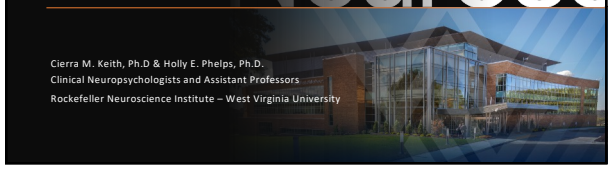
Rockefe
Neurosc

Neuropsychology
in the Era of Biomarkers and
Monoclonal Antibody Treatment



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Clinical Neuropsychologists and Assistant Professors
Rockefeller Neuroscience Institute – West Virginia University

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Primary Objectives:

1. Provide a brief review of the recent literature on biomarkers and monoclonal antibody treatment for AD.
1. Discuss the role and contributions of neuropsychology in determining candidacy for monoclonal antibody treatment as well as the importance of a multidisciplinary approach more broadly.
1. Discuss the limitations regarding issues of access, as well as other potential barriers impacting diverse groups.

2

Disclosures:

None

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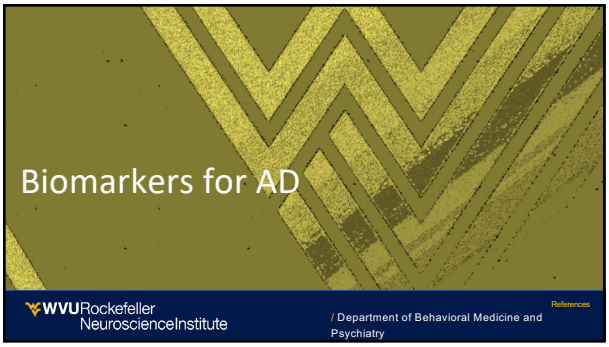
Biomarkers for AD
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/ Department of Behavioral Medicine and Psychiatry
References

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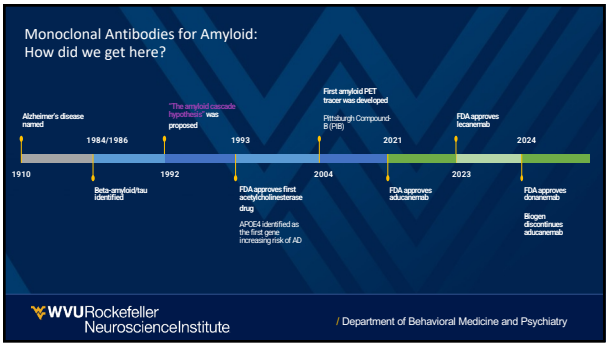
Monoclonal Antibodies for Amyloid:
How did we get here?
Alzheimer's disease named
1910
1984/1986
Beta-amyloid/tau identified
"The amyloid cascade hypothesis" was proposed
1992
1993
FDA approves first acetylcholinesterase drug
APOE4 identified as the first gene increasing risk of AD
First amyloid PET tracer was developed
Pittsburgh Compound-B (PiB)
2004
2021
FDA approves aducanemab
FDA approves lecanemab
2023
2024
FDA approves donanemab
Biogen discontinues aducanemab
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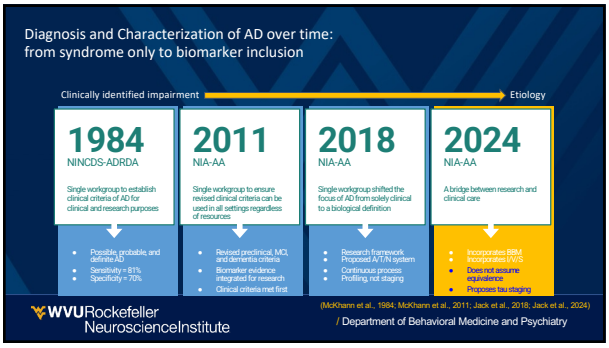
Diagnosis and Characterization of AD over time:
from syndrome only to biomarker inclusion
Clinically identified impairment
Etiology
1984
NINCDS-ADRDA
Single workgroup to establish clinical criteria of AD for clinical and research purposes
Possible, probable, and definite AD
Sensitivity = 81%
Specificity = 70%
2011
NIA-AA
Single workgroup to ensure revised clinical criteria can be used in all settings regardless of resources
Revised preclinical, MCI, and dementia criteria
Biomarker evidence integrated for research
Clinical criteria met first
2018
NIA-AA
Single workgroup shifted the focus of AD from solely clinical to a biological definition
Research framework
Proposed A/T/N system
Continuous process
Profiling, not staging
2024
NIA-AA
A bridge between research and clinical care
Incorporates BBM
Incorporates LEWS
Does not assume equivalence
Proposes tau staging
(McKhann et al., 1984; McKhann et al., 2011; Jack et al., 2018; Jack et al., 2024)
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Diagnosis of Alzheimer's Disease Involving Biomarkers

Fundamentals: *Defined by biology*

- AD is defined by its unique neuropathologic findings.
- AD exists on a continuum.
- AD is biomarker-based.
- Clinical presentation alone is not diagnostic of AD.

- Detection of ADNPC by biomarkers is equivalent to diagnosing the disease.
- Possible to detect disease-specific biomarkers in-vivo, even if asymptomatic.
- Symptoms are a result of the disease process.
- Clinical syndromes commonly seen in AD may be caused by other disorders.

(Jack et al., 2024)

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We have shifted our thinking of AD to a disease defined by biology rather than symptomatology, in order to modify the biological mechanisms, and hopefully the process of the disease itself.

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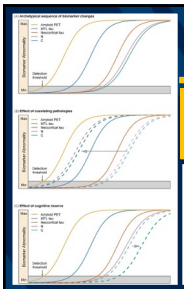
Temporal progression of AD biomarkers



	Cognitive Stage		
AT(N) profiles	Cognitively Unimpaired	MCI	Dementia
A-T-(N)-	Normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
A+T-(N)-	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
A+T+(N)- A+T-(N)+	Preclinical Alzheimer's disease	Alzheimer's disease with MCI	Alzheimer's disease with dementia
A+T+(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
A-T+(N)- A-T-(N)+ A-T+(N)+	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment.

Copathologies complicate the process

A-T+ individuals are not considered to be on the AD continuum (corresponds to PART)**

(Andersen et al., 2021; Jack et al., 2024)

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Measuring Amyloid Biomarkers:
Neuroimaging, CSF, and BBM

"Different biochemical pools of the same proteinopathy pathway"

		Method	Target	Notes
1	Neuroimaging	a-PET	Aβ	• **Gold standard** • Radioactive tracers measuring insoluble Aβ in plaques • **Clinical use:** florbetapir (2012), flutemetamol (2013), and florbetaben (2014) – 110 min half lives • **Research:** Pittsburgh Compound B (2004) – 20 min HL
2	Cerebrospinal fluid	Lumbar puncture	Aβ42 p-tau 217 p-tau 181 p-tau 231	• Fluid Aβ42-based assays may be abnormal slightly before a-PET, but typically highly concordant • These p-tau's have been proposed as biomarkers of Aβ42 due to time of onset, abnormal before tau-PET • Includes ratios: p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40
3	Blood-based biomarkers	Plasma draw	p-tau 217	• Includes ratios: % p-tau 217 • Assays can be highly variable in performance • Currently not FDA-approved as a stand-alone measure • Should be used in conjunction with follow-up tests • For approval, ideally should be equivalent to CSF

(Jack et al., 2024; Lai et al., 2024; Schindler et al., 2024)

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Sensitivity of the test ⟷ **Ability to rule OUT disease (if the test is negative)**

Specificity of the test ⟷ **Ability to rule IN disease (if the test is positive)**

Quick review…

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Measuring Amyloid Biomarkers:
Amyloid PET scan

Differentiating AD from normal controls	Sensitivity = 0.91 Specificity = 0.81
Diff. MCI from AD	Specificity = 0.49
Predicting conversion from MCI to AD	Sensitivity = 0.84 Specificity = 0.62
Visual inspections are the current standard in clinical practice	SUVr and Centiloid values used more in research; Not Aβ42 specific

Not good at distinguishing or predicting severity of CI

6%-16.5% of MCI patients convert to AD each year
Up to 20% of CU OA (>60 y/o) are A-positive

(Chapleau et al., 2022; Rodrigue et al., 2012; Ruan & Sun, 2022)

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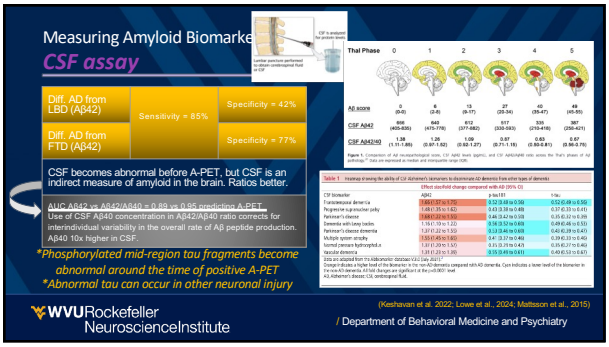
Measuring Amyloid Biomarke
CSF assay
Diff. AD from LBD (Aβ42)
Sensitivity = 85%
Specificity = 42%
Diff. AD from FTD (Aβ42)
Specificity = 77%
CSF becomes abnormal before A-PET, but CSF is an indirect measure of amyloid in the brain. Ratios better.
AUC Aβ42 vs Aβ42/Aβ40 = 0.88 vs 0.95 predicting A-PET
Use of CSF Aβ40 concentration in Aβ42/Aβ40 ratio corrects for interindividual variability in the overall rate of Aβ peptide production. Aβ40 10x higher in CSF.
*Phosphorylated mid-region tau fragments become abnormal around the time of positive A-PET
*Abnormal tau can occur in other neuronal injury
Thal Phase
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(Keshavan et al. 2022; Lowe et al., 2024; Mattsson et al., 2015)
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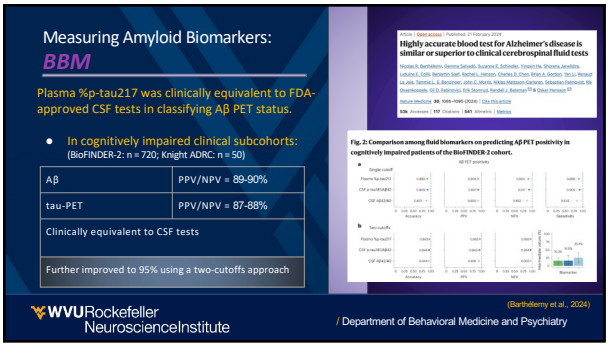
Measuring Amyloid Biomarkers:
BBM
Plasma %p-tau217 was clinically equivalent to FDA-approved CSF tests in classifying Aβ PET status.
In cognitively impaired clinical subcohorts:
(BioFINDER-2: n = 720; Knight ADRC: n = 50)
Aβ
PPV/NPV = 89-90%
tau-PET
PPV/NPV = 87-88%
Clinically equivalent to CSF tests
Further improved to 95% using a two-cutoffs approach
Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests
Fig. 2: Comparison among fluid biomarkers on predicting Aβ PET positivity in cognitively impaired patients of the BioFINDER-2 cohort.
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(Barthelemy et al., 2024)
/ Department of Behavioral Medicine and Psychiatry

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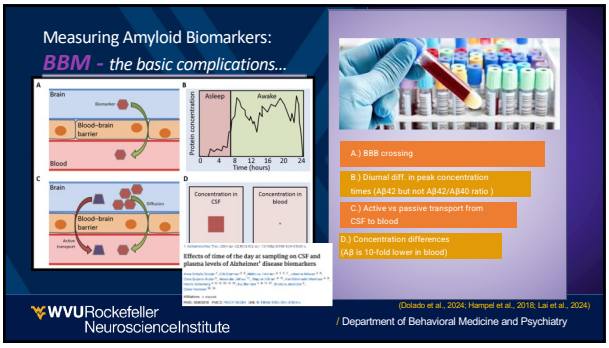
Measuring Amyloid Biomarkers:
BBM - the basic complications...
Brain
Blood-brain barrier
Blood
Asleep
Awake
Protein concentration
Time (hours)
Concentration in CSF
Concentration in blood
Effects of time of the day at sampling on CSF and plasma levels of Alzheimers' disease biomarkers
A.) BBB crossing
B.) Diurnal diff. in peak concentration times (Aβ42 but not Aβ42/Aβ40 ratio)
C.) Active vs passive transport from CSF to blood
D.) Concentration differences (Aβ is 10-fold lower in blood)
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(Dolado et al., 2024; Hampel et al., 2018; Lai et al., 2024)
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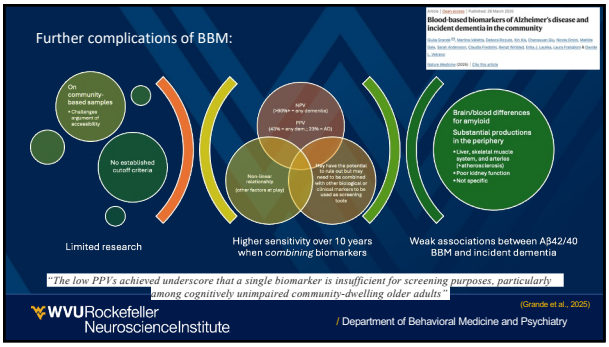

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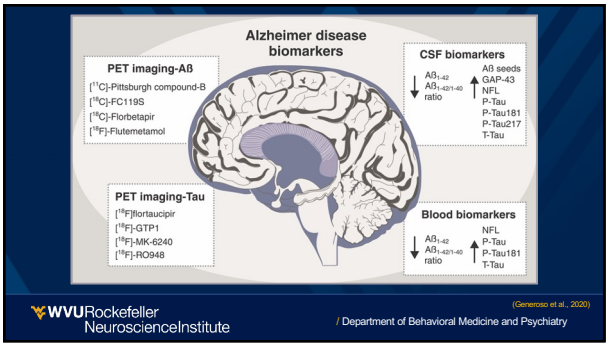

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Why not just give everyone an amyloid PET scan and call it a day?

