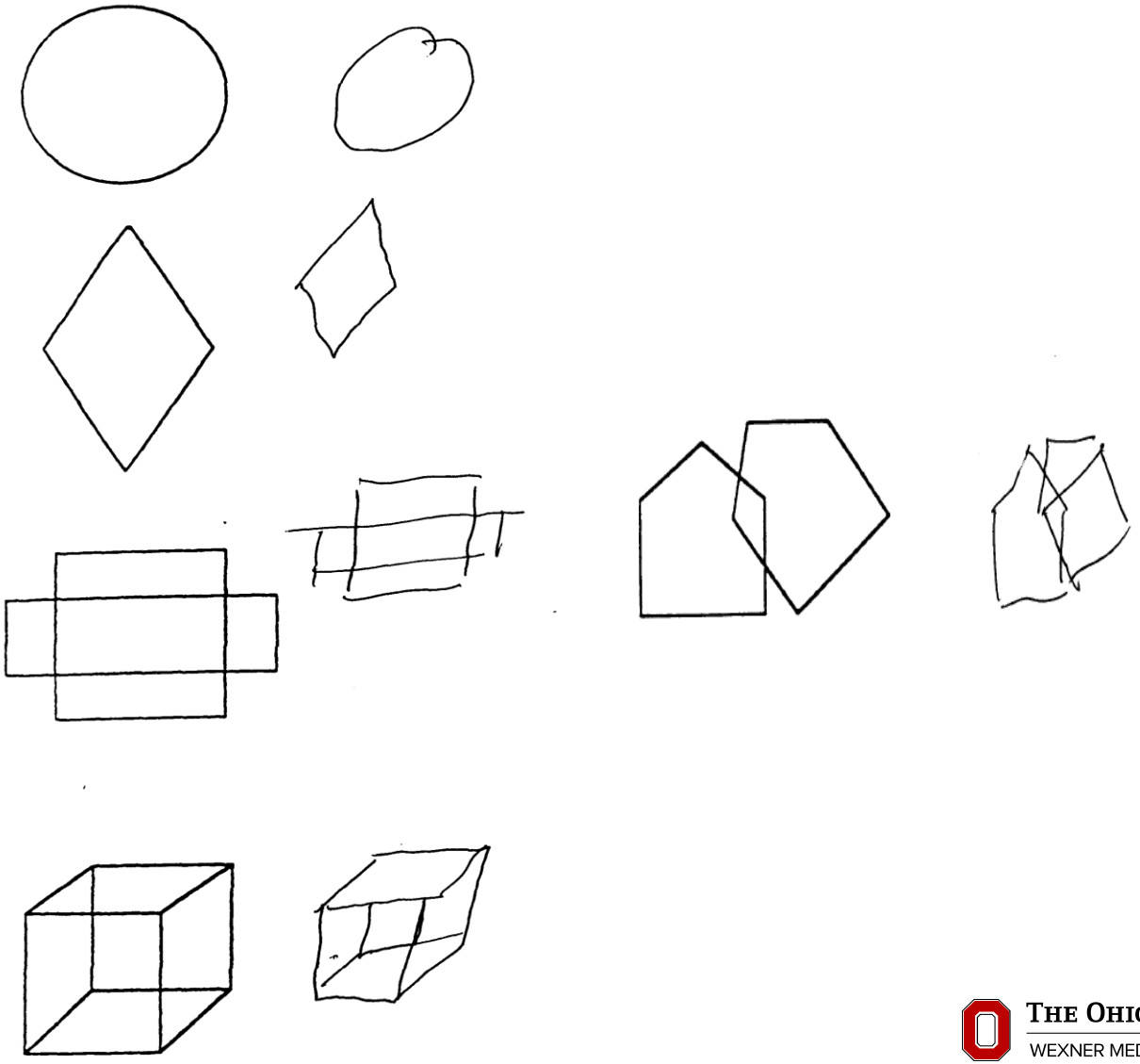
Construction Tests



Mental Status

Cortical:

- AD
- bvFTD: spares posterior cortical deficits

Subcortical:

- Depression
- Vascular dementia
- NPH
- Parkinson's disease dementia
- Huntington's disease

Mixed Cortical and Subcortical:

- Vascular dementia
- Dementia with Lewy bodies
- Rapidly evolving dementias

AD = Alzheimer's disease; FTD = Frontotemporal dementia; NPH = Normal pressure hydrocephalus

Barriers to Early Diagnosis of MCI and Dementia

- Patients with MCI and early dementia have impaired insight
- First present to the doctor an average of 3.5 years after cognitive symptoms start
- Physicians may not notice subtle cognitive deficits in routine office visits
- Often too much time or personnel resources required to administer testing

Barker WW et al. Alzheimer Dis Assoc Disord 2005;19:1-7

Brief Multi-domain Cognitive Assessment Tools

- Preference is to have tools that are practical, relevant, easy to use, and require minimal training
- Examples:
  - Mini-Mental State Examination (MMSE)[1]
  - Montreal Cognitive Assessment (MOCA)[2]
  - AD8 informant interview[3]
  - Saint Louis University Mental Status examination (SLUMS)[4]
  - Self-Administered Gerocognitive Examination (SAGE)[5] or the digital equivalent BrainTest[6]

1. Feher et al. Arch Neurol 1992; 49(1):87-92; 2. Nasreddine et al. J Am Geriatr Soc 2005; 53:695-699; 3. Galvin et al. Neurology 2006;67(11):1942-1948; 4. Tariq et al. Am J Geriatr Psychiatry 2006; 14(11):900-910; 5. Scharre et al. Alzheimer Dis Assoc Disord 2010; 24:64-71; 6. Scharre et al. Alzheimers Res Ther. 2017 Jun 27;9:44.

Comparative features of assessment tools

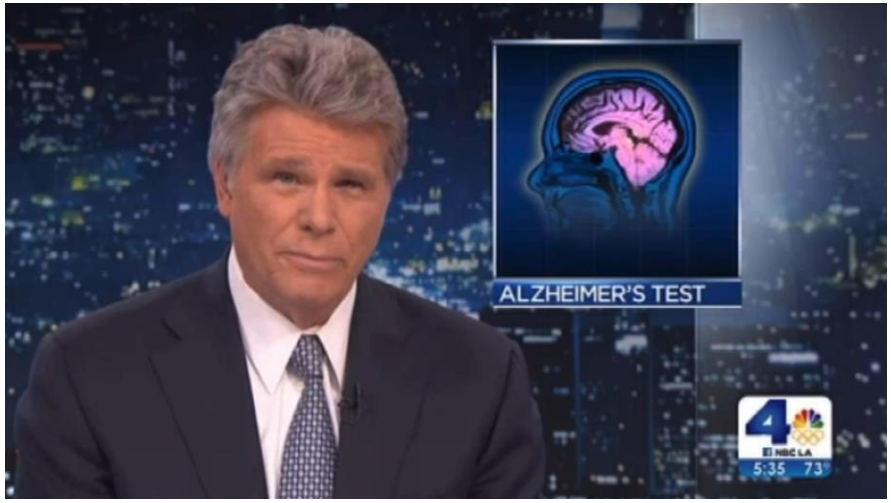
Features	MMSE	MoCA	AD8	SLUMS	SAGE/BrainTest
Scoring range	0-30 Higher score better	0-30 Higher score better	0-8 Score > 2 indicates impairment	0-30 Higher score better	0-22 Higher score better
Administration	Clinician with patient	Clinician with patient	Clinician with informant and patient	Clinician with patient	Patient (self-administered); SAGE (paper), BrainTest (digital, tablet)
Time to administer	7-10 minutes	10-13 minutes	3 minutes	10 minutes	10-15 minutes
Cost	$1.23 to PAR	free	free	free	SAGE: free BrainTest $25
Specificity/ sensitivity to detect dementia	84%/78% with cutoff 26 or less	87%/100% with cutoff of 25 or less	80%/84% with cutoff 2 or more	Comparable to MMSE but better at detecting mild Neurocognitive Disorders	95%/95% with a cutoff of ≤ 16 to detect dementia and 95%/79% (90%/71%, BrainTest) with a cutoff of ≤16 (15, BrainTest) to detect cognitive impairment
Obtaining test	Psychological Assessment Resources (PAR)	Mocatest.org	http://alzheimer.wustl.edu/about_us/pdfs/ad8form2005.pdf	medschool.slu.edu/aging successfully /pdfsurveys/slumsexam_05.pdf	SAGE: sagetest.osu.edu; BrainTest: https://braintest.com

SAGE Test

SAGE Test demonstrates high level of promotional sensitivity

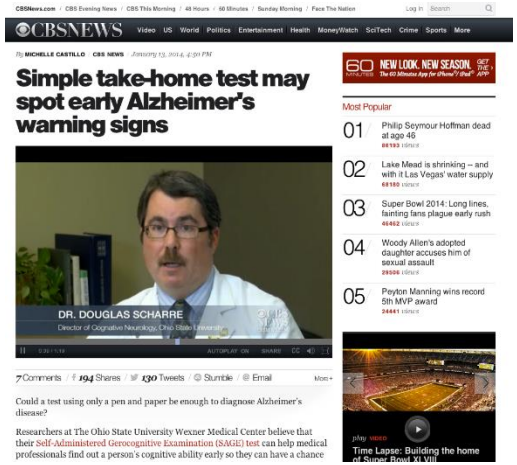
Increased Website Traffic

- The Wexner Medical center site had more visits in a single day on 1.13.14 than any other day over the last 10 years!
- The SAGE page had 181,000 pageviews on 1.13.14 which was a 17,000% increase from the prior day.
- SAGE/BrainTest web page remains the most visited in all of OSU Web presence since 2014