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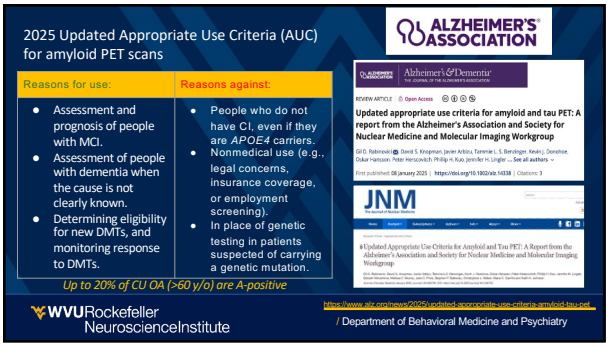
2025 Updated Appropriate Use Criteria (AUC) for amyloid PET scans
ALZHEIMER'S ASSOCIATION
Reasons for use:
Assessment and prognosis of people with MCI.
Assessment of people with dementia when the cause is not clearly known.
Determining eligibility for new DMTs, and monitoring response to DMTs.
Reasons against:
People who do not have CI, even if they are APOE4 carriers.
Nonmedical use (e.g., legal concerns, insurance coverage, or employment screening).
In place of genetic testing in patients suspected of carrying a genetic mutation.
Up to 20% of CU OA (>60 y/o) are A-positive
Updated appropriate use criteria for amyloid and tau PET: A report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup
JNM
Updated Appropriate Use Criteria for Amyloid and Tau PET: A Report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup
https://www.alz.org/news/2025/updated-appropriate-use-criteria-amyloid-tau-pet
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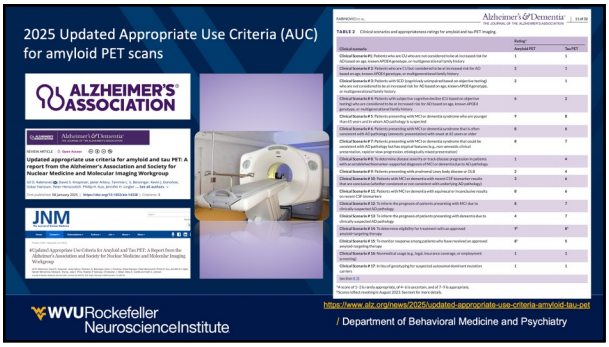
2025 Updated Appropriate Use Criteria (AUC) for amyloid PET scans
ALZHEIMER'S ASSOCIATION
Updated appropriate use criteria for amyloid and tau PET: A report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup
JNM
https://www.alz.org/news/2025/updated-appropriate-use-criteria-amyloid-tau-pet
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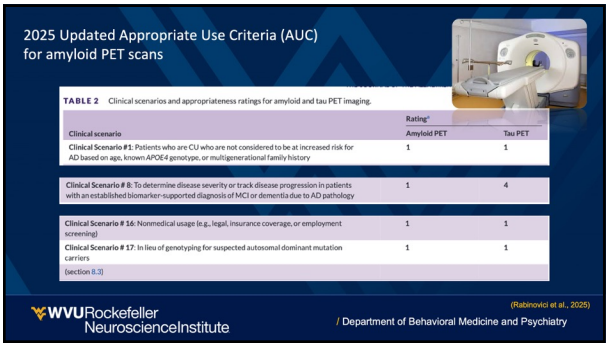
2025 Updated Appropriate Use Criteria (AUC) for amyloid PET scans
TABLE 2 Clinical scenarios and appropriateness ratings for amyloid and tau PET imaging.
Clinical scenario
Rating
Amyloid PET
Tau PET
Clinical Scenario #1: Patients who are CU who are not considered to be at increased risk for AD based on age, known APOE4 genotype, or multigenerational family history
1
1
Clinical Scenario # 8: To determine disease severity or track disease progression in patients with an established biomarker-supported diagnosis of MCI or dementia due to AD pathology
1
4
Clinical Scenario # 16: Nonmedical usage (e.g., legal, insurance coverage, or employment screening)
1
1
Clinical Scenario # 17: In lieu of genotyping for suspected autosomal dominant mutation carriers
1
1
(section 8.3)
(Rabinovici et al., 2025)
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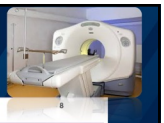
2025 Updated Appropriate Use Criteria (AUC) for amyloid PET scans



Clinical Scenario # 5: Patients presenting with MCI or dementia syndrome who are younger than 65 years and in whom AD pathology is suspected	9	8
Clinical Scenario # 6: Patients presenting with MCI or dementia syndrome that is often consistent with AD pathology (amnestic presentation) with onset at 65 years or older	8	6
Clinical Scenario # 7: Patients presenting with MCI or dementia syndrome that could be consistent with AD pathology but has atypical features (e.g., non-amnestic clinical presentation, rapid or slow progression, etiologically mixed presentation)	8	7
Clinical Scenario # 11: Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers	8	6
Clinical Scenario # 12: To inform the prognosis of patients presenting with MCI due to clinically suspected AD pathology	8	7
Clinical Scenario # 14: To determine eligibility for treatment with an approved amyloid-targeting therapy	9[a]	8[b]
Clinical Scenario # 15: To monitor response among patients who have received an approved amyloid-targeting therapy	8[b]	5

(Rabinovici et al., 2025)

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Putting it all together

Clinical Scenario # 5: Patients presenting with MCI or dementia syndrome who are younger than 65 years and in whom AD pathology is suspected	9	
Clinical Scenario # 6: Patients presenting with MCI or dementia syndrome that is often consistent with AD pathology (amnestic presentation) with onset at 65 years or older	8	
Clinical Scenario # 7: Patients presenting with MCI or dementia syndrome that could be consistent with AD pathology but has atypical features (e.g., non-amnestic clinical presentation, rapid or slow progression, etiologically mixed presentation)	8	
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Clinical Scenario # 14: To determine eligibility for treatment with an approved amyloid-targeting therapy	9[a]	
Clinical Scenario # 15: To monitor response among patients who have received an approved amyloid-targeting therapy	8[b]	

57 y/o male seeking evaluation for subtle cognitive changes in the context of a family history of AD.

- Neuropsych revealed subtle difficulties with aspects of executive functioning (e.g., organization of complex visual material, verbal fluency, and subtle signs on NBE), and difficulties with visual judgment. Performances otherwise were WNL, and memory performances were strong.
- Dx: Mild NCD

(Rabinovici et al., 2025)

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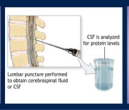
Putting it all together

"Different biochemical pools of the same proteinopathy pathway"

p-Tau/Abeta42 ratio **BELOW** the cutoff (≤ 0.028)

≤ 0.028 has a 92% NPA with normal amyloid PET

> 0.028 has a 92% PPA with abnormal amyloid PET



(2024) ALZHEIMER'S DISEASE EVALUATION, SPINAL FLUID

Status: Final result

Dx: Research study patient

Test Result Released: Yes (not seen)

0 Result Notes

Component Ref Range & Units (hover)	3 mo ago
p-Tau/Abeta42	0.009
AD INTERPRETATION	SEE COMMENTS

Comment: The normal p-Tau/Abeta42 ratio is not consistent with the presence of pathological changes associated with Alzheimer's disease.

The p-Tau/Abeta42 ratio provides better concordance with amyloid Positron Emission Tomography (PET) imaging when compared to Abeta42, phospho-Tau and total-Tau individually. A cut-off of 0.028 provides optimal balance between negative % agreement (NPA) and positive % agreement (PPA) when compared to amyloid PET results. A p-Tau/Abeta42 ratio of < or =0.028 has a 92% NPA with normal amyloid PET. A ratio of >0.028 has a 92% PPA with abnormal amyloid PET.

(Rabinovici et al., 2025)