Source: NBC Los Angeles, NBC4 News at 5 p.m. on Jan. 13, 2014

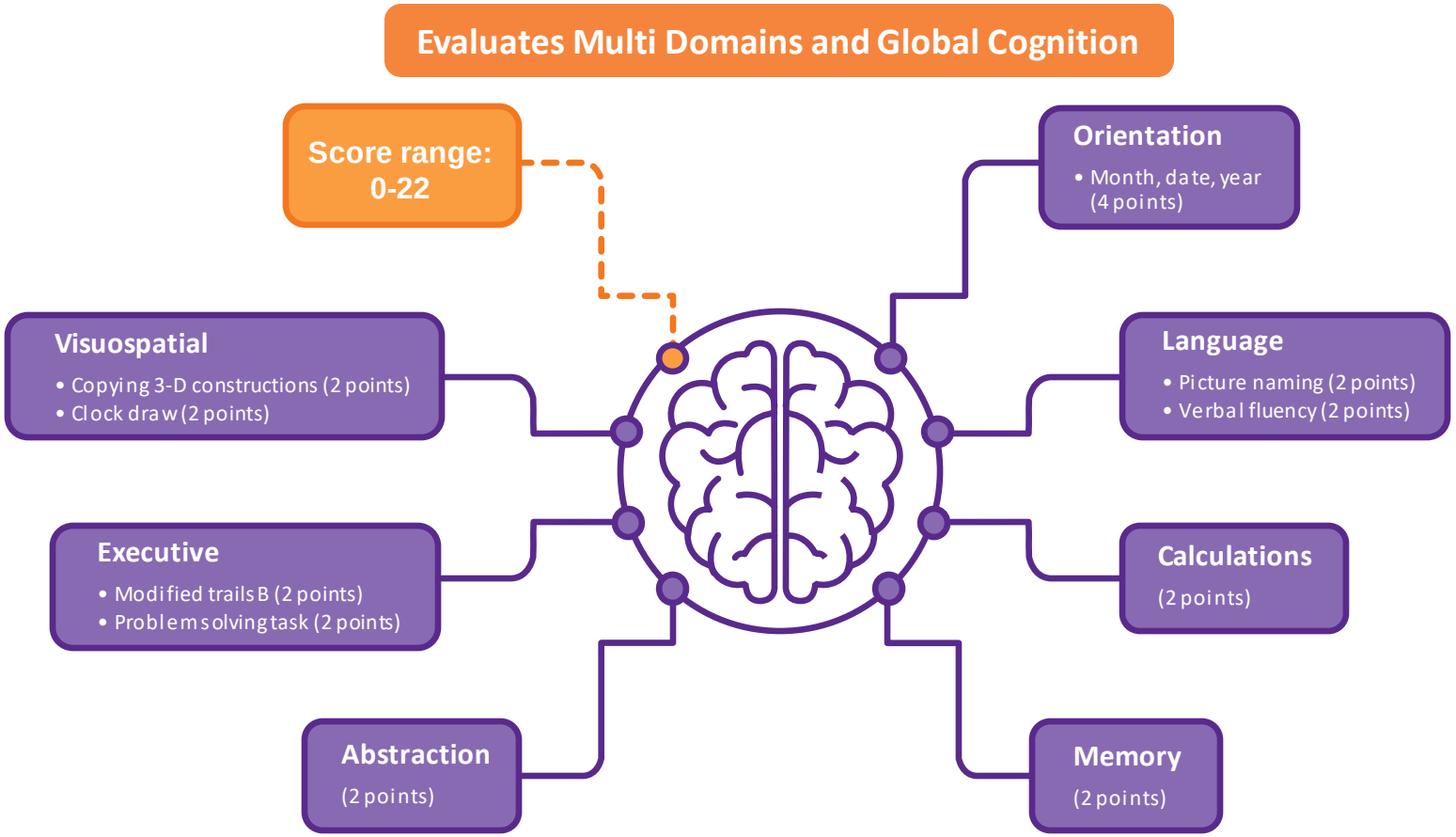
NBC Nightly News and the Today Show



CBS National News

Fox News

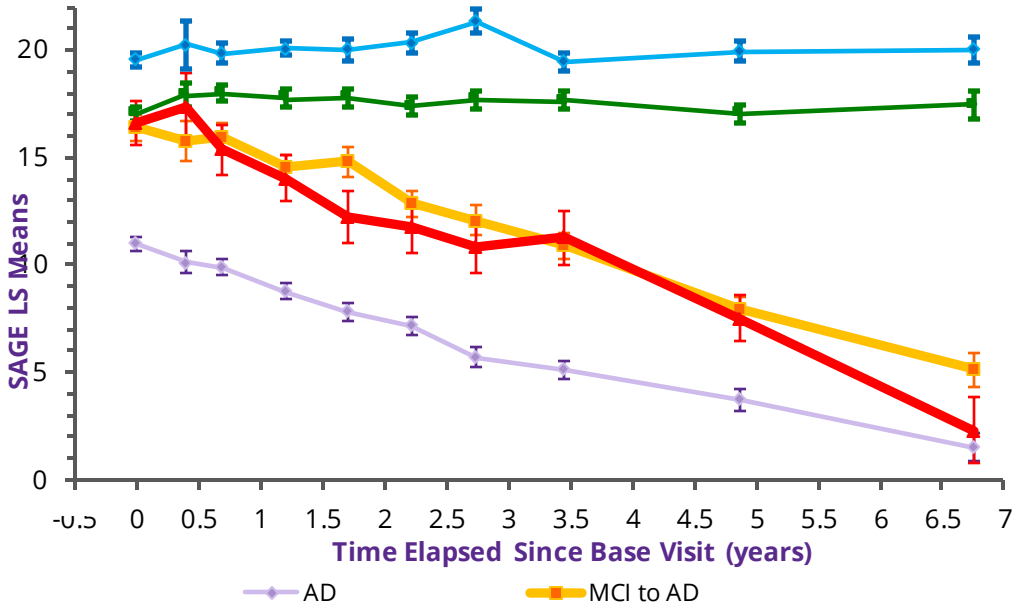
SAGE/BrainTest: Domains



SAGE: Change Over Time

- Significant Drop in SAGE Scores Revealed Dementia Conversion from MCI
- SAGE Scores of SCD Patients Were Significantly Higher than MCI Non-converters

SAGE Least Squares Mean Scores With Standard Error Bars



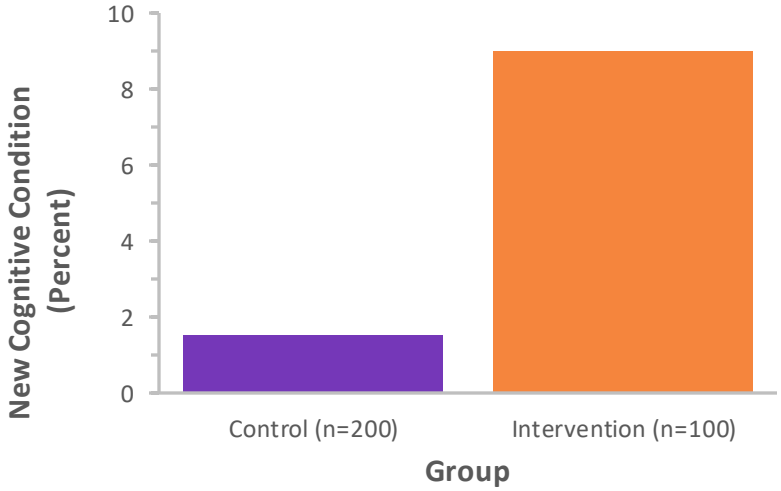
Alzheimers Res Ther. 2021; 13:192 doi: 10.1186/s13195-021-00930-4

SAGE/BrainTest: for the Early Detection of Cognitive Impairment at PCP Visits

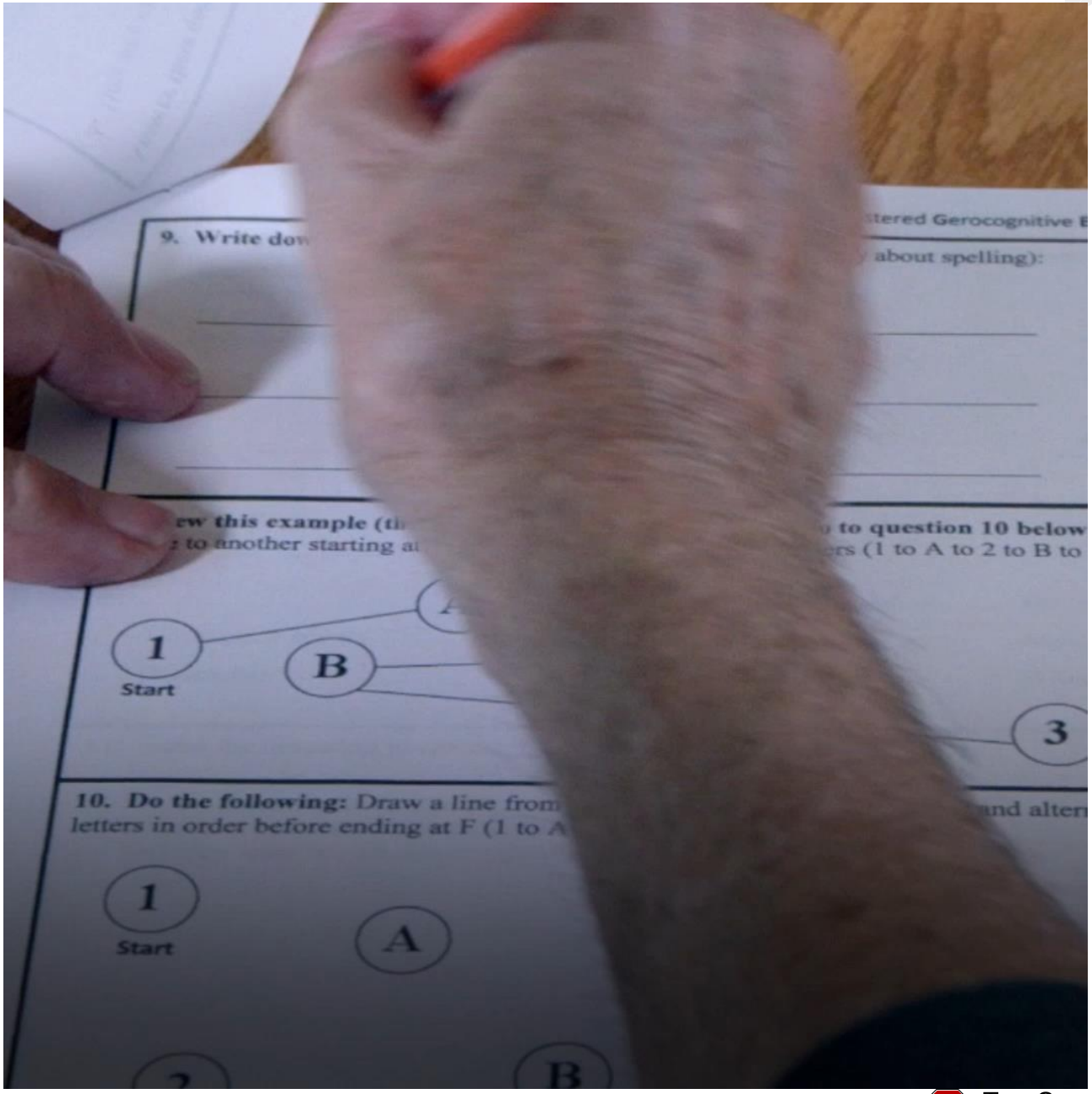
SAGE/BrainTest Usage Resulted in 6-Fold Detection of New Cognitive Conditions/Concerns

When SAGE was Utilized:

- PCPs documented detection of new cognitive conditions/concerns 6 times as often
- 9% vs 1.5%
- *p*=0.003



Scharre et al. American Academy of Neurology 2021 Annual Meeting Poster Presentation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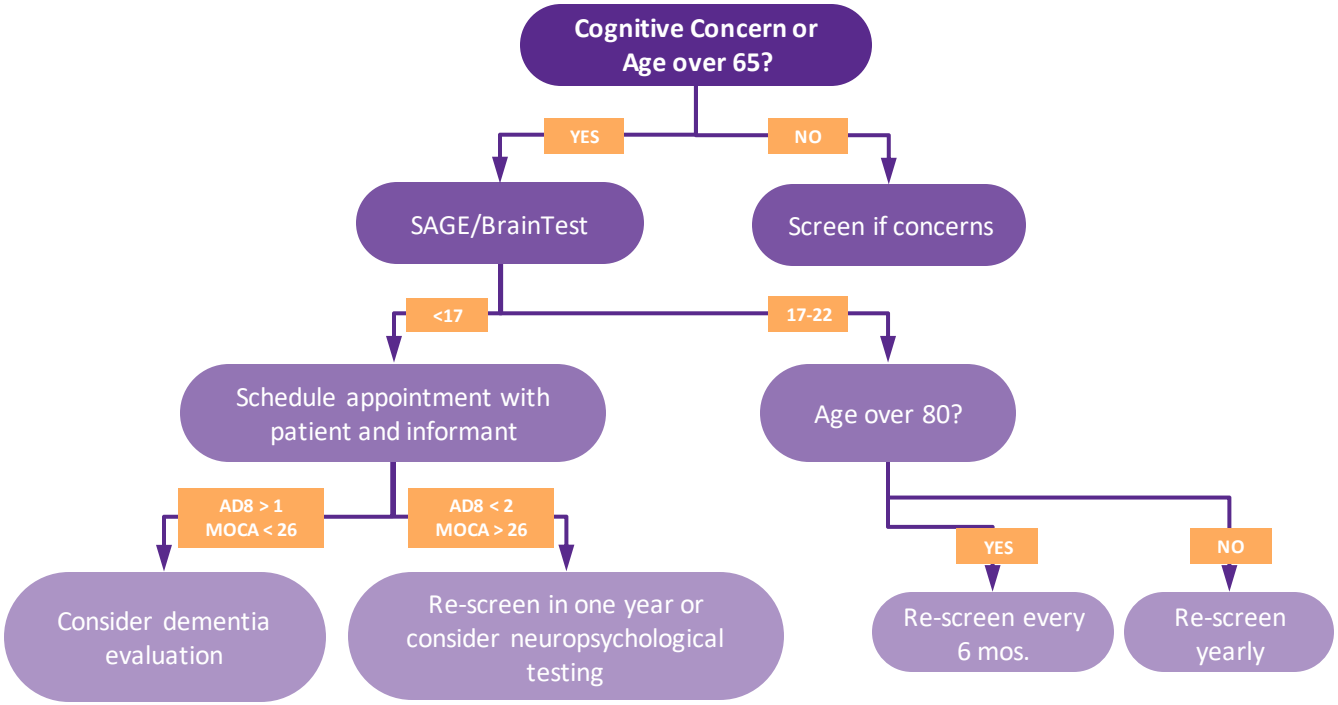
Staged Screening Approach

Consider a Staged Approach to Screening



Scharre et al. Alzheimer Dis Assoc Disord 2010;24:64-71 at SAGEtest.osu.edu;
Galvin et al. Neurology 2006;67:1942-1948;
Nasreddine et al. J Am Geriatr Soc 2005;53:695-699