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Putting it all together
Abeta42 analyte ABOVE the cutoff (> 834)
AUC Aβ42 vs Aβ42/Aβ40 = 0.89 vs 0.95 predicting A-PET
Use of CSF Aβ40 concentration in Aβ42/Aβ40 ratio corrects for interindividual variability in the overall rate of Aβ peptide production.
CSF is analyzed for protein levels
Lumbar puncture performed to obtain cerebrospinal fluid or CSF
ABETA42
1609
Comment:
----------ADDITIONAL INFORMATION----------
The testing method is an electrochemiluminescence assay manufactured by Roche Diagnostics Inc.
Effective May 31, 2023, a formulation change was implemented in the Roche Elecsys Abeta42 reagent (Generation I to Generation II). The Elecsys β-Amyloid (1-42) CSF II assay was restandardized using certified reference materials (CRMs) (RM-DA480/-481/-482/IFCC. Internal studies indicate a reduction in measured Abeta42 concentration (an approximate 19% decrease at the reference value) under specified assay collection conditions when using the new reagent formulation. Accordingly, the reference value has been changed from >1026 pg/mL (Gen I) to >834 pg/mL (Gen II).
Values obtained with different assay methods or kits may be different and cannot be used interchangeably.
Review | Open access | Published: 22 April 2019
Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease
Oskar Hansson, Sylvain Lehmann, Markus Otto, Henrik Zetterberg & Piotr Lewczuk
Alzheimer's Research & Therapy 11, Article number: 34 (2019) | Cite this article
44k Accesses | 357 Citations | 30 Altmetric | Metrics
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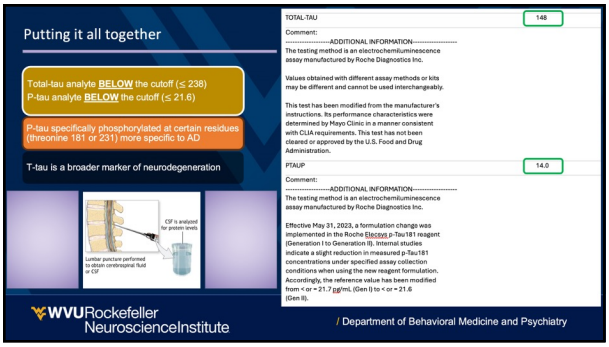
Putting it all together
Total-tau analyte BELOW the cutoff (≤ 238)
P-tau analyte BELOW the cutoff (≤ 21.6)
P-tau specifically phosphorylated at certain residues (threonine 181 or 231) more specific to AD
T-tau is a broader marker of neurodegeneration
CSF is analyzed for protein levels
Lumbar puncture performed to obtain cerebrospinal fluid or CSF
TOTAL-TAU
148
Comment:
----------ADDITIONAL INFORMATION----------
The testing method is an electrochemiluminescence assay manufactured by Roche Diagnostics Inc.
Values obtained with different assay methods or kits may be different and cannot be used interchangeably.
This test has been modified from the manufacturer's instructions. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.
PTAUP
14.0
Comment:
----------ADDITIONAL INFORMATION----------
The testing method is an electrochemiluminescence assay manufactured by Roche Diagnostics Inc.
Effective May 31, 2023, a formulation change was implemented in the Roche Elecsys p-Tau181 reagent (Generation I to Generation II). Internal studies indicate a slight reduction in measured p-Tau181 concentrations under specified assay collection conditions when using the new reagent formulation. Accordingly, the reference value has been modified from < or ~ 21.7 pg/mL (Gen I) to < or ~ 21.6 (Gen II).
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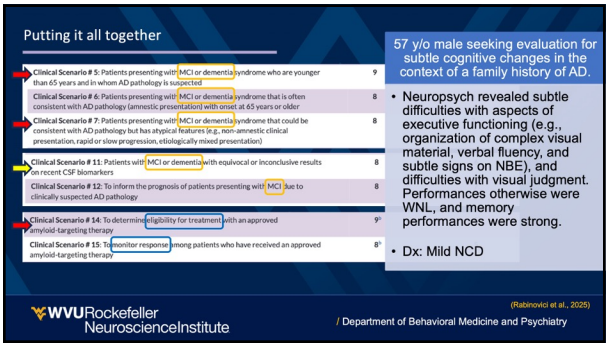
Putting it all together
Clinical Scenario # 5: Patients presenting with MCI or dementia syndrome who are younger than 65 years and in whom AD pathology is suspected 9
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Clinical Scenario # 11: Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers 8
Clinical Scenario # 12: To inform the prognosis of patients presenting with MCI due to clinically suspected AD pathology 8
Clinical Scenario # 14: To determine eligibility for treatment with an approved amyloid-targeting therapy 9b
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57 y/o male seeking evaluation for subtle cognitive changes in the context of a family history of AD.
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(Rabinovici et al., 2025)
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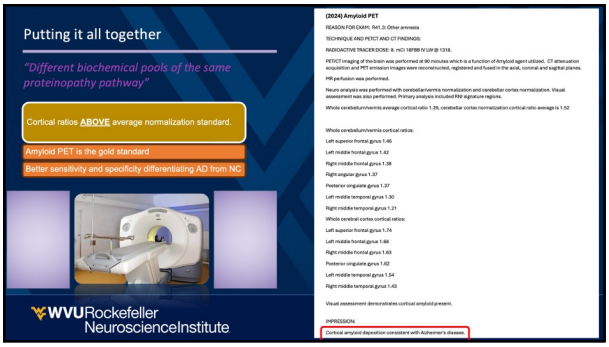
Putting it all together
"Different biochemical pools of the same proteinopathy pathway"
Cortical ratios ABOVE average normalization standard.
Amyloid PET is the gold standard
Better sensitivity and specificity differentiating AD from NC
(2024) Amyloid PET
REASON FOR EXAM: Pet 2i Other amnesia
TECHNIQUE AND PETCT AND CT FINDINGS:
RADIOACTIVE TRACER DOSE: 8. mCi 18FBB IV LIV @ 1316.
PET/CT imaging of the brain was performed at 90 minutes which is a function of Amyloid agent utilized. CT attenuation acquisition and PET emission images were reconstructed, registered and fused in the axial, coronal and sagittal planes.
MR perfusion was performed.
Neuro analysis was performed with cerebellar/vermis normalization and cerebellar cortex normalization. Visual assessment was also performed. Primary analysis included FAV signature regions.
Whole cerebellum/vermis average cortical ratio 1.28, cerebellar cortex normalization cortical ratio average is 1.52
Whole cerebellum/vermis cortical ratios:
Left superior frontal gyrus 1.46
Left middle frontal gyrus 1.42
Right middle frontal gyrus 1.38
Right angular gyrus 1.37
Posterior cingulate gyrus 1.37
Left middle temporal gyrus 1.30
Right middle temporal gyrus 1.21
Whole cerebral cortex cortical ratios:
Left superior frontal gyrus 1.74
Left middle frontal gyrus 1.66
Right middle frontal gyrus 1.63
Posterior cingulate gyrus 1.62
Left middle temporal gyrus 1.54
Right middle temporal gyrus 1.43
Visual assessment demonstrates cortical amyloid present.
IMPRESSION:
Cortical amyloid deposition consistent with Alzheimer's disease.
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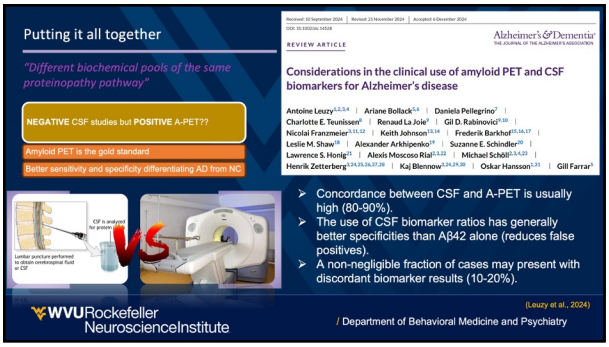
Putting it all together
"Different biochemical pools of the same proteinopathy pathway"
NEGATIVE CSF studies but POSITIVE A-PET??
Amyloid PET is the gold standard
Better sensitivity and specificity differentiating AD from NC
Alzheimer's & Dementia
REVIEW ARTICLE
Considerations in the clinical use of amyloid PET and CSF biomarkers for Alzheimer's disease
Antoine Leuzy | Ariane Bollack | Daniela Pellegrino | Charlotte E. Teunissen | Renaud La Joie | Gil D. Rabinovici | Nicolai Franzmeier | Keith Johnson | Frederik Barkhof | Leslie M. Shaw | Alexander Arkhipenko | Suzanne E. Schindler | Lawrence S. Honig | Alexis Moscoso Rial | Michael Schöll | Henrik Zetterberg | Kaj Blennow | Oskar Hansson | Gill Farrar
Lumbar puncture performed to obtain cerebrospinal fluid or CSF
CSF is analyzed for protein ratio
VS
Concordance between CSF and A-PET is usually high (80-90%).
The use of CSF biomarker ratios has generally better specificities than Aβ42 alone (reduces false positives).
A non-negligible fraction of cases may present with discordant biomarker results (10-20%).
(Leuzy et al., 2024)
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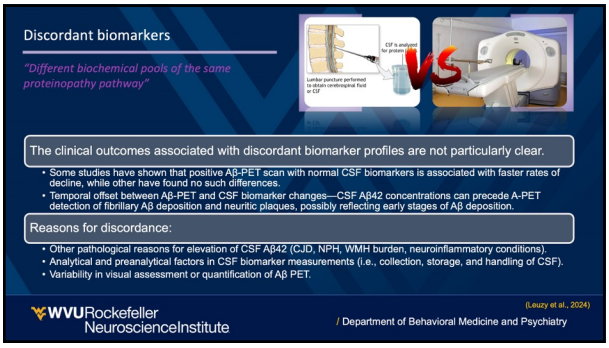
Discordant biomarkers
"Different biochemical pools of the same proteinopathy pathway"
Lumbar puncture performed to obtain cerebrospinal fluid or CSF
CSF is analyzed for protein ratio
VS
The clinical outcomes associated with discordant biomarker profiles are not particularly clear.
Some studies have shown that positive Aβ-PET scan with normal CSF biomarkers is associated with faster rates of decline, while other have found no such differences.
Temporal offset between Aβ-PET and CSF biomarker changes—CSF Aβ42 concentrations can precede A-PET detection of fibrillary Aβ deposition and neuritic plaques, possibly reflecting early stages of Aβ deposition.
Reasons for discordance:
Other pathological reasons for elevation of CSF Aβ42 (CJD, NPH, WMH burden, neuroinflammatory conditions).
Analytical and preanalytical factors in CSF biomarker measurements (i.e., collection, storage, and handling of CSF).
Variability in visual assessment or quantification of Aβ PET.
(Leuzy et al., 2024)
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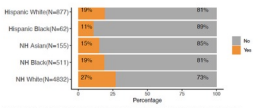
A point about biomarkers in diverse populations

- Most early iteration of research studies include a large proportion of white individuals.
- Blood biomarker screening for AD trials detects lower rates of brain amyloid among Hispanic and black people (TRAILBLAZER-ALZ2 &3, AHEAD 3-45, and New IDEAS studies).
- Sociocultural and environmental factors possibly lead to more occurrences of non-AD dementia in diverse populations.



Plasma Eligible? *Measured by the same blood test, different ethnic and racial groups had different rates of amyloid positivity (orange, eligible; grey, ineligible). (Courtesy of Doris Molina-Henry, University of Southern California, San Diego.)*

(Molina-Henry et al., 2024; https://www.alzforum.org/news/research-news/biomarkers-suggest-black-and-hispanic-people-less-likely-have-amyloid#interga

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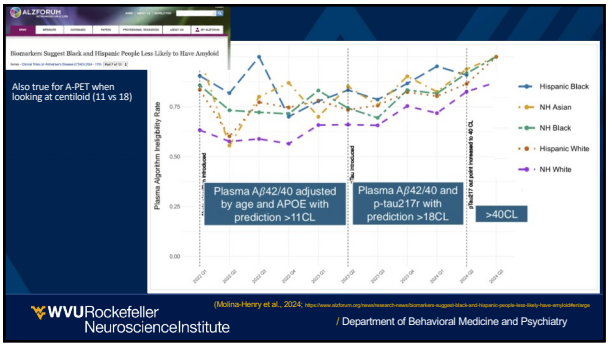

(Molina-Henry et al., 2024, https://www.alzforum.org/news/research-news/biomarkers-suggest-black-and-hispanic-people-less-likely-have-amyloid#interga

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Where does Neuropsychology find itself in the Era of Biomarkers?

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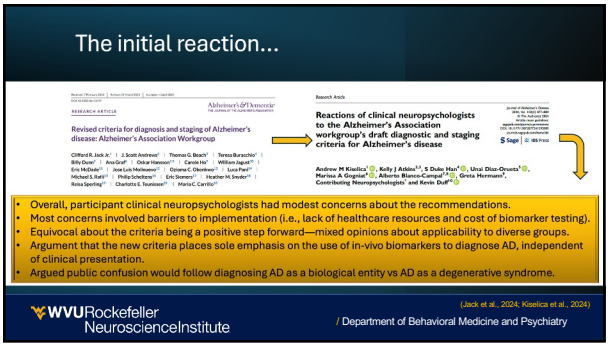
The initial reaction...
Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup
Reactions of clinical neuropsychologists to the Alzheimer's Association workgroup's draft diagnostic and staging criteria for Alzheimer's disease
• Overall, participant clinical neuropsychologists had modest concerns about the recommendations.
• Most concerns involved barriers to implementation (i.e., lack of healthcare resources and cost of biomarker testing).
• Equivocal about the criteria being a positive step forward—mixed opinions about applicability to diverse groups.
• Argument that the new criteria places sole emphasis on the use of in-vivo biomarkers to diagnose AD, independent of clinical presentation.
• Argued public confusion would follow diagnosing AD as a biological entity vs AD as a degenerative syndrome.
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(Jack et al., 2024; Kiselica et al., 2024)
/ Department of Behavioral Medicine and Psychiatry

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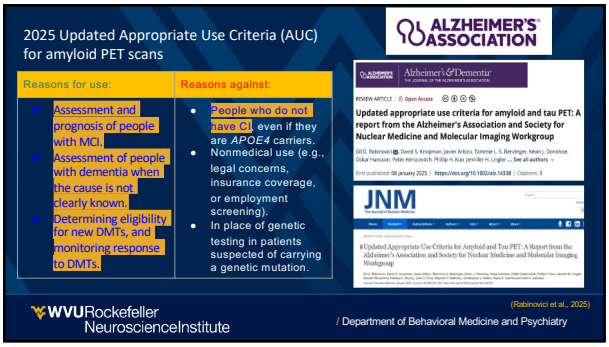
2025 Updated Appropriate Use Criteria (AUC) for amyloid PET scans
ALZHEIMER'S ASSOCIATION
Reasons for use:
• Assessment and prognosis of people with MCI.
• Assessment of people with dementia when the cause is not clearly known.
• Determining eligibility for new DMTs, and monitoring response to DMTs.
Reasons against:
• People who do not have CI even if they are APOE4 carriers.
• Nonmedical use (e.g., legal concerns, insurance coverage, or employment screening).
• In place of genetic testing in patients suspected of carrying a genetic mutation.
Updated appropriate use criteria for amyloid and tau PET: A report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup
JNM
Updated Appropriate Use Criteria for Amyloid and Tau PET: A Report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup
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(Rabinovici et al., 2025)
/ Department of Behavioral Medicine and Psychiatry

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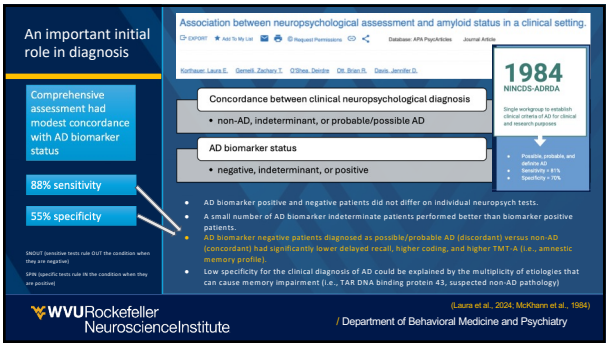
An important initial role in diagnosis
Comprehensive assessment had modest concordance with AD biomarker status
88% sensitivity
55% specificity
SNOUT (sensitive tests rule OUT the condition when they are negative)
SPIN (specific tests rule IN the condition when they are positive)
Association between neuropsychological assessment and amyloid status in a clinical setting.
Concordance between clinical neuropsychological diagnosis
• non-AD, indeterminant, or probable/possible AD
AD biomarker status
• negative, indeterminant, or positive
1984
NINCDS-ADRDA
Single workgroup to establish clinical criteria of AD for clinical and research purposes
• Possible, probable, and definite AD
• Sensitivity = 81%
• Specificity = 70%
• AD biomarker positive and negative patients did not differ on individual neuropsych tests.
• A small number of AD biomarker indeterminate patients performed better than biomarker positive patients.
• AD biomarker negative patients diagnosed as possible/probable AD (discordant) versus non-AD (concordant) had significantly lower delayed recall, higher coding, and higher TMT-A (i.e., amnestic memory profile).
• Low specificity for the clinical diagnosis of AD could be explained by the multiplicity of etiologies that can cause memory impairment (i.e., TAR DNA binding protein 43, suspected non-AD pathology)
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(Laura et al., 2024; McKhann et al., 1984)
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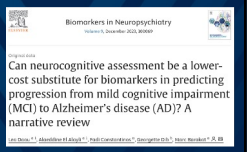
An important *ongoing* role in prognosis

- Biomarkers do not necessarily provide a better *predictive* accuracy and could lead to overdiagnosis (i.e., if stable)
- In this way, cognitive assessment seems to be a more cost-effective, less invasive, and easily accessible option.
- Benefit of measuring *functional* cognitive impairment.

{ Criteria: specific, sensitive, robust, simple, accurate, inexpensive, non-invasive, simple to perform, reliable, and reproducible }


Biomarkers in Neuropsychiatry

Can neurocognitive assessment be a lower-cost substitute for biomarkers in predicting progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD)? A narrative review

Other caveats:

Cognitive decline is non-linear	*Different subtypes of MCI*	*Normal variability on assessment*
Differences in methodologies such as follow-up times and repeated evals	*Homogenous and diverse populations make universal cutoff values challenging*	*Still no one perfect measure of predicting progression*

(Cui et al., 2011; Daou et al., 2023)

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Monoclonal Antibody Treatment for AD

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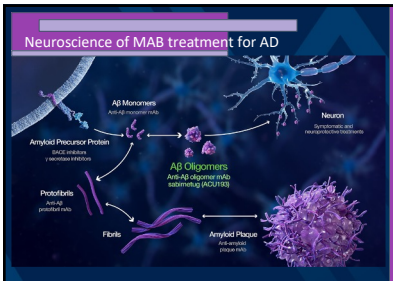
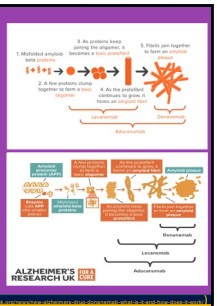
Neuroscience of MAB treatment for AD





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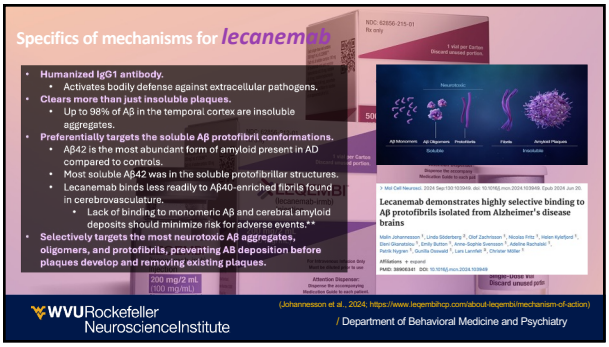
Specifics of mechanisms for lecanemab
Humanized IgG1 antibody.
Activates bodily defense against extracellular pathogens.
Clears more than just insoluble plaques.
Up to 98% of Aβ in the temporal cortex are insoluble aggregates.
Preferentially targets the soluble Aβ protofibril conformations.
Aβ42 is the most abundant form of amyloid present in AD compared to controls.
Most soluble Aβ42 was in the soluble protofibrillar structures.
Lecanemab binds less readily to Aβ40-enriched fibrils found in cerebrovasculature.
Lack of binding to monomeric Aβ and cerebral amyloid deposits should minimize risk for adverse events.**
Selectively targets the most neurotoxic Aβ aggregates, oligomers, and protofibrils, preventing AB deposition before plaques develop and removing existing plaques.
Lecanemab demonstrates highly selective binding to Aβ protofibrils isolated from Alzheimer's disease brains
(Johanneson et al., 2024; https://www.leqembihcp.com/about-leqembi/mechanism-of-action)
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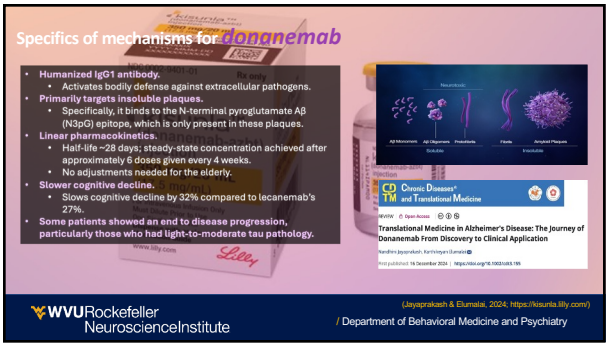
Specifics of mechanisms for donanemab
Humanized IgG1 antibody.
Activates bodily defense against extracellular pathogens.
Primarily targets insoluble plaques.
Specifically, it binds to the N-terminal pyroglutamate Aβ (N3pG) epitope, which is only present in these plaques.
Linear pharmacokinetics.
Half-life ~28 days; steady-state concentration achieved after approximately 6 doses given every 4 weeks.
No adjustments needed for the elderly.
Slower cognitive decline.
Slows cognitive decline by 32% compared to lecanemab's 27%.
Some patients showed an end to disease progression, particularly those who had light-to-moderate tau pathology.
Translational Medicine in Alzheimer's Disease: The Journey of Donanemab From Discovery to Clinical Application
(Jayaprakash & Elumalai, 2024; https://kisunla.lilly.com/)
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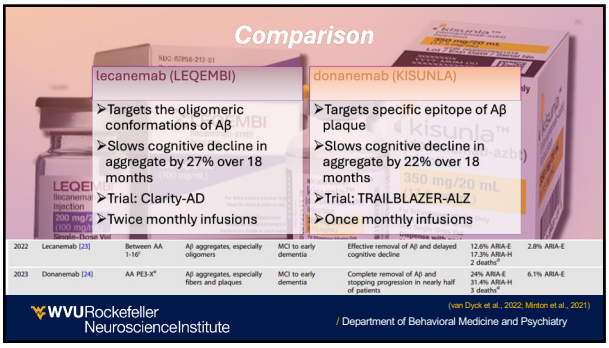
Comparison
lecanemab (LEQEMBI)
Targets the oligomeric conformations of Aβ
Slows cognitive decline in aggregate by 27% over 18 months
Trial: Clarity-AD
Twice monthly infusions
donanemab (KISUNLA)
Targets specific epitope of Aβ plaque
Slows cognitive decline in aggregate by 22% over 18 months
Trial: TRAILBLAZER-ALZ
Once monthly infusions
2022 Lecanemab [23] Between AA 1-16 Aβ aggregates, especially oligomers MCI to early dementia Effective removal of Aβ and delayed cognitive decline 12.6% ARIA-E 17.3% ARIA-H 2 deaths# 2.8% ARIA-E
2023 Donanemab [24] AA PE3-X# Aβ aggregates, especially fibers and plaques MCI to early dementia Complete removal of Aβ and stopping progression in nearly half of patients 24% ARIA-E 31.4% ARIA-H 3 deaths# 6.1% ARIA-E
(van Dyck et al., 2022; Minton et al., 2021)
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MAB Risks and Adverse Effects

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Infusion-related reactions (IRRs)

- More common after the first few infusions
- Flu-like symptoms such as vomiting, chills, fever, headache, rash, abdominal discomfort, etc.
- Most cases are mild and can be treated with acetaminophen, diphenhydramine, and sometimes steroids

Rate for lecanemab = 26.4% | Rate for donanemab = 8.7%

ALZHEIMER'S RESEARCH UK FOR A CURE

(Cummings et al., 2023; Rabinovici et al., 2025)

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Grading of infusion reactions [75,76].

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, acetaminophen, NSAIDs, narcotics, i.v. fluids); prophylactic medication indicated for ≤ 24 h	Prolonged recurrence of symptoms following initial improvement; hospitalization may be indicated for clinical sequelae (e.g., poorly controlled hypertension)	Life-threatening consequences; urgent intervention indicated (may require pressor or ventilatory support)	Death

Infusion-related reactions (IRRs)

Grade of severity


The Journal of Prevention of Alzheimer's Disease

Lecanemab: Appropriate Use Recommendations

The Journal of Prevention of Alzheimer's Disease

Donanemab: Appropriate use recommendations

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Amyloid-Related Imaging Abnormalities (ARIA)

ARIA-E

ARIA-H

- A spectrum of MRI findings associated with immunotherapies for AD
- Increased vascular permeability following an inflammatory response (leaky vessels)
- Risk is greatest earlier in treatment course

(Hampel et al., 2023)

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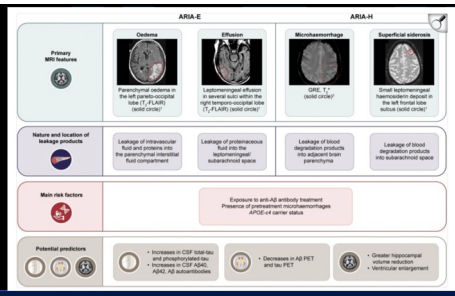

(Hampel et al., 2023)

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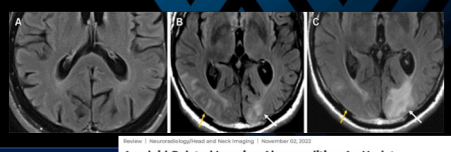
ARIA-E

- Increased signal that represents edema, effusion, or exudate without diffusion-restriction
- Most commonly affects occipital, followed by parietal, frontal, and temporal regions



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Amyloid-Related Imaging Abnormalities: An Update

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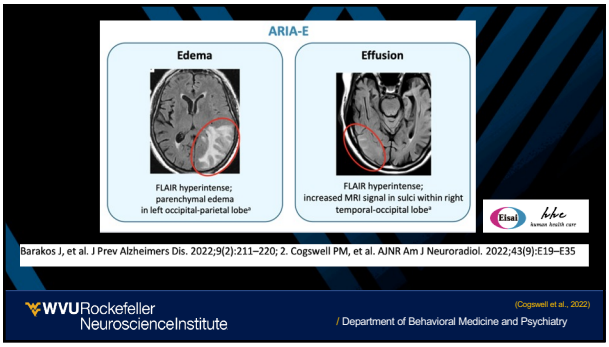
ARIA-E
Edema
Effusion
FLAIR hyperintense;
parenchymal edema
in left occipital-parietal lobe[a]
FLAIR hyperintense;
increased MRI signal in sulci within right
temporal-occipital lobe[a]
Barakos J, et al. J Prev Alzheimers Dis. 2022;9(2):211–220; 2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35
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(Cogswell et al., 2022)
/ Department of Behavioral Medicine and Psychiatry