Laboratory Evaluation

Recommended for all dementias

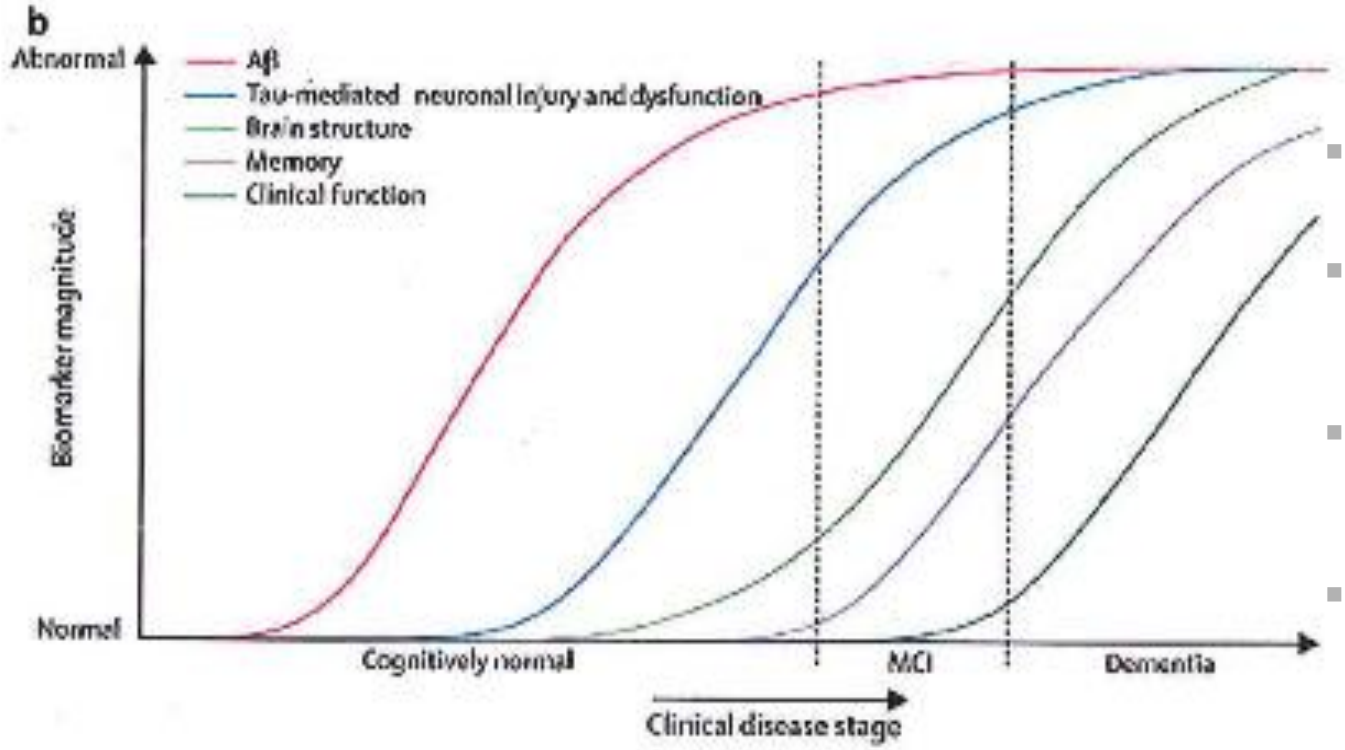
- CBC
- Electrolytes, calcium, glucose, BUN, creatinine, LFT
- B12, folate
- TSH, T4
- FTA

Optional Evaluations

Consider for rapidly evolving dementias

- Sed rate, inflammatory markers
- HIV, Lyme
- CXR, EKG
- Urinalysis
- Assays for heavy metals, toxins
- LP
- EEG

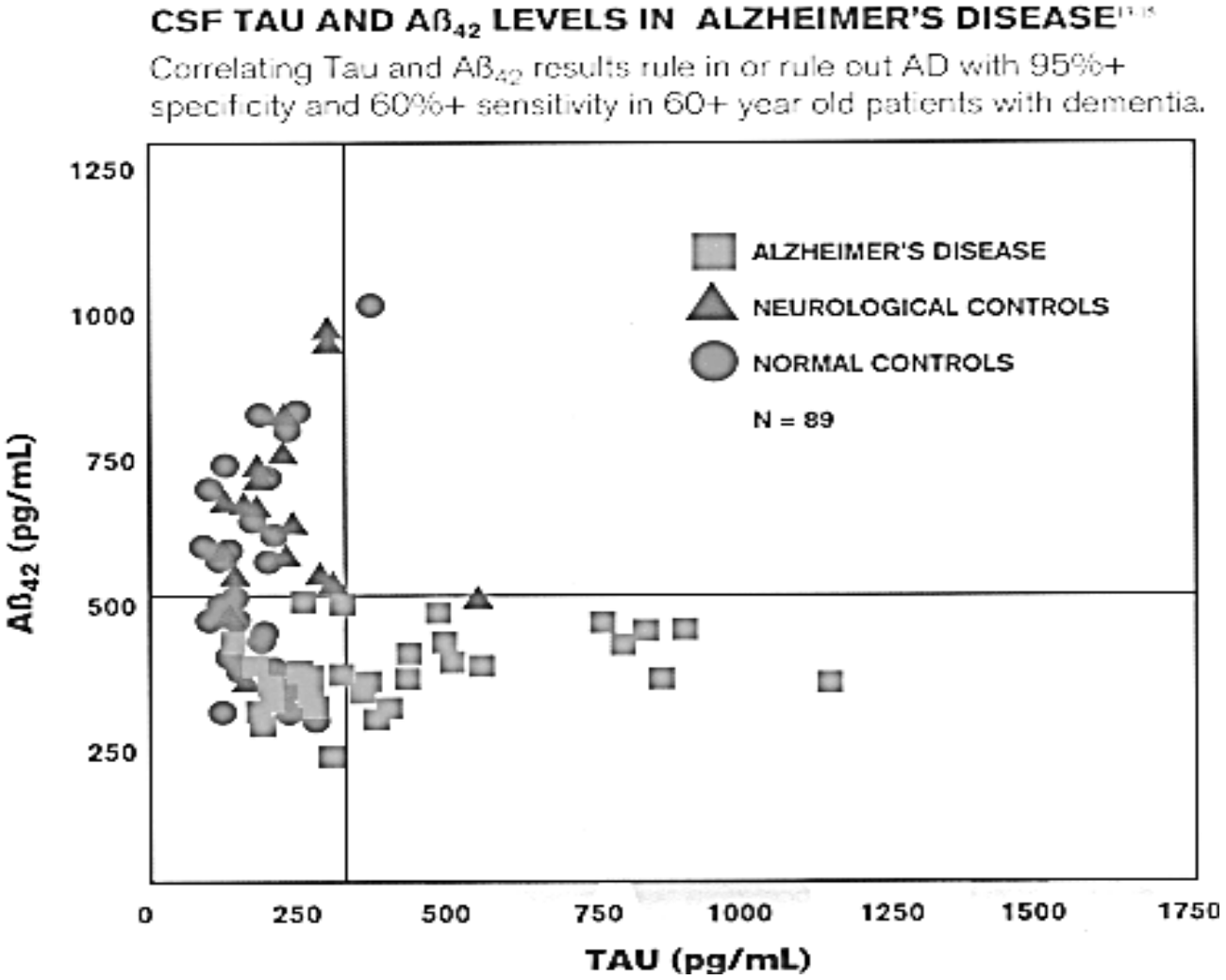
Biomarkers in AD



- Amyloid-β: CSF/ amyloid PET
- Synaptic dysfunction: FDG-PET/fMRI
- Tau-mediated neuronal injury: CSF/tau PET
- Brain structure: volumetric MRI

Jack et al. Lancet Neurol 9:119-129, 2010; Trojanowski J, Shaw L. et al., ADNI Biomarker Core Team, 2011

CSF AD Biomarkers

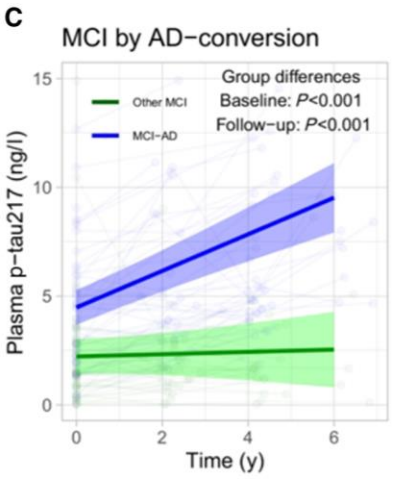


Elevated CSF tau and low Aβ42 is 95% specific and 60% sensitive for AD

Motter et al. Ann Neurol 1995;38:643-48

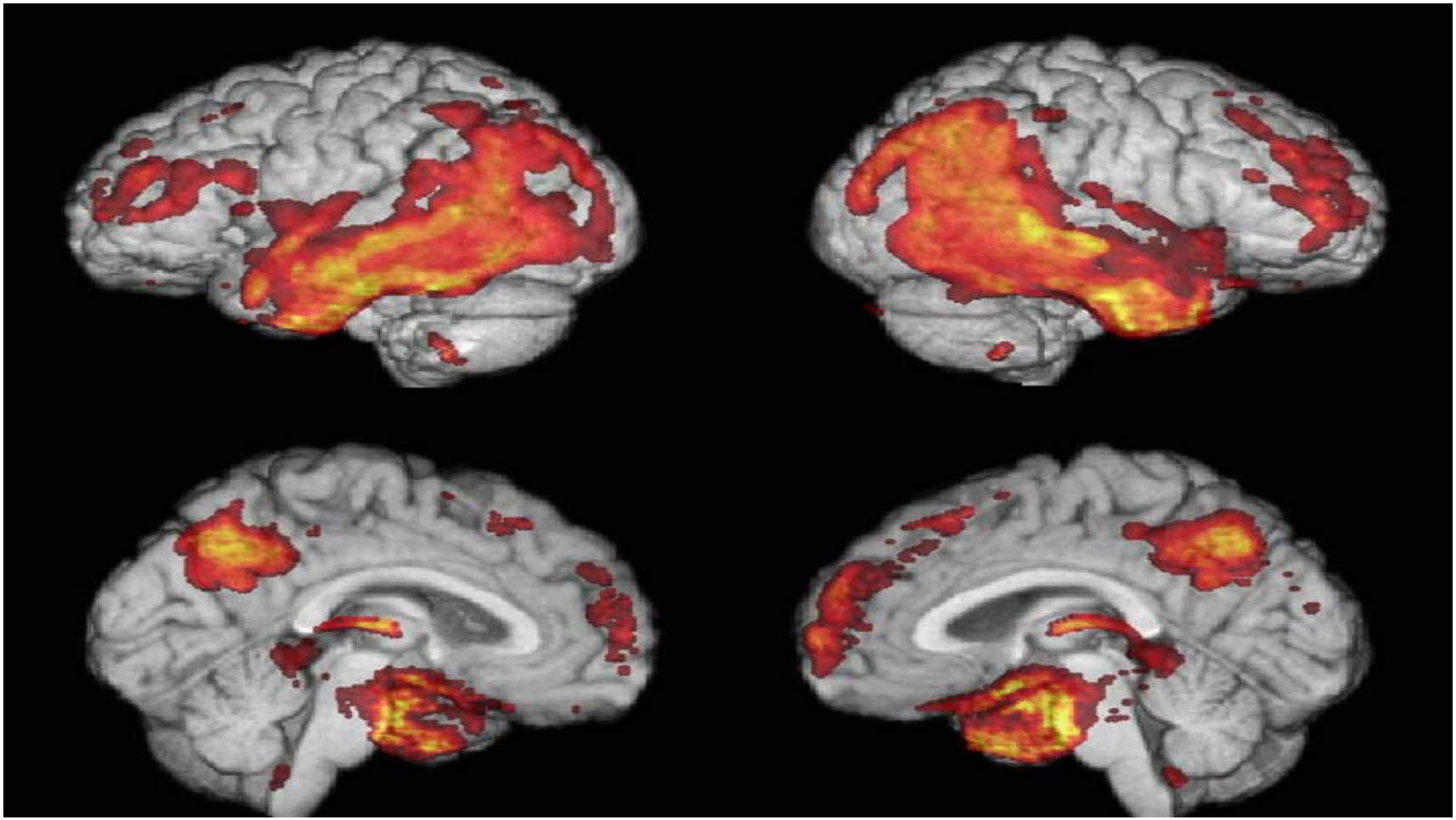
Blood Biomarkers in AD

- Plasma biomarker tests are not currently FDA approved
  - Preliminary studies have shown differences in plasma concentrations of Aβ42 and Aβ42/40 ratio[1,2], t-tau[3] and p-tau[4] in patients with AD compared with cognitively normal controls
- PrecivityAD test[5]
  - CLIA approved; not FDA approved; validation results not published
  - Looks at amyloid beta 42/40 ratio and ApoE proteotype (similar to Apo E genotype)
  - Reported specificity is 77% and sensitivity 92%
- Plasma biomarker p-tau tests are not currently clinically available[6,7]
  - p-tau181: predicted progression to AD
  - P-tau 217: increased in subjects before cognitive impairment or tau PET scans and at same time as tau CSF