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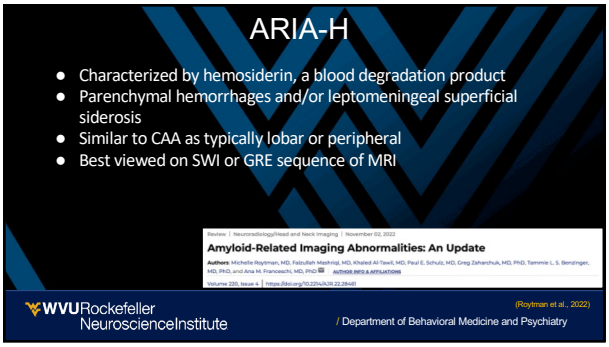
ARIA-H
Characterized by hemosiderin, a blood degradation product
Parenchymal hemorrhages and/or leptomeningeal superficial siderosis
Similar to CAA as typically lobar or peripheral
Best viewed on SWI or GRE sequence of MRI
Amyloid-Related Imaging Abnormalities: An Update
WVU Rockefeller NeuroscienceInstitute
(Roytman et al., 2022)
/ Department of Behavioral Medicine and Psychiatry

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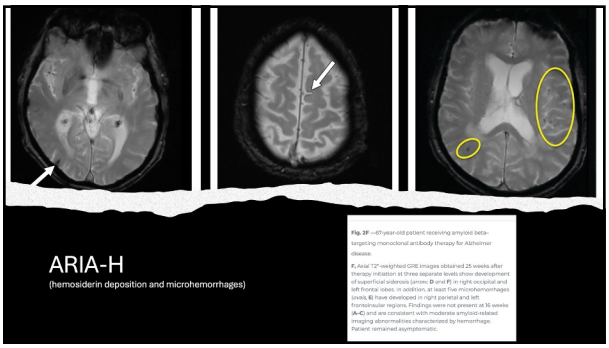
ARIA-H
(hemosiderin deposition and microhemorrhages)

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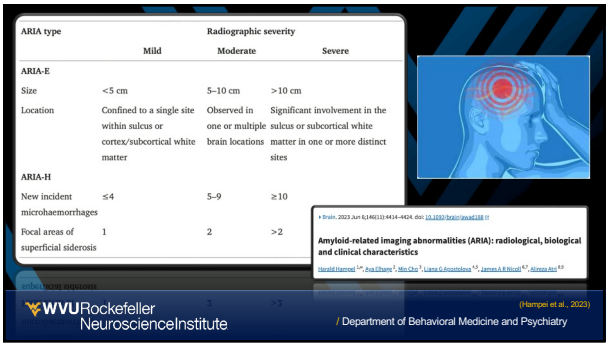
ARIA type
Radiographic severity
Mild
Moderate
Severe
ARIA-E
Size
<5 cm
5–10 cm
>10 cm
Location
Confined to a single site within sulcus or cortex/subcortical white matter
Observed in one or multiple brain locations
Significant involvement in the sulcus or subcortical white matter in one or more distinct sites
ARIA-H
New incident microhaemorrhages
≤4
5–9
≥10
Focal areas of superficial siderosis
1
2
>2
Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics
WVU Rockefeller NeuroscienceInstitute
(Hampel et al., 2023)
Department of Behavioral Medicine and Psychiatry

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When to alter MAB treatment
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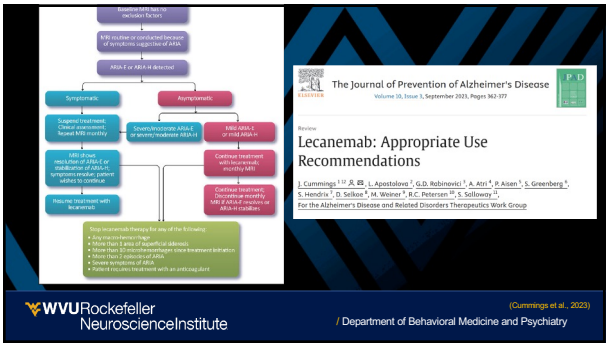
Symptomatic
Asymptomatic
The Journal of Prevention of Alzheimer's Disease
Review
Lecanemab: Appropriate Use Recommendations
For the Alzheimer's Disease and Related Disorders Therapeutics Work Group
WVU Rockefeller NeuroscienceInstitute
(Cummings et al., 2023)
Department of Behavioral Medicine and Psychiatry

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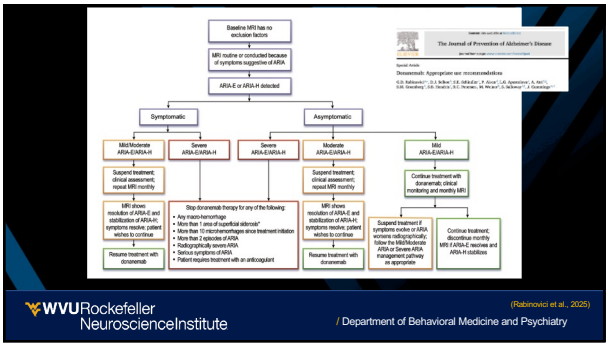
Baseline MRI has no exclusion factors
MRI routine or conducted because of symptoms suggestive of ARIA
ARIA-E or ARIA-H detected
Symptomatic
Asymptomatic
Mild/Moderate ARIA-E/ARIA-H
Severe ARIA-E/ARIA-H
Severe ARIA-E/ARIA-H
Moderate ARIA-E/ARIA-H
Mild ARIA-E/ARIA-H
Suspend treatment; clinical assessment; repeat MRI monthly
Suspend treatment; clinical assessment; repeat MRI monthly
Continue treatment with donanemab; clinical monitoring and monthly MRI
MRI shows resolution of ARIA-E and stabilization of ARIA-H; symptoms resolve; patient wishes to continue
Resume treatment with donanemab
Stop donanemab therapy for any of the following:
• Any macro-hemorrhage
• More than 1 area of superficial siderosis*
• More than 10 microhemorrhages since treatment initiation
• More than 2 episodes of ARIA
• Radiographically severe ARIA
• Serious symptoms of ARIA
• Patient requires treatment with an anticoagulant
MRI shows resolution of ARIA-E and stabilization of ARIA-H; symptoms resolve; patient wishes to continue
Resume treatment with donanemab
Suspend treatment if symptoms evolve or ARIA worsens radiographically; follow the Mild/Moderate ARIA or Severe ARIA management pathway as appropriate
Continue treatment; discontinue monthly MRI if ARIA-E resolves and ARIA-H stabilizes
The Journal of Prevention of Alzheimer's Disease
Donanemab: Appropriate use recommendations
WVU Rockefeller Neuroscience Institute
(Rabinovici et al., 2025)
/ Department of Behavioral Medicine and Psychiatry

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Commonalities in Stopping Treatment
Imaging-related
Any macro-hemorrhage
More than 1 area of superficial siderosis
More than 10 microhemorrhages since treatment initiation
More than 2 episodes of ARIA
Non-imaging-related
Severe symptoms of ARIA
ANTICOAGULANT
Patient requires treatment of an anticoagulant
WVU Rockefeller Neuroscience Institute
(Cummings et al., 2023; Rabinovici et al., 2025)
/ Department of Behavioral Medicine and Psychiatry

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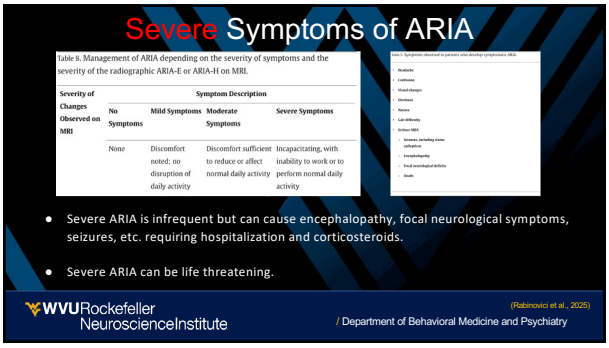
Severe Symptoms of ARIA
Table 8. Management of ARIA depending on the severity of symptoms and the severity of the radiographic ARIA-E or ARIA-H on MRI
Severity of Changes Observed on MRI
Symptom Description
No Symptoms
Mild Symptoms
Moderate Symptoms
Severe Symptoms
None
Discomfort noted; no disruption of daily activity
Discomfort sufficient to reduce or affect normal daily activity
Incapacitating, with inability to work or to perform normal daily activity
Table 5. Symptoms observed in patients who develop symptomatic ARIA
Headache
Confusion
Visual changes
Dizziness
Nausea
Gait difficulty
Serious ARIA
Seizures, including status epilepticus
Encephalopathy
Focal neurological deficits
Death
• Severe ARIA is infrequent but can cause encephalopathy, focal neurological symptoms, seizures, etc. requiring hospitalization and corticosteroids.
• Severe ARIA can be life threatening.
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(Rabinovici et al., 2025)
/ Department of Behavioral Medicine and Psychiatry

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lecanemab

Gene type	Risk of ARIA	Risk of symptomatic ARIA	Risk of severe ARIA
Two copies APOE 4	45%	9%	3%
One copy APOE 4	19%	2%	1%
No copies APOE 4	13%	1%	1%

donanemab

Gene type	Risk of ARIA	Risk of symptomatic ARIA	Risk of severe ARIA
Two copies APOE 4	55%	18%	3%
One copy APOE 4	36%	7%	2%
No copies APOE 4	25%	4%	1%

(Mintun et al., 2021; van Dyke et al., 2022)

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Who is eligible for MAB treatment?

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Lecanemab Eligibility

- **Inclusion:**
  - Diagnosis of MCI or mild dementia due to AD with positive biomarker for brain amyloid (amyloid PET or CSF)
  - MMSE 22-30 used in trial (though some nuance in clinic)
  - Has appropriate social support
  - Ability to undergo regular MRIs


The Journal of Prevention of Alzheimer's Disease

Lecanemab: Appropriate Use Recommendations

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Lecanemab Eligibility


The Journal of Prevention of Alzheimer's Disease

Lecanemab: Appropriate Use Recommendations

- **Exclusion:**
  - Cognitive impairment not primarily driven by AD
  - > 4 microhemorrhages or a single macrohemorrhage > 10mm
  - Superficial siderosis
  - Vasogenic edema
  - > 2 lacunar infarct or stroke in major vascular territory
  - Severe (Fazekas grade 3) white matter disease
  - CAA
  - Major vascular event or seizure within 12 months

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Lecanemab Eligibility


The Journal of Prevention of Alzheimer's Disease

Lecanemab: Appropriate Use Recommendations

- **Exclusion:**
  - Neuropsychiatric symptoms at a severity that might interfere with comprehension or adherence
  - Uncontrolled bleeding disorder
  - On anticoagulation (some physician discretion)
  - Current systemic treatment for immunological disease (physician discretion)
  - Other unstable medical conditions (e.g., cardiac disease, cancer, renal disease)

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Donanemab Eligibility

- **Inclusion:**
  - Diagnosis of MCI or mild dementia due to AD with positive biomarker for brain amyloid *(Clinical Stage 3 and 4 with positive Core 1 biomarker)*
    - *Not recommending use of blood-based biomarkers solely*
  - *MMSE 20-28* used in trial (though some nuance in clinic)
  - Has appropriate social support
  - Ability to undergo regular MRIs


Special Article

Donanemab: Appropriate use recommendations

G.D. Rabinovici, D.J. Selkoe, S.E. Schindler, P. Aisen, L.G. Apostolova, A. Atri, S.M. Greenberg, S.B. Hendrix, R.C. Petersen, M. Weiner, S. Salloway, J. Cummings

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Donanemab Eligibility

- **Exclusion:**
  - Cognitive impairment not primarily driven by AD
  - > 4 microhemorrhages or a single macrohemorrhage *> 1 cm*
  - *>1 area of superficial siderosis*
  - Vasogenic edema
  - > 2 lacunar infarct or stroke in major vascular territory
  - Severe (Fazekas grade 3) white matter disease
  - CAA
  - Major vascular event or seizure within 12 months

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Special Article

Donanemab: Appropriate use recommendations

G.D. Rabinovici[a,*], D.J. Selkoe[b], S.E. Schindler[c], P. Aisen[d], L.G. Apostolova[e], A. Atri[f,g], S.M. Greenberg[h], S.B. Hendrix[i], R.C. Petersen[j], M. Weiner[k], S. Salloway[l,1], J. Cummings[m,1]

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Donanemab Eligibility

- **Other imaging findings:**
  - Risk in patients with cerebral contusion, encephalomalacia, aneurysm and other vascular malformations, CNS infections, and brain tumors (except small meningioma or cyst) is unclear as these patient were excluded from clinical trials

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Special Article

Donanemab: Appropriate use recommendations

G.D. Rabinovici[a,*], D.J. Selkoe[b], S.E. Schindler[c], P. Aisen[d], L.G. Apostolova[e], A. Atri[f,g], S.M. Greenberg[h], S.B. Hendrix[i], R.C. Petersen[j], M. Weiner[k], S. Salloway[l,1], J. Cummings[m,1]