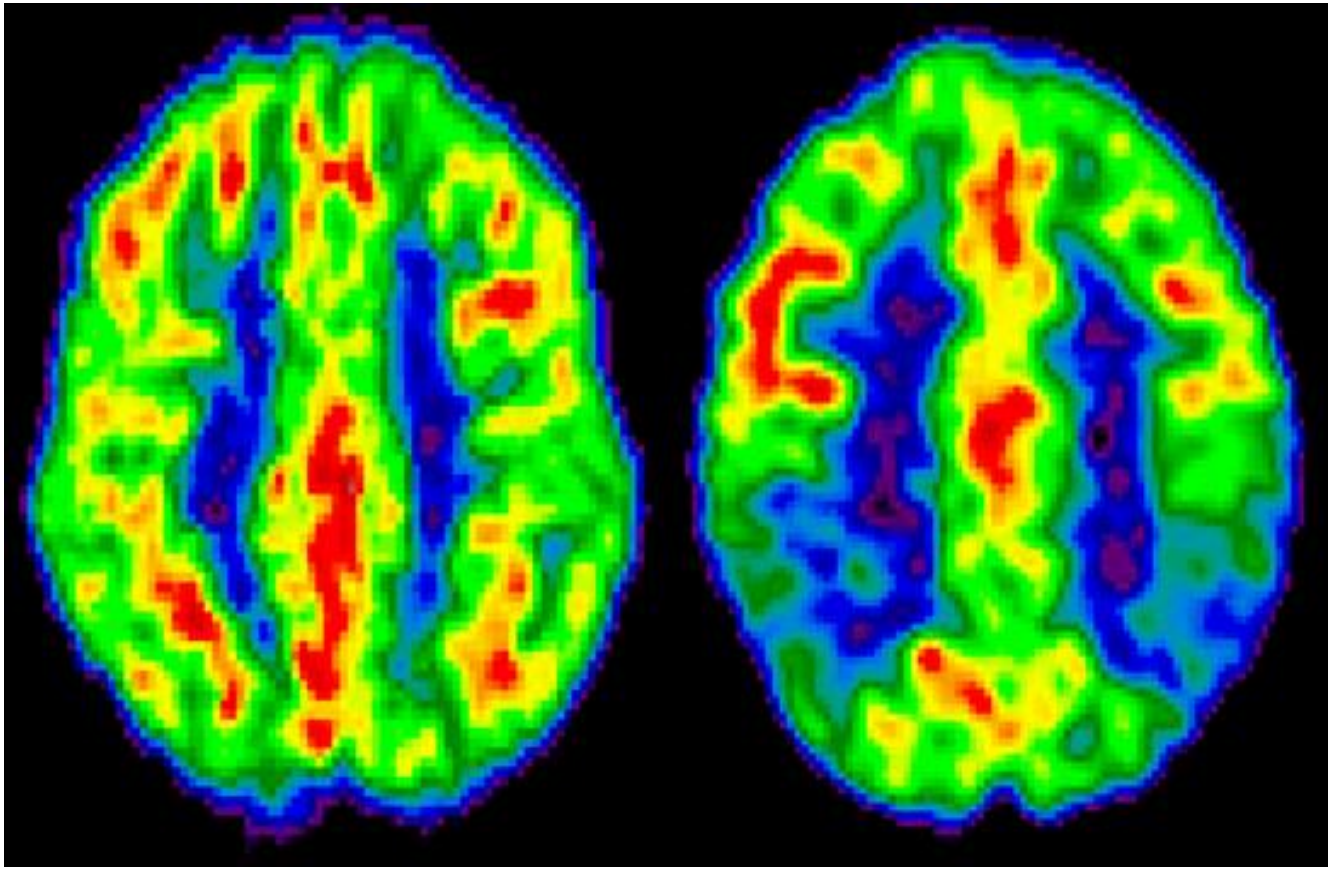
1. Nakamura A, et al. Nature 2018;554:249–254; 2. Teunissen CE, et al. J Alzheimers Dis 2018;62:1857–1863; 3. Olsson B, et al. Lancet Neurol 2016;15:673–684; 4. Yang CC, et al. J Alzheimers Dis 2018;61:1323–1332; 5. Schindler et al. Neurology 93:e1647–e1659; 6. Brain 2020;143 (11):3170–3172; 7. JAMA Neurology 2021;78(2):149-156

Gray Matter Reductions in AD Using Voxel Based Morphometry



Alexander GE et al., ADNI MRI Core Team, 2007

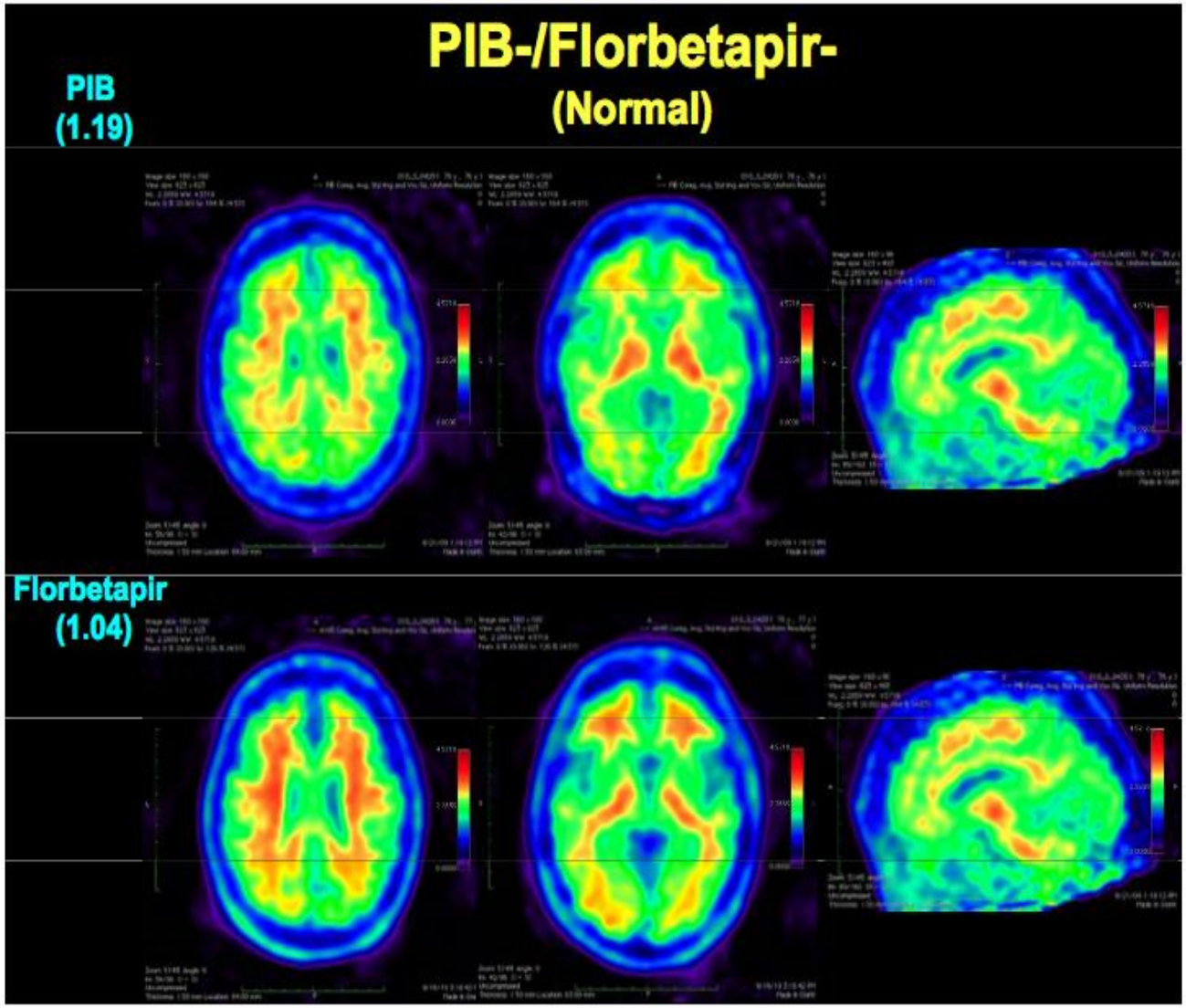
Typical AD PET Scan



Normal Brain **AD Brain**

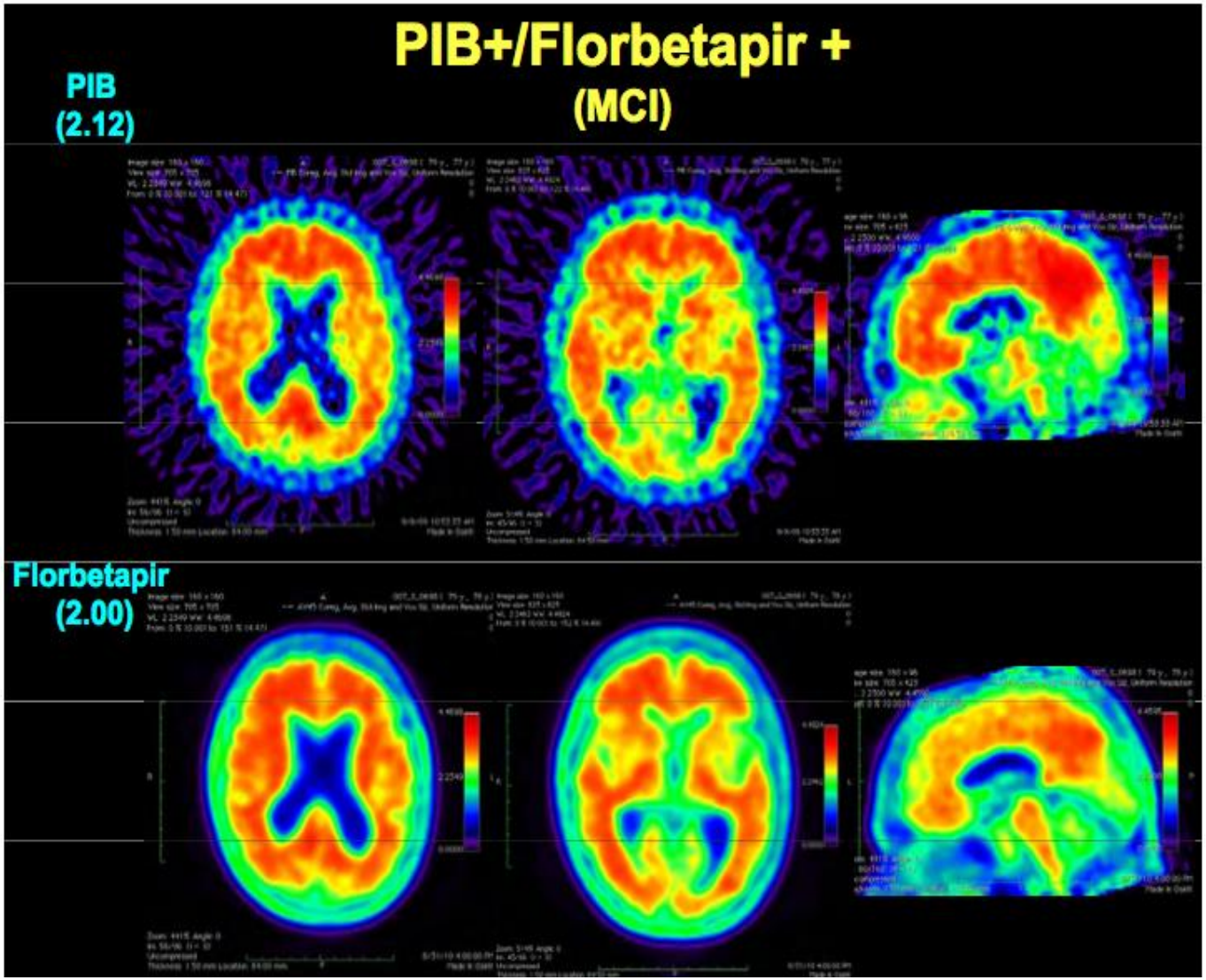
Provided courtesy of M. Mega, MD, PhD, Department of Neurology, UCLA School of Medicine.

Amyloid PET Imaging



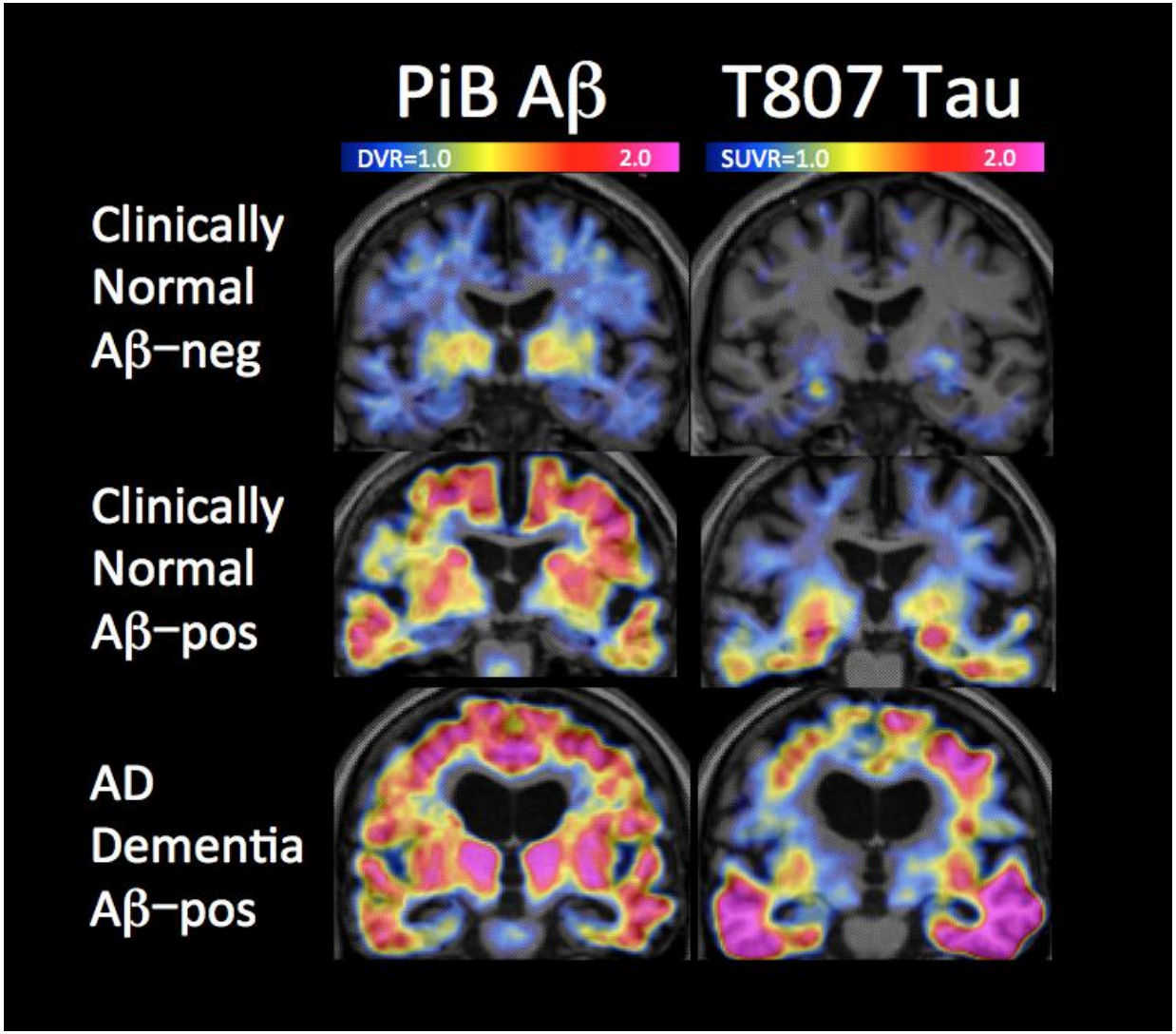
Jagust W. et al., ADNI-GO PET Core Team, 2011

Amyloid PET Imaging

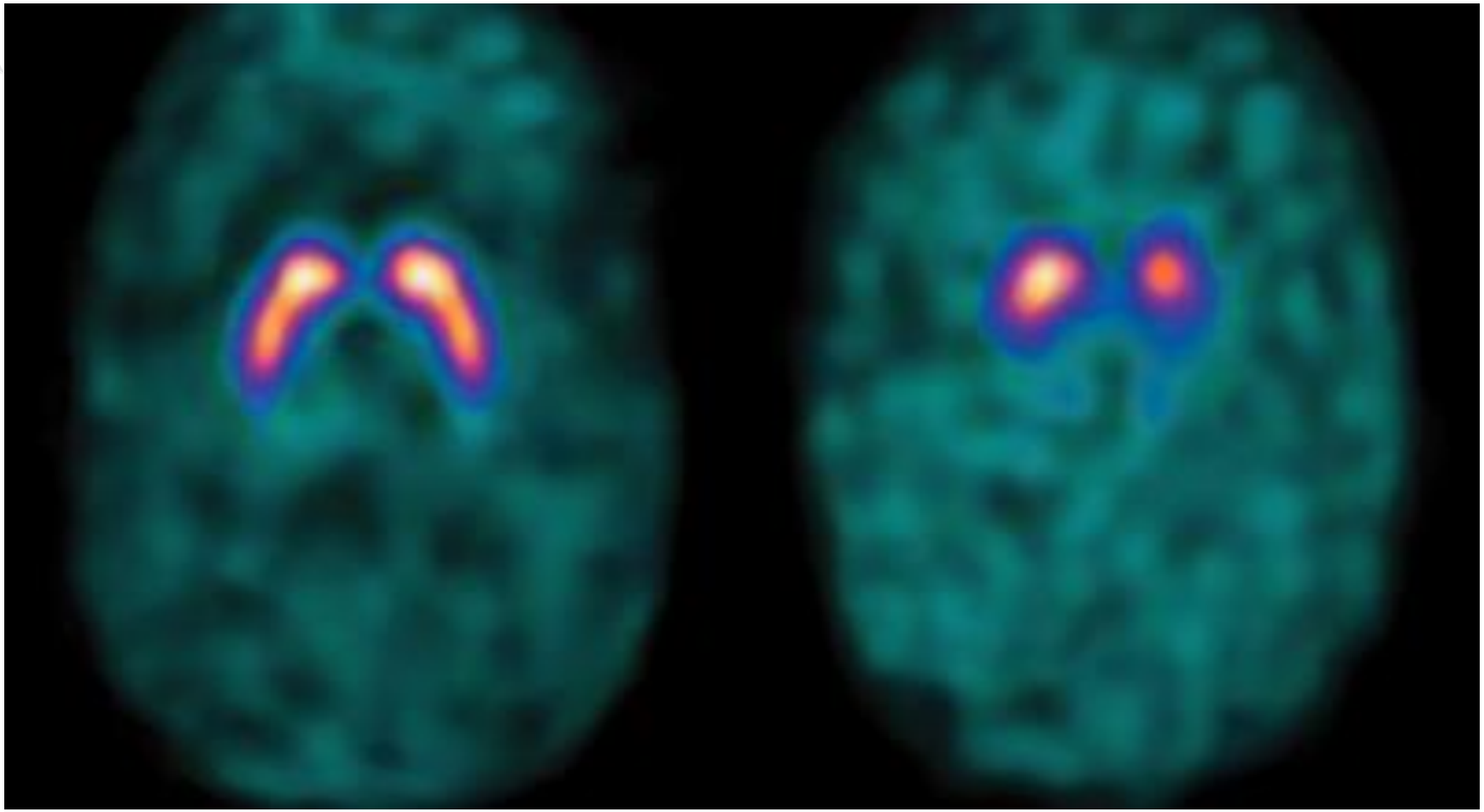


Jagust W. et al., ADNI-GO PET Core Team, 2011

Amyloid PET and Tau PET



Dopamine Transporter SPECT DaTscan for Lewy body dementia/Parkinsonism

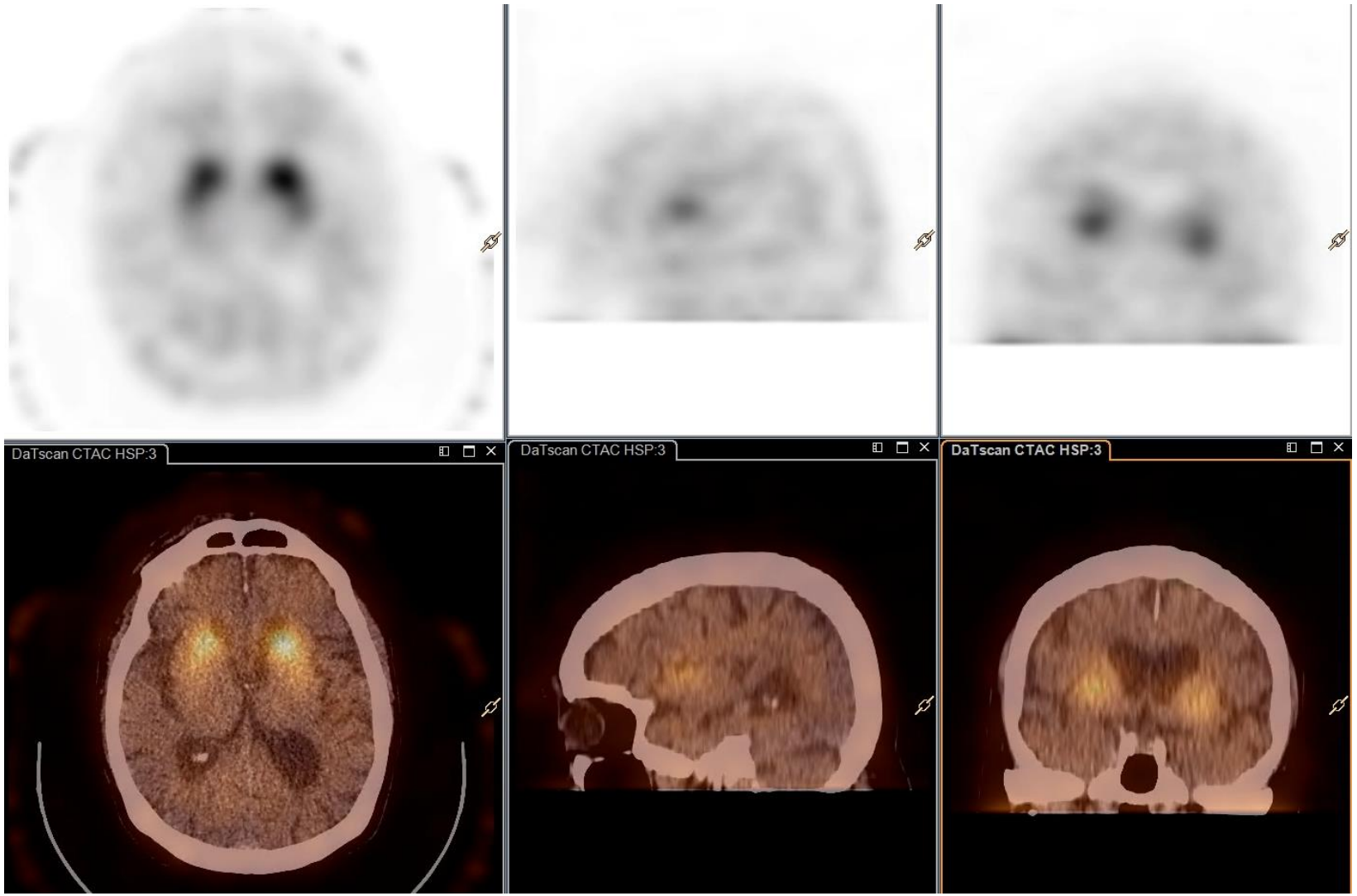


DaTscan Normal

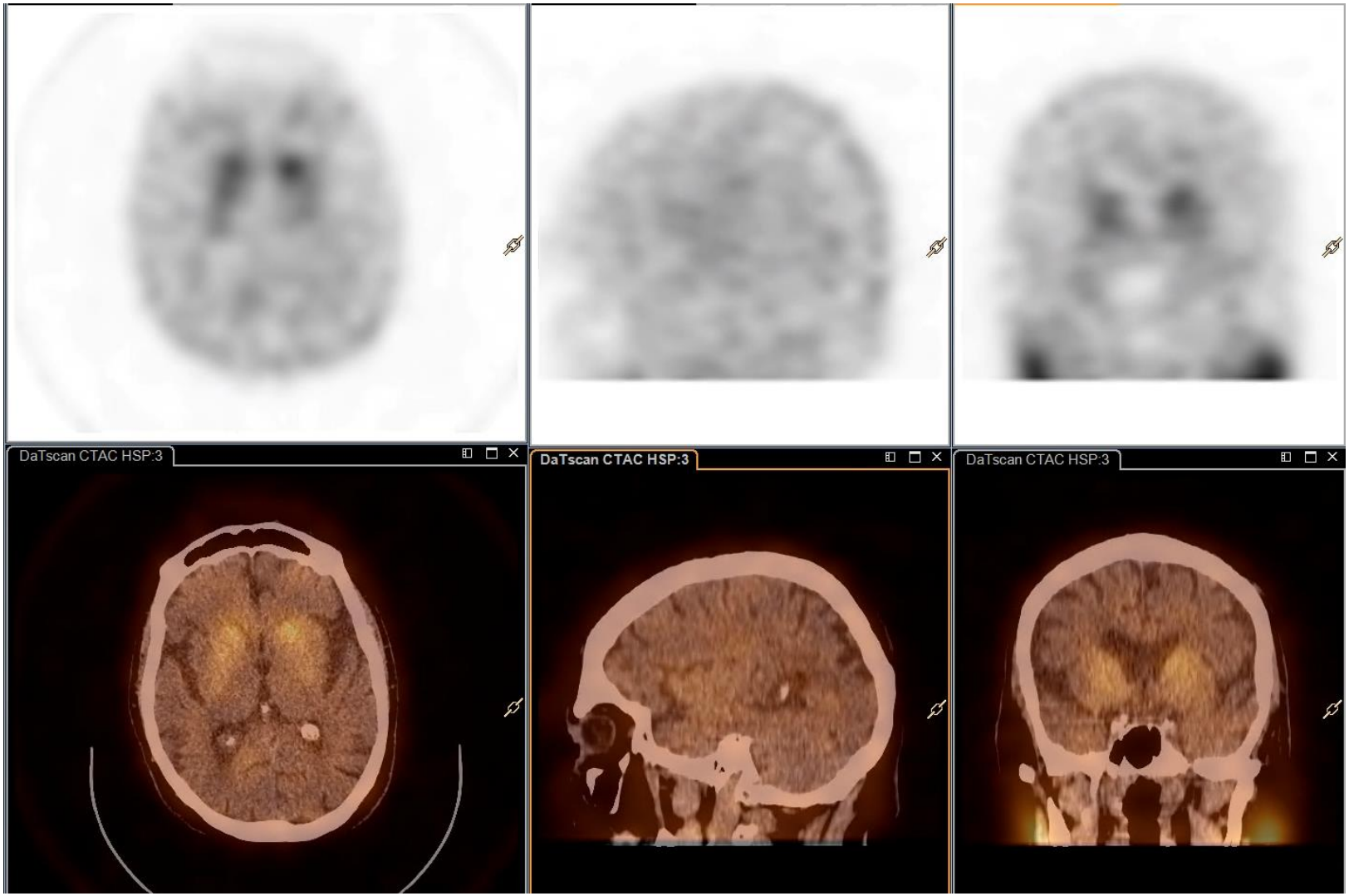
DaTscan Abnormal

Surendranathan A, O'Brien JT. Evidence-Based Mental Health 2018;21:61-65

Imaging Normal DaTscan



Imaging Abnormal DaTscan



Diagnosis of AD

Stages[1]