65

Donanemab Eligibility

- **Exclusion:**
  - Neuropsychiatric symptoms at a severity that might interfere with comprehension or adherence
  - Uncontrolled bleeding disorder
  - On anticoagulation (some physician discretion)
  - Current systemic treatment for immunological disease (physician discretion)
  - Other unstable medical conditions (e.g., cardiac disease, cancer, renal disease)
  - *Active SI or ongoing drug or alcohol use disorder*

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Special Article

Donanemab: Appropriate use recommendations

G.D. Rabinovici[a,*], D.J. Selkoe[b], S.E. Schindler[c], P. Aisen[d], L.G. Apostolova[e], A. Atri[f,g], S.M. Greenberg[h], S.B. Hendrix[i], R.C. Petersen[j], M. Weiner[k], S. Salloway[l,1], J. Cummings[m,1]

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Limitations in Applicability to Minorities

Characteristic	Lecanemab (N=859)	Placebo (N=875)
Age — yr	71.4±7.9	71.0±7.8
Sex — no. (%)		
Female	443 (51.6)	464 (53.0)
Male	416 (48.4)	411 (47.0)
Race — no. (%)†		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Other or missing	37 (4.3)	26 (3.0)
Hispanic ethnic group — no. (%)†	107 (12.5)	108 (12.3)

ORIGINAL ARTICLE

Lecanemab in Early Alzheimer's Disease

Authors: Christopher H. van Dyck, M.D., Chad J. Swanson, Ph.D., Paul Aisen, M.D., Randall J. Bateman, M.D., Christopher Chen, B.M., B.Ch., Michelle Gee, Ph.D., Michiro Kanekiyo, M.S., et al., and Takeshi Iwatsubo, M.D. Author Info & Affiliations

Published November 29, 2022 | N Engl J Med 2023;388:9-21 | DOI: 10.1056/NEJMoa2212948 | VOL. 388 NO. 1

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Limitations in Applicability to Minorities

Variable	Donanemab (N=131)	Placebo (N=126)	Total (N=272)†
Female sex — no. (%)	68 (51.9)	65 (51.6)	145 (53.3)
Age — yr	75.0±5.6	75.4±5.4	75.2±5.5
Race or ethnic group — no. (%)‡			
Asian	1 (0.8)	2 (1.6)	3 (1.1)
Black	5 (3.8)	3 (2.4)	8 (2.9)
White	122 (93.1)	121 (96.0)	258 (94.9)
Other	3 (2.3)	0	3 (1.1)
Hispanic ethnic group — no. (%)‡	5 (3.8)	3 (2.4)	9 (3.3)
Education ≥13 yr — no. (%)	97 (74.0)	102 (81.0)	209 (76.8)

ORIGINAL ARTICLE

Donanemab in Early Alzheimer's Disease

Authors: Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., et al., and Daniel M. Skovronsky, M.D., Ph.D. Author Info & Affiliations

Published March 13, 2021 | N Engl J Med 2021;384:1691-1704 | DOI: 10.1056/NEJMoa2100708 | VOL. 384 NO. 18

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Important Topics for Discussion

- Managing expectations
  - Monoclonal antibody therapy does not cure disease or reverse symptoms
  - Clinical trials show slowing of 20-30% over the course of 18 months
  - We are still learning what the anticipated benefits are beyond that time
- Risks
  - Possible side effects and why MUST complete MRIs as scheduled
  - Impact of individual APOE 4 status
- tPA in case of a stroke - risks vs benefits

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Neuropsychology's Role with MAB

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Table 11
Clinical resources required for the safe and effective use of donanemab.

- Clinician skilled in the assessment of cognition to identify individuals with mild cognitive impairment or mild dementia due to Alzheimer's disease
- MRI available for baseline assessment of cerebrovascular pathology and for monitoring of amyloid related imaging abnormalities (ARIA)
- Radiologists, neurologists, or other clinicians expert in the identification and interpretation of cerebrovascular lesions and ARIA
- Capability to perform amyloid positron emission tomography or lumbar puncture to determine the amyloid status of treatment candidates
- Radiologists, nuclear medicine specialists, neurologists, or other specialists skilled in the interpretation of amyloid imaging or CSF biomarker test results
- Expertise in counseling patients about the meaning and implications of APOE genotyping
- Expertise in communicating with patients and care partners regarding anticipated benefits, potential harm, and requirements for administration and monitoring while on donanemab.
- Infusion centers with availability for monthly infusion
- Knowledgeable staff at infusion sites capable of recognizing and managing infusion reactions
- Communication channels established between experts interpreting MRIs and clinicians treating patients with donanemab
- Communication channels established between clinicians treating patients with donanemab and the patient and care partner
- Availability of hospital resources including intensive care unit
- Expertise in the management of seizures and status epilepticus for patients with severe or serious ARIA
- Protocol with standard operating procedures for management of serious and severe ARIA

What can neuropsychologists bring to the table?

- Assessment
- Counseling on genotyping
- Counseling on MAB treatment
- Facilitating communication

(Rabinovici et al., 2025)

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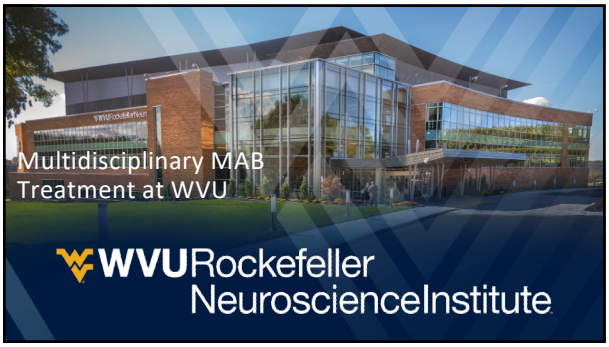

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WVU Multidisciplinary Memory Health Clinic
One-stop shop for workup for neurodegenerative conditions
Efficient and team-oriented approach for patients to undergo a workup for developing dementia conditions
Led by a neuropsychologist*
WestVirginiaUniversity.
WVURockefeller NeuroscienceInstitute
Department of Behavioral Medicine and Psychiatry

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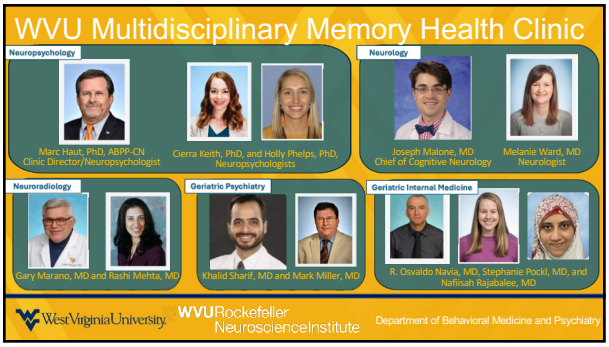
WVU Multidisciplinary Memory Health Clinic
Neuropsychology
Marc Haut, PhD, ABPP-CN
Clinic Director/Neuropsychologist
Cierra Keith, PhD, and Holly Phelps, PhD
Neuropsychologists
Neurology
Joseph Malone, MD
Chief of Cognitive Neurology
Melanie Ward, MD
Neurologist
Neuroradiology
Gary Marano, MD and Rashi Mehta, MD
Geriatric Psychiatry
Khalid Sharif, MD and Mark Miller, MD
Geriatric Internal Medicine
R. Osvaldo Navia, MD, Stephanie Pockl, MD, and Nafiisah Rajabalee, MD
WestVirginiaUniversity.
WVURockefeller NeuroscienceInstitute
Department of Behavioral Medicine and Psychiatry

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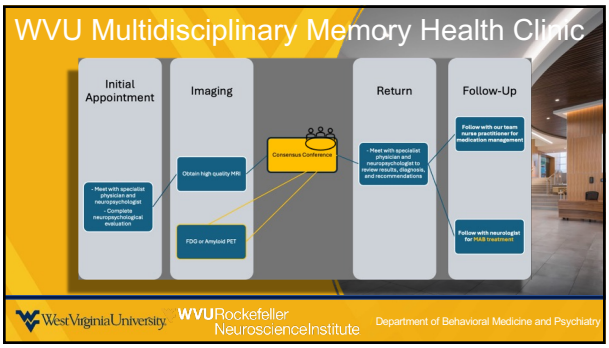
WVU Multidisciplinary Memory Health Clinic
Initial Appointment
Meet with specialist physician and neuropsychologist
Complete neurocognitive evaluation
Imaging
Obtain high quality MRI
FDG or Amyloid PET
Consensus Conference
Return
Meet with specialist physician and neuropsychologist to review results, diagnosis, and recommendations
Follow-Up
Follow with our team nurse practitioner for medication management
Follow with neurologist for FAAB treatment
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Department of Behavioral Medicine and Psychiatry

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WVU Multidisciplinary Memory Health Clinic

- For patients who might be a candidate for MAB
  - If no clear contraindications are identified during initial team conference review, we proceed with amyloid PET and APOE testing
  - After completion, patients are discussed again in conference to verify no contraindications and identity any potential areas of additional risk or concern with proceeding
  - Risks/potential benefits are then reviewed in detail with the patient and family/support system

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WVU Multidisciplinary Memory Health Clinic

Neuropsychologists can offer:

- A more thorough understanding of the patient's level of impairment, an important marker of disease progression
  - An MMSE does not tell the whole story
  - Possible implications of pattern of impairment (e.g., primary language variant versus amnestic)
  - Level of insight

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WVU Multidisciplinary Memory Health Clinic

- Identification of individualized factors that may impact a patient's ability to comprehend and/or obtain treatment
  - Do they have adequate social support? MAB treatment is very involved.
  - The impact of estimated premorbid functioning, limited formal education, etc.
  - Cultural background
  - Capacity issues

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- Identification of neuropsychiatric factors which may impact risk and response to treatment
  - Hallucinations, delusions, depression, anxiety, irritability, apathy
  - When is it recommended that patients be "tuned up" from a psychiatric standpoint prior to starting MAB therapy

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WVU Multidisciplinary Memory Health Clinic

Our Population

- Primarily rural population spanning multiple states
- Minimal diversity in race/ethnicity
- Substantial diversity in SES and educational background
- More rural and lower SES tend to present later in disease process
- Advocacy and outreach efforts
- Research efforts
- Setting up infusion sites throughout the state for easier access
- Capitalize on resiliency and connectedness

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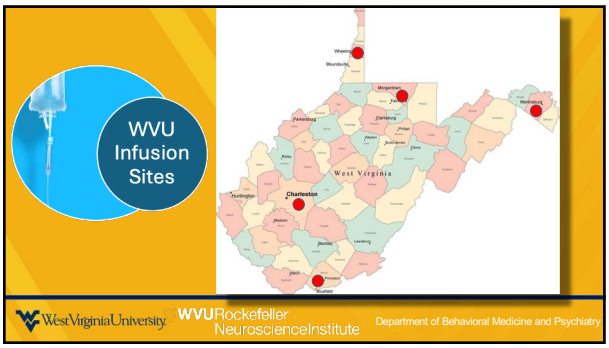

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Case 1

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Case 1

- 53-year-old, right-handed white man
- Referred by PCP for cognitive decline
- Educational history:
  - Bachelor's degree
  - Had attentional problems in childhood; eventually diagnosed with ADHD
- Occupation: Military policy development
- Came with his wife

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Case 1

- Symptoms
  - Losing train of thought
  - Word finding problems
  - Memory decline (forgetting conversations and repeating self)
  - Trouble comprehending what he is reading
  - Interfering with work performance (difficulty staying on task, forgetting meetings, superiors have noticed)
  - Wife has noticed memory decline as well
  - Onset approximately 6 months ago

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Case 1

- Functional status
  - Having difficulty at work
  - Relying more on compensatory strategies to take medications
  - Wife reported that he seems more confused while driving familiar routes at times
  - Otherwise no issues reported with ADLs/IADLs

85

Case 1

- Neuropsychiatric symptoms
  - Longstanding depression and anxiety with recent worsening (sees a therapist)
  - Has been on numerous psychotropic meds
  - Worsening irritability
  - No hallucinations or delusions
  - No SI/HI
  - No REM sleep behavior
- Substance use history
  - None

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Case 1

- Motor symptoms
  - Slightly reduced balance; no tremor
- Medical history
  - ADHD, sleep apnea (CPAP adherent), depression, hypertension
  - Had a few suspected seizures in the setting of Wellbutrin; resolved once discontinued; had normal EEG
- Family history
  - No known history of neurodegenerative conditions

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Case 1

Medications:

- lisdexamfetamine (VYVANSE) 40 mg Oral Capsule
- hydroCHLOROthiazide (HYDRODIURIL) 25 mg Oral Tablet
- NIFEdipine (PROCARDIA XL) 30 mg Oral Tablet Extended Rel 24 hr
- cholecalciferol, vitamin D3, 25 mcg (1,000 unit) Oral Tablet

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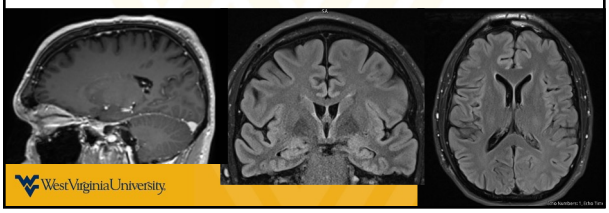
Case 1

Brain MRI:

- Read as generally WNL with mild white matter disease



WestVirginiaUniversity.