- Preclinical stage[2]: No clinical or cognitive symptoms but AD brain pathology has started (amyloid and tau proteins accumulation, cellular changes)
- Mild Cognitive Impairment due to AD (Prodromal AD)[3]: Decline from baseline cognitive abilities that are not so severe that they need hands-on assistance for daily activities they usually do themselves **plus** AD brain pathology
- AD Dementia[4]: Decline from baseline cognitive abilities that are severe enough to require hands-on assistance for daily activities they usually did for themselves **plus** AD brain pathology

1. Jack et al. Alzheimers Dement. 2018;14:535-562; 2. Sperling et al. Alzheimers Dement. 2011;7:280-92;
3. Albert et al. Alzheimers Dement. 2011;7:270-9; 4. McKhann et al. Alzheimers Dement. 2011;7:263-9

Dementia with Lewy Bodies: Clinical Criteria

- Essential feature: Dementia
- Core clinical features:
  - Fluctuating cognition/attention/alertness
  - Recurrent visual hallucinations
  - REM sleep behavior disorder (may precede cognitive decline)
  - 1 or more features of Parkinsonism (bradykinesia, rest tremor, or rigidity)

McKeith et al. Neurology 2017;89:88-100

Dementia with Lewy Bodies: Clinical Criteria

- Supportive clinical features:
  - Severe neuroleptic sensitivity
  - Postural instability
  - Repeated falls
  - Syncope or other transient unresponsive episodes
  - Severe autonomic dysfunction (constipation, orthostatic hypotension, urinary incontinence)
  - Hypersomnia
  - Hyposmia
  - Hallucinations in other modalities
  - Systematized delusions
  - Apathy, anxiety, and depression

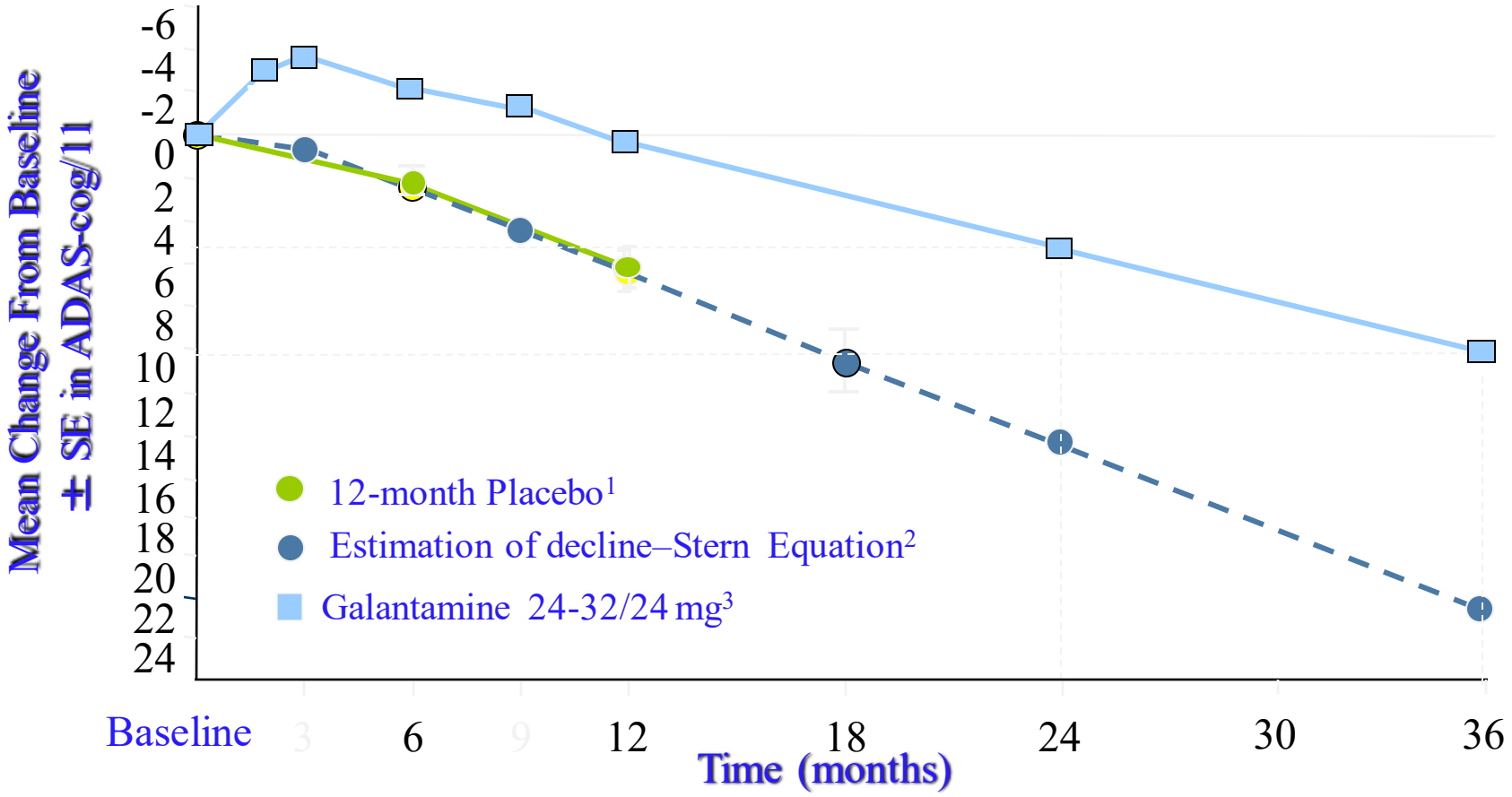
McKeith et al. Neurology 2017;89:88-100

Cognitive Rx in AD

Efficacy of Cholinesterase Inhibitors

- Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Razadyne)
- All of them work
- Up to 80% of patients show no decline after 6 months of treatment; 50% no decline after 1 year
- Need to give for ≥ 12 months to determine utility
- Always titrate to highest dose

Galantamine: 36-month Change From Baseline in ADAS-cog/11



1. Torfs K et al Poster presented at the Sixth International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy, April 2000. 2. Stern RG et al. *Am J Psychiatry*. 1994;151:3. 3. Data on file. Janssen Pharmaceutica.

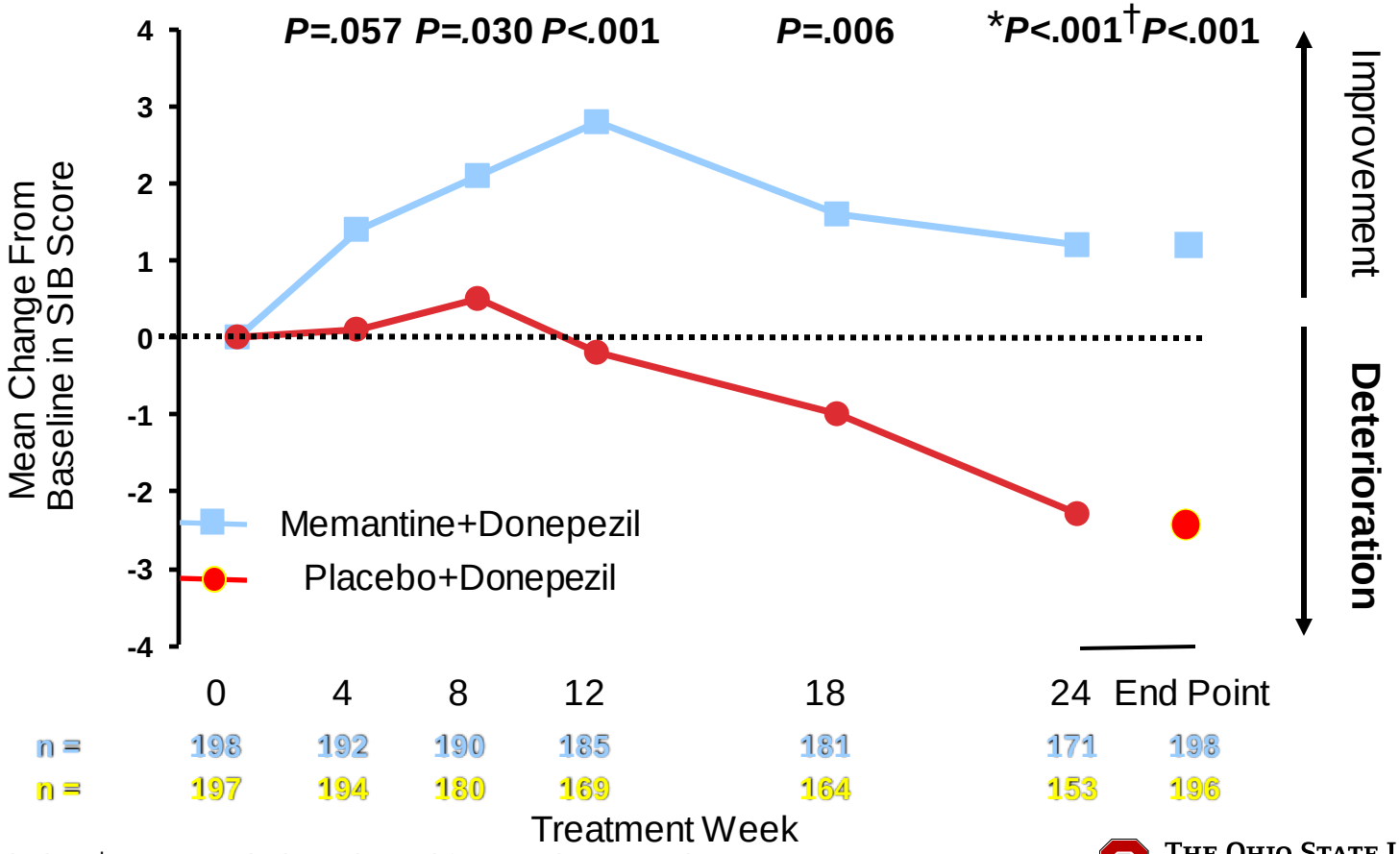
Cognitive Rx in AD

NMDA Antagonists: Memantine (Namenda)

- N-methyl-D-aspartate (NMDA) antagonists potentially prevent neuronal injury by reducing excitatory amino acid toxicity by glutamate
- Give in addition to cholinesterase inhibitor
- Side effects include headache, dizziness, fatigue, confusion

Results: Cognition—SIB

Memantine + Donepezil Produced Sustained Improvement in Cognition Above Baseline Compared With Donepezil Alone



*OC analysis. †LOCF analysis. Adapted from Tariot P, et al. *JAMA*. 2004;291:317-324. Data on file, Forest Laboratories, Inc.