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		Age: 53, Ethn: C, Ed: 16, DH: R			
		Raw	SS	%tile	Notes
PREMORBID FUNCTIONING					
Test of Premorbid Function (TOPF)		54	111	77	
ATTENTION & WORKING MEMORY					
Digit Span (WAIS-IV)		23	*8*	25	
Forward		*10*	*10*	50	
Backward		*7*	*8*	25	
Sequencing		*6*	*7*	16	
Symbol Digit Modalities Test					
Written		27	55	0.3	
Oral Retest		21	36	<0.1	
VISUAL-SPATIAL					
Judgment of Line Orientation*	FM-V	21	88	22	
Block Design (WAIS-IV)		24	6	9	
Rey-O (Copy Only)*		17		≤1	
LANGUAGE					
Boston Naming Test*		60	124	95	
FAS		49	104	61	
Animal Naming		20	94	34	

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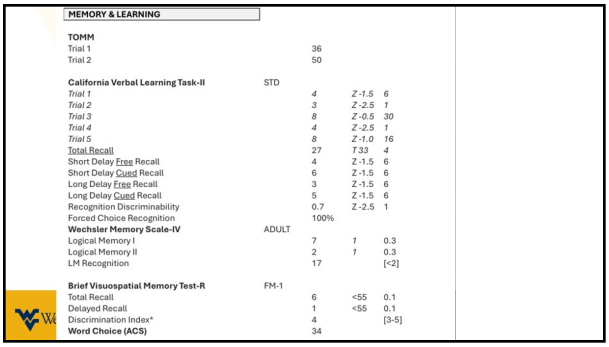

MEMORY & LEARNING				
TOMM				
Trial 1		36		
Trial 2		50		
California Verbal Learning Task-II	STD			
Trial 1		*4*	*Z -1.5*	*6*
Trial 2		*3*	*Z -2.5*	*1*
Trial 3		*8*	*Z -0.5*	*30*
Trial 4		*4*	*Z -2.5*	*1*
Trial 5		*8*	*Z -1.0*	*16*
Total Recall		27	*T 33*	*4*
Short Delay Free Recall		4	Z -1.5	6
Short Delay Cued Recall		6	Z -1.5	6
Long Delay Free Recall		3	Z -1.5	6
Long Delay Cued Recall		5	Z -1.5	6
Recognition Discriminability		0.7	Z -2.5	1
Forced Choice Recognition		100%		
Wechsler Memory Scale-IV	ADULT			
Logical Memory I		7	*1*	0.3
Logical Memory II		2	*1*	0.3
LM Recognition		17		[<2]
Brief Visuospatial Memory Test-R	FM-1			
Total Recall		6	<55	0.1
Delayed Recall		1	<55	0.1
Discrimination Index*		4		[3-5]
Word Choice (ACS)		34		

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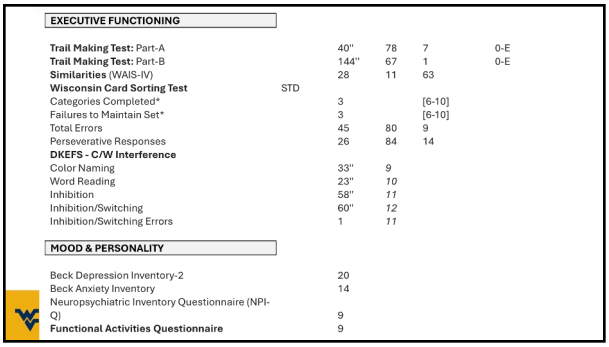

EXECUTIVE FUNCTIONING					
Trail Making Test: Part-A		40''	78	7	0-E
Trail Making Test: Part-B		144''	67	1	0-E
Similarities (WAIS-IV)		28	11	63	
Wisconsin Card Sorting Test	STD				
Categories Completed*		3		[6-10]	
Failures to Maintain Set*		3		[6-10]	
Total Errors		45	80	9	
Perseverative Responses		26	84	14	
DKEFS - C/W Interference					
Color Naming		33''	*9*		
Word Reading		23''	*10*		
Inhibition		58''	*11*		
Inhibition/Switching		60''	*12*		
Inhibition/Switching Errors		1	*11*		

MOOD & PERSONALITY	
Beck Depression Inventory-2	20
Beck Anxiety Inventory	14
Neuropsychiatric Inventory Questionnaire (NPI-Q)	9
Functional Activities Questionnaire	9

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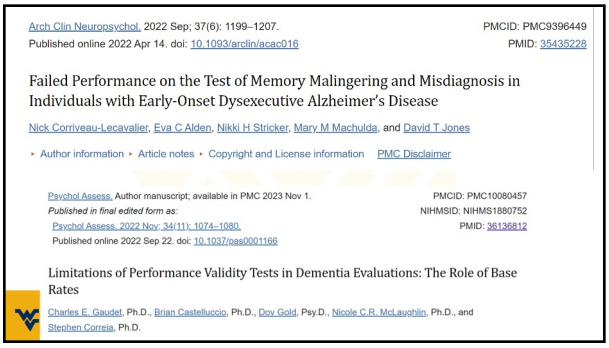

Arch Clin Neuropsychol. 2022 Sep; 37(6): 1199–1207. PMCID: PMC9396449
Published online 2022 Apr 14. doi: 10.1093/arclin/acac016 PMID: 35435228

Failed Performance on the Test of Memory Malingering and Misdiagnosis in Individuals with Early-Onset Dysexecutive Alzheimer's Disease

Nick Corriveau-Lecavalier, Eva C Alden, Nikki H Stricker, Mary M Machulda, and David T Jones

▸ Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Psychol Assess. Author manuscript; available in PMC 2023 Nov 1. PMCID: PMC10080457
Published in final edited form as: NIHMSID: NIHMS1880752
Psychol Assess. 2022 Nov; 34(11): 1074–1080. PMID: 36136812
Published online 2022 Sep 22. doi: 10.1037/pas0001166

Limitations of Performance Validity Tests in Dementia Evaluations: The Role of Base Rates

Charles E. Gaudet, Ph.D., Brian Castelluccio, Ph.D., Dov Gold, Psy.D., Nicole C.R. McLaughlin, Ph.D., and Stephen Correia, Ph.D.

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Case 1

- Sent to multidisciplinary clinic
- Unable to get amyloid PET at that time, but CSF was positive for AD
- P-Tau/Abeta 42 ratio = .191; Abeta42 = 616; total-Tau = 949; p-Tau = 117.6
- APOE e3/e4
- Mild Neurocognitive Disorder (MCI) due to Alzheimer's disease

REFERENCE VALUES ⓘ

Beta-amyloid (1-42) (Abeta42): >834 pg/mL

Total-Tau: < or =238 pg/mL

Phosphorylated-Tau 181: < or =21.6 pg/mL

p-Tau/Abeta42: < or =0.028

MAYO CLINIC LABORATORIES

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Case 1

- No exclusions identified for MAB, placed on aducanumab (this was prior to lecanemab approval)
  - No excluding brain MRI findings, no contraindicating medical conditions or medications, wife is primary social support
- Added an SSRI (he had not yet tried Lexapro) and Aricept
- Patient opted to discontinue working, helped facilitate application for disability

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Case 1

- Has since transitioned to lecanemab (aducanumab discontinued)
- No adverse effects but ongoing cognitive and function decline
- Follows with our geriatric psychiatry team as well given worsening neuropsychiatric symptoms

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Case 2

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Case 2

- 45-year-old, right-handed, white woman
- Referred by PCP for cognitive decline
- Educational history: Bachelor's degree + additional Master's level courses
- Occupation: Labor relations specialist

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Case 2

- Symptoms
  - Reported memory and word finding declines
  - Initially noticed more pauses in speech for word searching
  - Repeats herself and misplaces things
  - Husband and children have noticed this
    - On questionnaires, husband reported noticing moderate change in memory and word finding as well as severe worsening in depression and anxiety
  - 2-3 year gradually progressive course

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Case 2

- Functional status
  - More difficulties writing contracts at work, time management struggles (missing deadlines), word finding issues during contract negotiations, etc.
  - Has left the stove on at home
  - Otherwise no difficulties with driving, navigating, managing meds or finances

100

Case 2

- Neuropsychiatric
  - Longstanding depression and anxiety now worsening
  - Worsening irritability
  - Has been on several psychotropic meds
  - Follows with psychiatry and a therapist
  - No SI/HI, no hallucinations/delusions
  - Sleep is poor; taking trazodone
  - History of trauma w/out subsequent PTSD symptoms
  - No pertinent substance use history

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Case 2

- Motor and sensory symptoms
  - Has seen a general neurologist for MS work up due to foot drop, vertigo, decreased balance, weakness
  - Has participated in vestibular therapy
- Medical history
  - GERD, Crohn's disease, hypertension, hyperlipidemia, PCOS, GAD, MDD
- Family medical history
  - Late onset dementia in several grandparents

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Medication	Sig
• buPROPion (WELLBUTRIN SR) 150 mg Oral tablet sustained-release 12 hr	Take 1 Tablet (150 mg total) by mouth Twice daily
• ergocalciferol, vitamin D2, (DRISDOL) 1,250 mcg (50,000 unit) Oral Capsule	TAKE 1 CAPSULE BY MOUTH ONE TIME PER WEEK
• esomeprazole magnesium (NEXIUM) 40 mg Oral Capsule, Delayed Release(E.C.)	TAKE 1 CAPSULE BY MOUTH DAILY BEFORE MEAL
• ferrous sulfate (FEOSOL) 325 mg (65 mg iron) Oral Tablet	
• Ibuprofen (MOTRIN) 800 mg Oral Tablet	Take 1 Tablet (800 mg total) by mouth Three times a day as needed for Pain
• ondansetron (ZOFRAN) 8 mg Oral Tablet	Take 1 Tablet (8 mg total) by mouth Every 8 hours as needed for Nausea/Vomiting
• ondansetron (ZOFRAN) 8 mg Oral Tablet	Take 1 Tablet (8 mg total) by mouth Every 8 hours as needed for Nausea/Vomiting
• OZEMPIC 0.25 mg or 0.5 mg (2 mg/3 mL) Subcutaneous Pen Injector	INJECT 0.5MG UNDER THE SKIN EVERY WEEK (Patient not taking: Reported on 6/17/2024)
• OZEMPIC 1 mg/dose (4 mg/3 mL) Subcutaneous Pen Injector	INJECT 1 MG SUBCUTANEOUSLY EVERY 7 DAYS
• phentermine (ADIPEX-P) 37.5 mg Oral Tablet	
• rosuvastatin (CRESTOR) 20 mg Oral Tablet	Take 1 Tablet (20 mg total) by mouth Once a day
• traZODone (DESYREL) 50 mg Oral Tablet	TAKE 1/2 TO 1 TABLET BY MOUTH AT BEDTIME AS NEEDED FOR INSOMNIA

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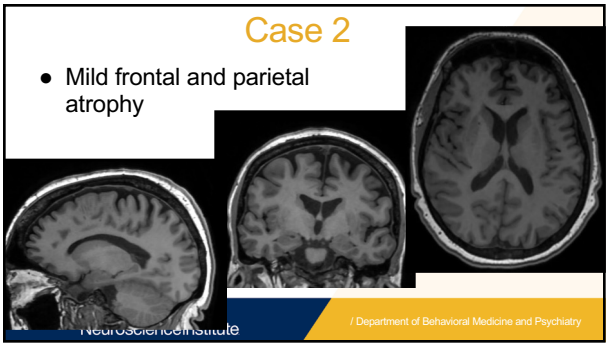
Case 2