Aducanumab/Lecanemab

- Human immunoglobulin G1 monoclonal antibody
- Aducanumab (ADU) binds to soluble aggregated (oligomers and fibrils), lecanemab (LEC) to soluble protofibrils and both to insoluble forms of Aβ [1, 2]
- Phase 3 Trials:18 month, randomized, double-blind, placebo-controlled (ADU, n=3285; LEC, n=1795)
- ADU high dose (up to 10 mg/kg) and low dose (up to 6 mg/kg) and placebo: randomized 1:1:1
- LEC (100 mg/ml) and placebo; randomized 1:1
- Primary Endpoint: CDR-SB at 18 months
- Secondary Endpoints: MMSE, ADAS-cog 13 (14 and ADCOMS for LEC), ADCS-ADL-MCI, biomarkers

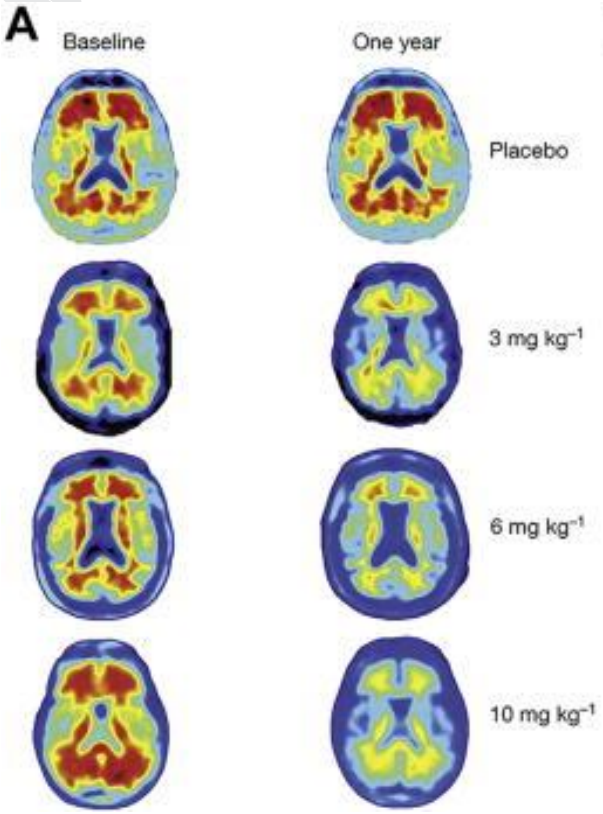
1. Budd et al, J Prev Alzheimers Dis. 2017;4:255-263; 2. Van Dyck et al, NEJM. 2022; DOI:10.1056/NEJMoa2212948

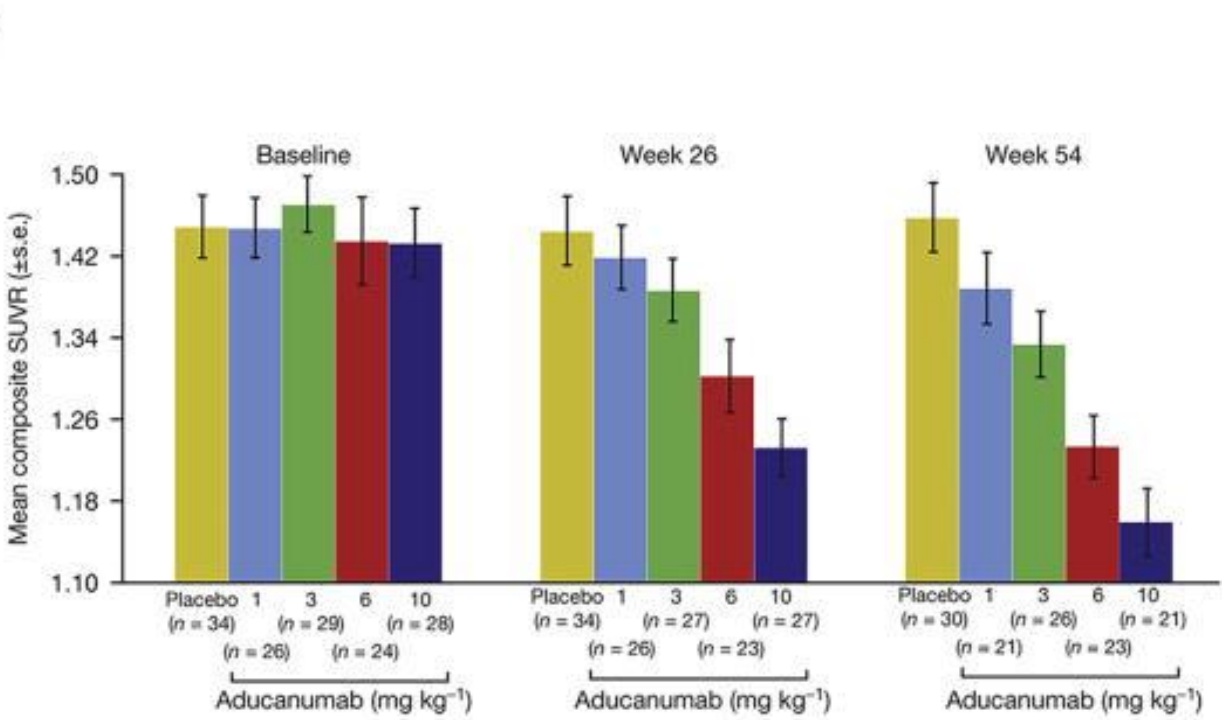
Top Line Cognitive and Functional Findings primary & secondary endpoints, week 78

	Aducanumab[1]		Lecanumab[2]	
	Placebo Decline (n=548)	High dose difference vs. placebo (%) p-value (n=547)	Placebo decline (n=875)	Difference vs placebo (%) p-value (n=859)
CDR-SB	1.74	0.39 (-22%) 0.0120	1.66	0.45 (-27%) <0.001
MMSE or ADCOMS	-3.3 (MMSE)	0.6 (-18%) 0.0493	0.214 (ADCOMS)	-0.050 (-23%) <0.001
ADAS-Cog 13/14	5.162	-1.400 (-27%) 0.0097	5.58	-1.44 (-27%) <0.001
ADCS-ADL-MCI	-4.3	1.7 (-40%) 0.0006	-5.5	2.0 (-37%) <0.001

1. Haeberlein et al. Alzheimer's Dement. 2020;16(Suppl. 9):e047259; https://investors.biogen.com/static-files/8e58afa4-ba37-4250-9a78-2ecfb63b1dcb
2. Van Dyck et al, NEJM. 2022; DOI:10.1056/NEJMoa2212948

Aducanumab





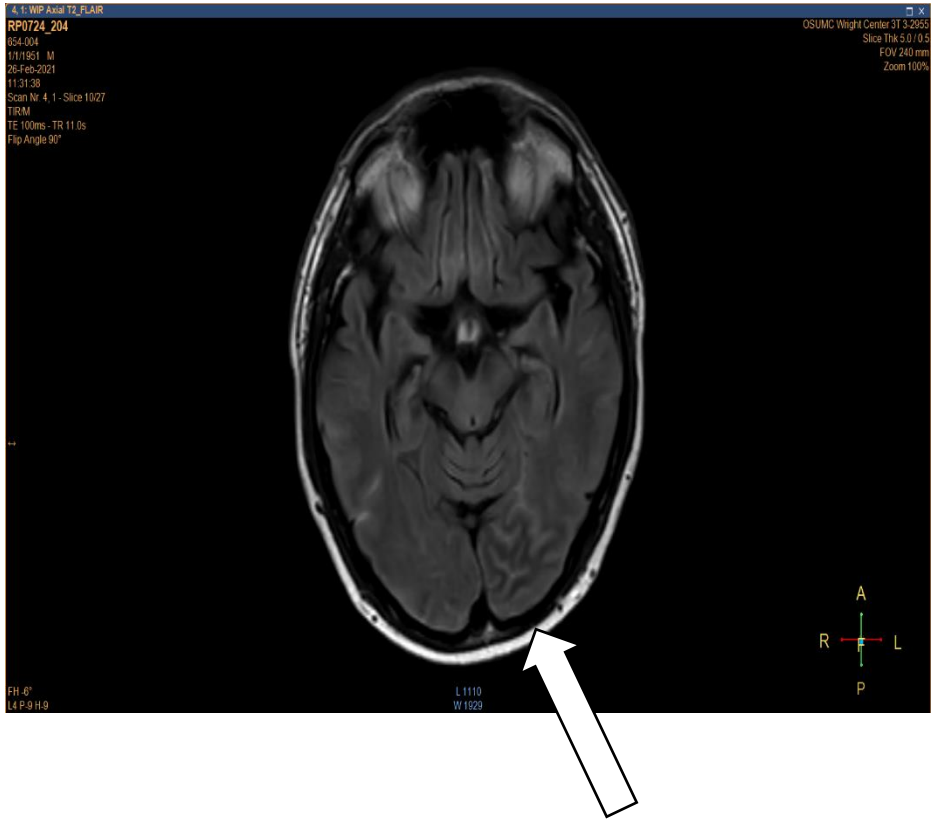
Van Dyke. Biol Psychiatry 2018;83:311-3219

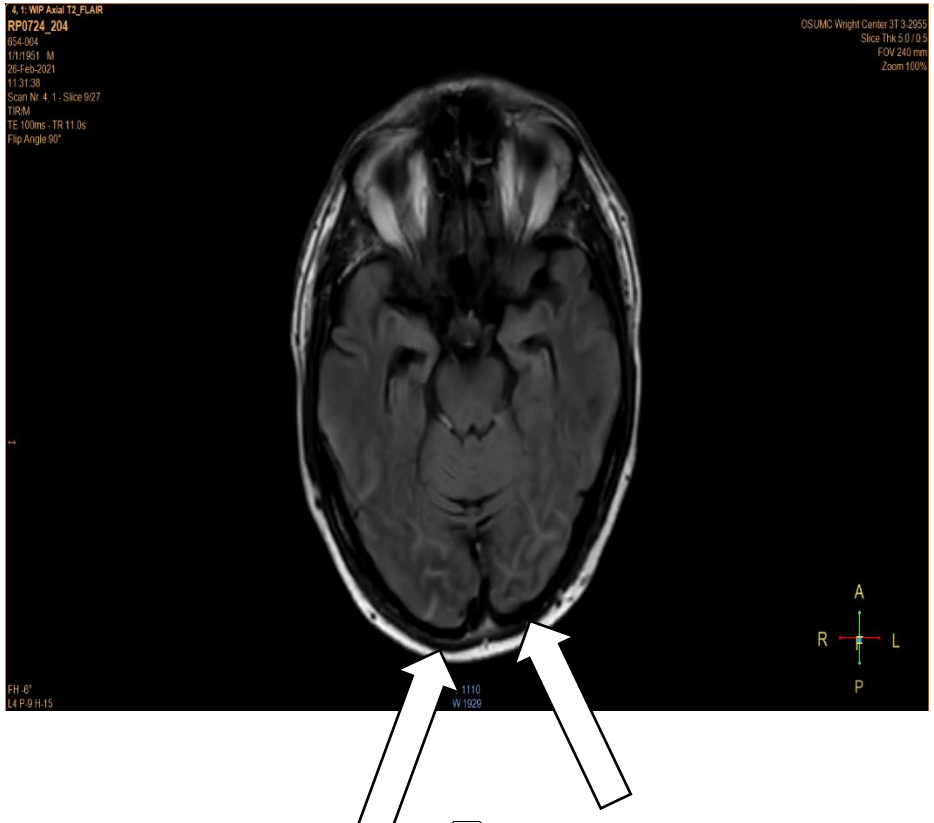
Top Line Adverse Event Findings

- Discontinuation of treatment rates: ADU: 25% high dose, 16.3% placebo; LEC: 7%; 3% placebo
- AE: ADU High dose 91%, placebo 87%; LEC 89%, placebo 82%
- SAE: ADU High dose 12.4%, placebo 13.4%; LEC 14%, placebo 11.3%
- Deaths: ADU High dose 8, placebo 6; LEC 6, placebo 7
- ARIA-E: ADU High dose 34.8%, placebo 2.6%; LEC 12.6%, placebo 1.7%
- ARIA-H microhemorrhage: ADU High dose 18.1%, placebo 6.3%; LEC 14%, placebo 7.7%
- 98% (ADU) and 94% (LEC) of the time the MRI findings of ARIA E resolved
- Apo E4 status ADU: positive had 42% and negative had 20% ARIA-E
- Apo E4 status LEC: positive had 15.8% and negative had 5.4% ARIA-E
- Symptomatic ARIA: ADU High dose 24.4%, placebo 5.6%
- Symptomatic ARIA: LEC 2.8%, placebo 0%

Haeberlein et al. Alzheimer's Dement. 2020;16(Suppl. 9):e047259; https://investors.biogen.com/static-files/8e58afa4-ba37-4250-9a78-2ecfb63b1dcb

Amyloid Related Imaging Abnormalities: ARIA-Edema (ARIA-E)