- Mild frontal and parietal atrophy



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		Raw	SS	%tile
COGNITIVE STATUS				
Mini Mental State Examination (MMSE)		29		
PREMORBID FUNCTIONING				
Word Reading (WRAT-4)	BLUE	68	116	86
ATTENTION & WORKING MEMORY				
Digit Span (WAIS-IV)				
Forward		*12*	*12*	*75*
Backward		*9*	*10*	50
Sequencing		*13*	*16*	*98*
Total		34	*14*	91
RDS-1		10		
RDS-2		19		
VISUAL-SPATIAL				
Judgment of Line Orientation*	RBANS	12	83	13
Rey-O (Copy Only)*		35		>16
LANGUAGE				
Boston Naming Test*		56	88	21
FAS		55	112	79
Animal Naming		18	82	12

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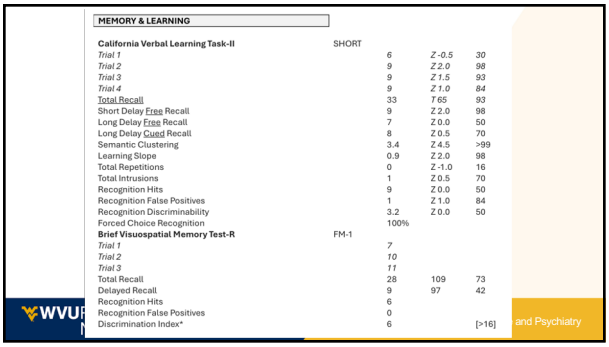

MEMORY & LEARNING				
California Verbal Learning Task-II	SHORT			
Trial 1		*6*	*Z -0.5*	*30*
Trial 2		*9*	*Z 2.0*	*98*
Trial 3		*9*	*Z 1.5*	*93*
Trial 4		*9*	*Z 1.0*	*84*
Total Recall		33	T 65	93
Short Delay Free Recall		9	Z 2.0	98
Long Delay Free Recall		7	Z 0.0	50
Long Delay Cued Recall		8	Z 0.5	70
Semantic Clustering		3.4	Z 4.5	>99
Learning Slope		0.9	Z 2.0	98
Total Repetitions		0	Z -1.0	16
Total Intrusions		1	Z 0.5	70
Recognition Hits		9	Z 0.0	50
Recognition False Positives		1	Z 1.0	84
Recognition Discriminability		3.2	Z 0.0	50
Forced Choice Recognition		100%		
Brief Visuospatial Memory Test-R	FM-1			
Trial 1		*7*		
Trial 2		*10*		
Trial 3		*11*		
Total Recall		28	109	73
Delayed Recall		9	97	42
Recognition Hits		6		
Recognition False Positives		0		
Discrimination Index*		6		[>16]

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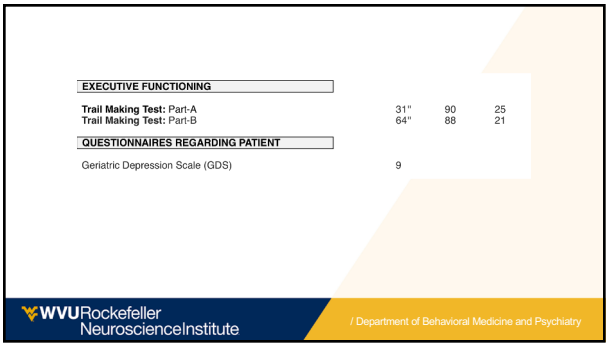

EXECUTIVE FUNCTIONING				
Trail Making Test: Part-A		31"	90	25
Trail Making Test: Part-B		64"	88	21
QUESTIONNAIRES REGARDING PATIENT				
Geriatric Depression Scale (GDS)		9		

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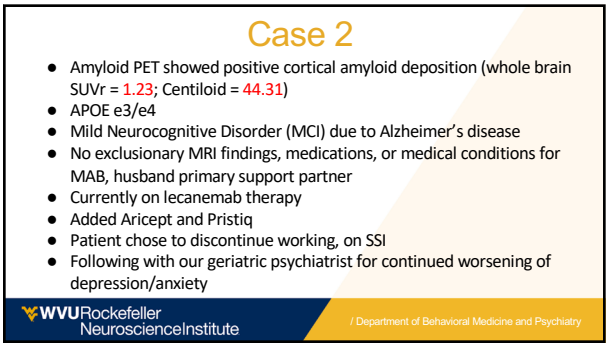

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Case 3

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Case 3

- 77-year-old, right-handed, white man
- Education: High school graduate
- Occupation: Still working as administrative assistant for fire chief

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Case 3

- Symptoms
  - Primarily presenting for memory issues
  - Wife reported that he rapidly forgets information and repeats himself
  - Forgets having walked that dog sometimes within minutes
  - 1-2 years gradual decline

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Case 3

- Functional status
  - Did not report any interference with his work performance (very structured/routine-based job)
  - Did recently get a new boss which has resulted in some frustration with work
  - Manages the finances but has overpaid a couple times this year
  - Otherwise no issues with ADLs/IADLs

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Case 3

- Neuropsychiatric
  - Described as more irritable
  - No psychiatric history
  - No SI/HI, no hallucinations or delusions
  - No sleep issues

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Case 3

- Motor and sensory symptoms
  - No motor changes; wears hearing aids
- Medical history
  - Prostate cancer (surgically treated), hyperlipidemia, migraines
- Family medical history
  - Unknown; adopted

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Case 3

Current Outpatient Medications

Medication	Sig
• aspirin (ECOTRIN) 325 mg Oral Tablet, Delayed Release (E.C.)	Take 1 Tablet (325 mg total) by mouth Once a day
• cetirizine (ZYRTEC) 10 mg Oral Tablet	Take 1 Tablet (10 mg total) by mouth Once a day
• QULIPTA 60 mg Oral Tablet	Take 1 Tablet (60 mg total) by mouth Once a day
• rosuvastatin (CRESTOR) 20 mg Oral Tablet	Take 1 Tablet (20 mg total) by mouth Once a day
• vitamin D3-folic acid 500 unit- 1 mg Oral Tablet	Take by mouth

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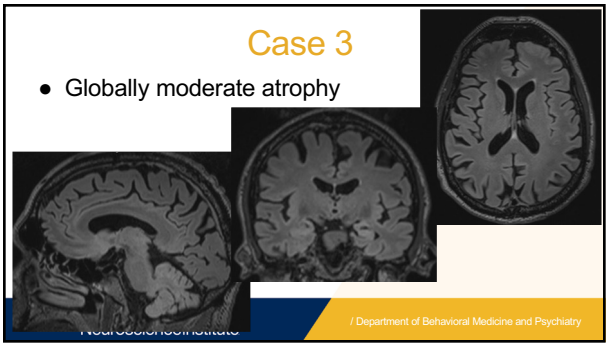
Case 3

- Globally moderate atrophy



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Age: 77, Ethn: C, Ed: 12, DH: R

		Raw	SS	%tile
COGNITIVE STATUS				
Mini Mental State Examination (MMSE)		23		
PREMORBID FUNCTIONING				
Word Reading (WRAT-4)	BLUE	57	100	50
ATTENTION & WORKING MEMORY				
Digit Span (WAIS-IV)				
Forward		*10*	*10*	*50*
Backward		*7*	*9*	*37*
Sequencing		*1*	*2*	*0.8*
Total		18	7	16
RDS-1		9		
RDS-2		9		
VISUAL-SPATIAL				
Judgment of Line Orientation*	RBANS	18	109	73
Clock Drawing				

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LANGUAGE			
Boston Naming Test®	45	88	21
FAS	33	94	34
Animal Naming	14	91	27
MEMORY & LEARNING			
California Verbal Learning Task-II	SHORT		
Trial 1	*4*	*Z -1.0*	*16*
Trial 2	*4*	*Z -1.5*	*6*
Trial 3	*6*	*Z -0.5*	*30*
Trial 4	*6*	*Z -1.0*	*16*
Total Recall	20	T 42	21
Short Delay Free Recall	3	Z -2.0	2
Long Delay Free Recall	1	Z -1.5	6
Long Delay Cued Recall	2	Z -2.5	1
Semantic Clustering	-0.8	Z -0.5	30
Learning Slope	0.8	Z 2.5	99
Total Repetitions	1	Z 0.5	70
Total Intrusions	1	Z 0.0	50
Recognition Hits	8	Z 0.0	50
Recognition False Positives	2	Z 1.0	84
Recognition Discriminability	2.4	Z 0.0	50
Forced Choice Recognition	100%		

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EXECUTIVE FUNCTIONING			
Trail Making Test: M			
TMT-M 1 (Part-A)	44"	96	39
TMT-M 2	38"		
TMT-M 3	28"		
TMT-M 4	22"		
TMT-M 5	24"		
TMT-M Delay	28"		
Trail Making Test: Part-B	113"	98	45
Similarities (WAIS-IV)	6	3	1
QUESTIONNAIRES REGARDING PATIENT			
Geriatric Depression Scale (GDS)	1		
Functional Activities Questionnaire (FAQ)	2		
Neuropsychiatric Inventory Questionnaire (NPI-Q)	0		

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Case 3

- Amyloid PET obtained given symptoms, pattern of impairment, and atrophy
- Did not show significant cortical amyloid deposition
- FDG PET then obtained to look for pattern consistent with other neurodegenerative conditions
  - Showed primarily parietal hypometabolism

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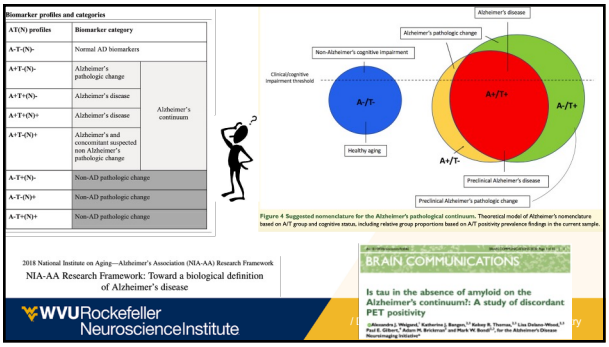

Biomarker profiles and categories

A/T(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	Alzheimer's continuum
A+T+(N)+	Alzheimer's disease	Alzheimer's continuum
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	Alzheimer's continuum
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Figure 4 Suggested nomenclature for the Alzheimer's pathological continuum. Theoretical model of Alzheimer's nomenclature based on A/T group and cognitive status, including relative group proportions based on A/T positivity prevalence findings in the current sample.

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

BRAIN COMMUNICATIONS

Is tau in the absence of amyloid on the Alzheimer's continuum?: A study of discordant PET positivity

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Case 3

- Presents most like Alzheimer's without evidence amyloid
- Mild Neurocognitive Disorder (MCI) due to SNAP (suspected non-Alzheimer's disease etiology)
- Aricept and SSRI
- Continue to monitor

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Non Pharmacological Discussions

- Lifestyle modifications - MIND diet, physical activity, socialization, optimize sleep
- Discussion about the interaction between neuropsychiatric and cognitive symptoms
- Issues of safety and future planning

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Learning Points from Case Examples

- Without neuropsychological evaluation documenting declines/impairment, these patients' symptoms may have been misattributed to their psychiatric status
- Longstanding and/or worsening psych symptoms can be a marker of neurodegenerative conditions in some cases
- PVTs can be misleading in dementia cases
- While some of these cases are heartbreaking, it is powerful to provide knowledge and support
- Clinical phenotype does not perfectly match pathology

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Take home points

- Biomarkers can be another helpful tool to understand etiology/disease
  - While there are limitations and all tools can be misused, that does not mean we should forego the tool entirely
- Monoclonal antibody therapy is by no means a cure but represents an advancement in treatment options for AD
- Neuropsychologists play a crucial role both in characterizing and staging of cognitive and functional impairment as well as identifying potential contraindications for MAB therapy

WestVirginiaUniversity.

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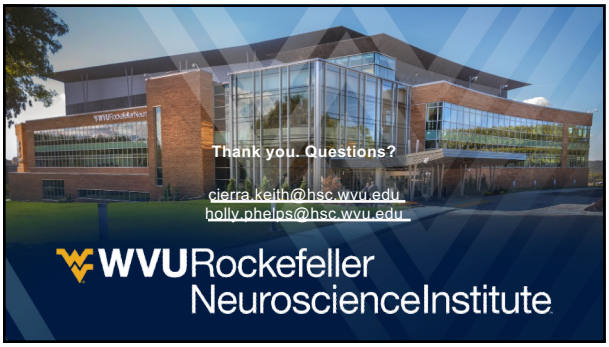

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