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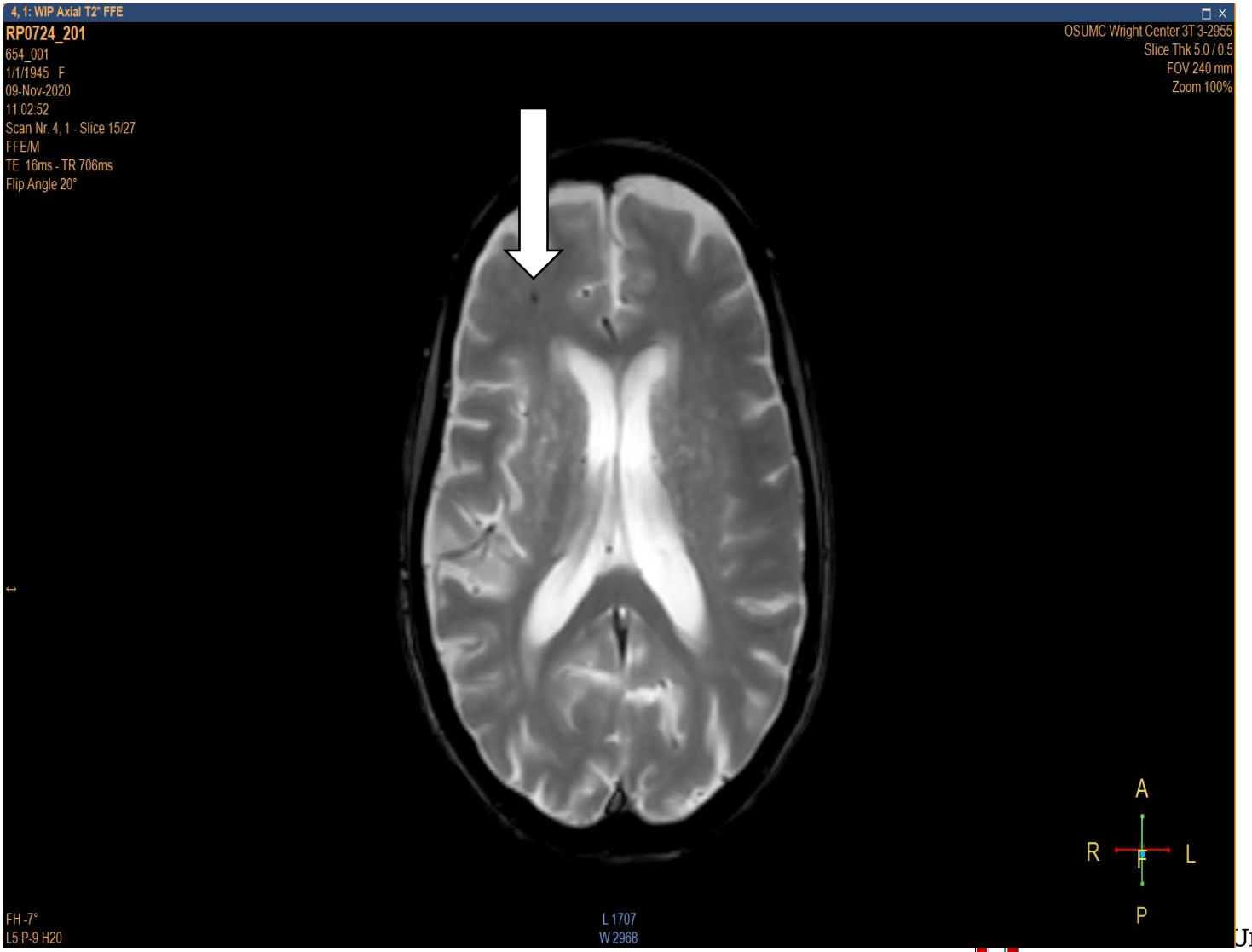
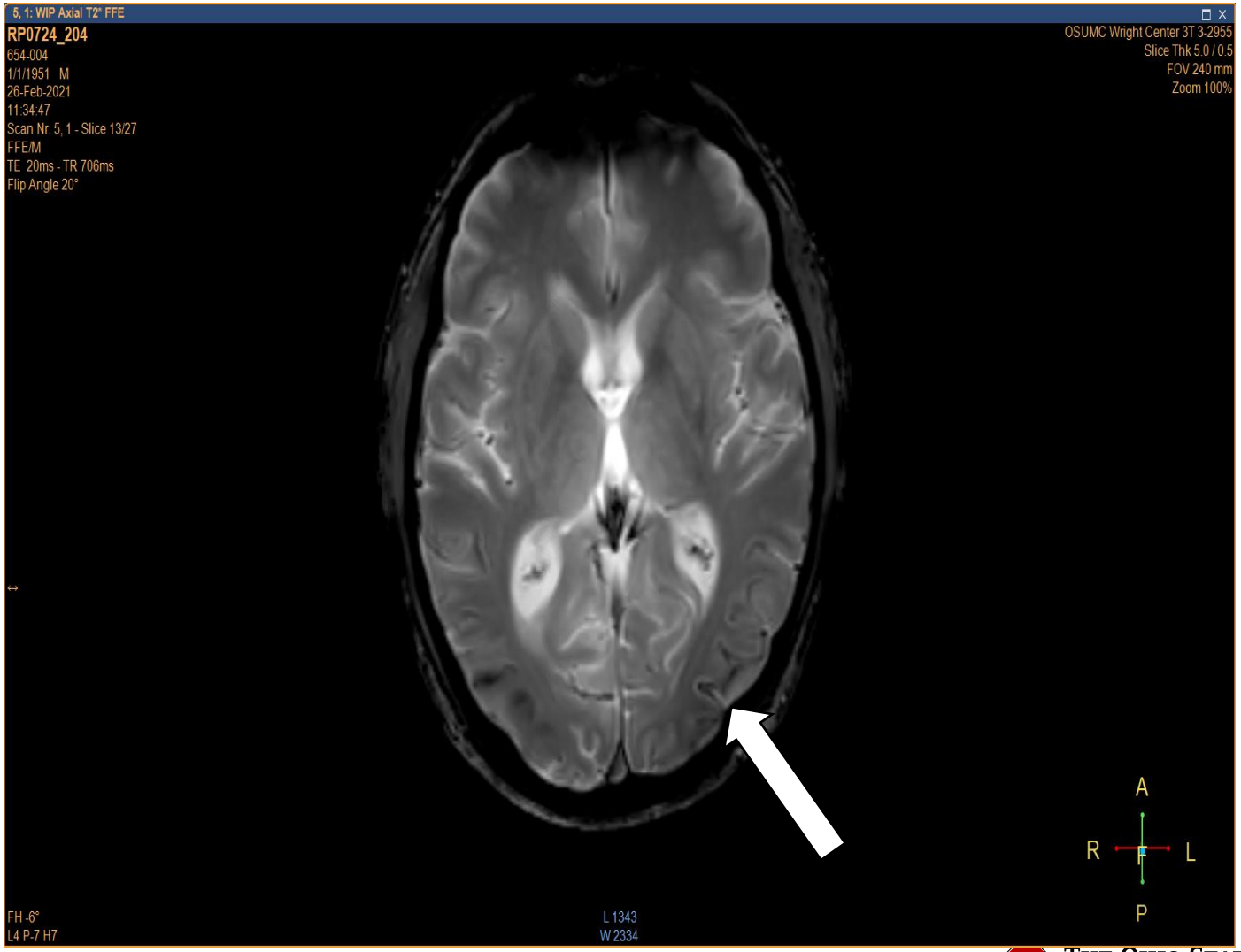
WEXNER MEDICAL CENTER

ARIA-Hemorrhage (ARIA-H)



ARIA-superficial siderosis

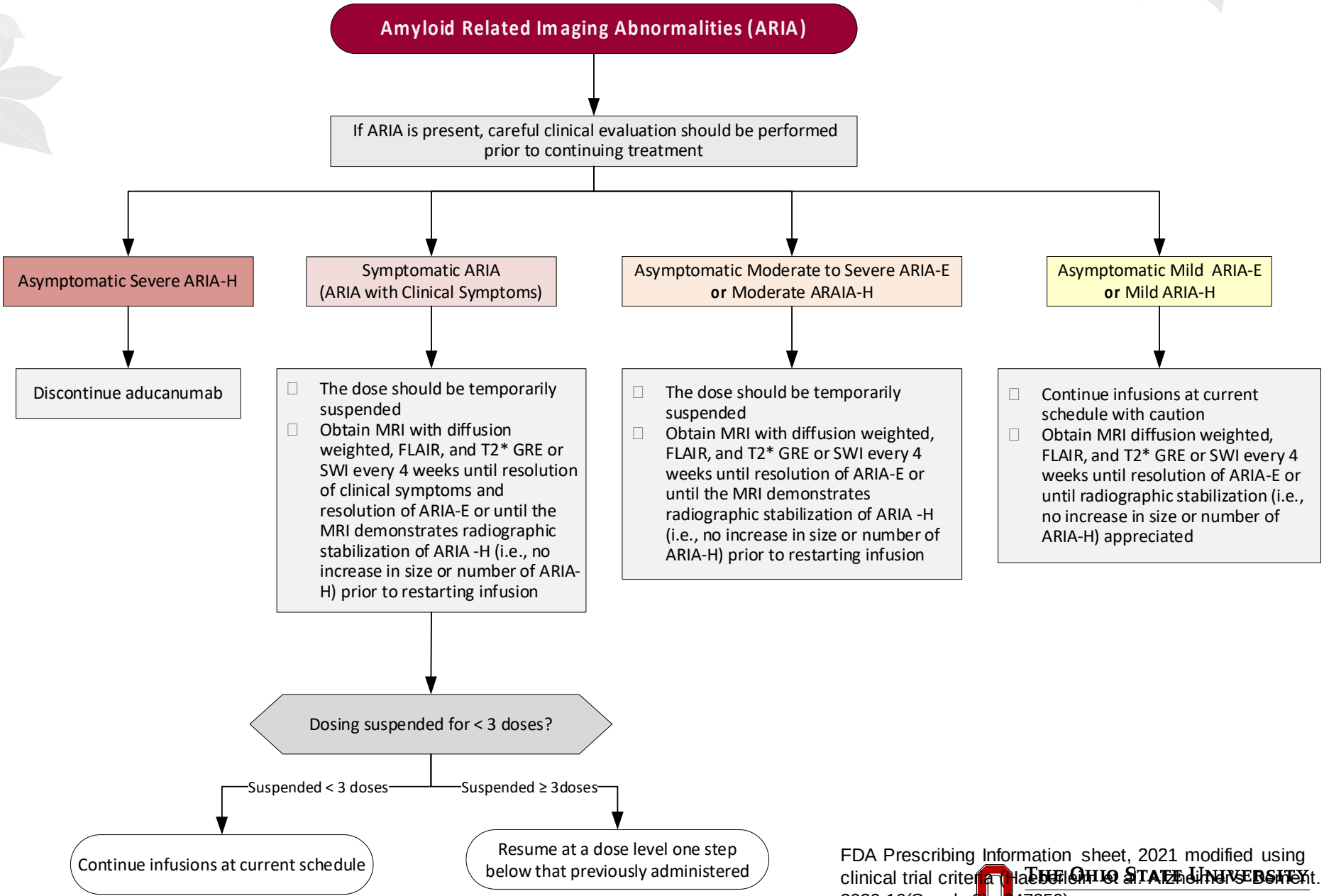


ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

FDA Prescribing Information sheet, 2021

ARIA findings and infusion holding or discontinuation



FDA Prescribing Information sheet, 2021 modified using clinical trial criteria (Haeberlein et al. Alzheimer's Dement. 2020;16(Suppl. 9):e047259)

Current Approved Treatments for DLB

- Rivastigmine approved for PDD by FDA
- Donepezil approved for DLB in Japan
- Memantine not approved; a few studies with trends
- Hints that cholinesterase inhibitors and memantine may have disease modifying characteristics

Promising Treatments for DLB: Neflamapimod

- Neflamapimod: a small molecule inhibits mitogen-activated serine/theronine protein kinase (p38 MAPK alpha)
- 2020 Positive (improved cognitive composite) phase 2 trial for mild to moderate DLB
- Intra-cellular enzyme p38 MAPK alpha stimulates pro-inflammatory cytokines by microglia producing inflammation-induced synaptic toxicity

Center for Cognitive and Memory Disorders – Trials

- Novel therapeutic medication trials for Mild Cognitive Impairment (MCI) progressing to AD
  - Monoclonal antibody against amyloid
  - Monoclonal antibody against tau (does not enter cells)
  - Transdermal nicotine for patients with MCI
  - Treating Glutamate dysfunction in Alzheimer's disease
  - Treatment trials to improve synaptic density and health
  - Anti-inflammatory agents to treat AD
  - Varoglutamstat to reduce N3pE, a toxic form of the amyloid protein activating inflammation
  - CT1812 to target and displace amyloid oligomers bound to neuronal receptors

Center for Cognitive and Memory Disorders – Trials

- Innovative therapeutic device clinical trials for AD:
  - Deep Brain Stimulation – Neuropacemaker inserted into the frontal lobes on both sides to improve cognitive, behavioral, and functional impairments in AD subjects
  - Low intensity focused ultrasound – temporary breakdown of blood brain barrier designed to remove amyloid from the brain: active study
  - BDNF (brain derived neurotrophic factor) gene therapy phase I, first in human clinical trial AAV2 vector-mediated delivery to entorhinal cortex for MCI due to AD or mild AD dementia

Center for Cognitive and Memory Disorders – Trials

- Discovering new treatments for the behavioral disturbances in dementia:
  - Escitalopram for agitation
  - Dextromethorphan/quinidine for the treatment of agitation in patients with AD
  - CVL-871 is a dopamine D1 receptor partial agonist for the treatment dementia related apathy

Center for Cognitive and Memory Disorders – Trials

- Discover, standardize, and validate biomarkers for AD treatment trials:
  - ADNI4
  - Banking serum and cerebrospinal fluid for future studies in patients with dementia with Lewy bodies, vascular dementia, frontotemporal dementia, MCI, and Alzheimer's disease
- Trial-ready cohort for preclinical/prodromal Alzheimer's disease:
  - Global Alzheimer's Platform
  - ICARES for aducanumab
- Pre-clinical trial to prevent AD using BAN2401 amyloid monoclonal antibody treatment

Future Rx Strategies

- Anti-amyloid strategies
- Tau interventions
- Anti-inflammatory strategies
- Combined drug treatments
- Gene therapy

OSU Memory Disorders Research Center
Fitting the Pieces Together

OSU Memory Disorders Research Center

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