



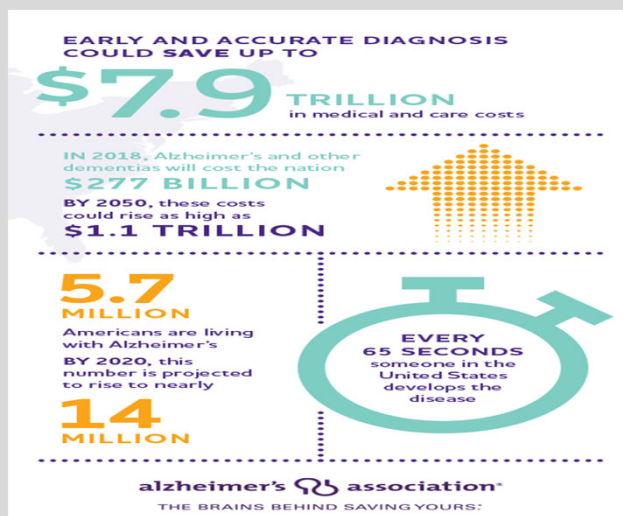
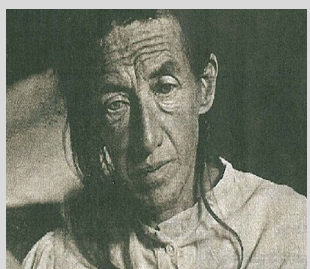
# Latest Discoveries in Alzheimer's Disease

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*Department of Neurology*  
*The Ohio State University Wexner Medical Center*

**MedNet21**  
 Center for Continuing Medical Education

**THE OHIO STATE UNIVERSITY**  
 WEXNER MEDICAL CENTER

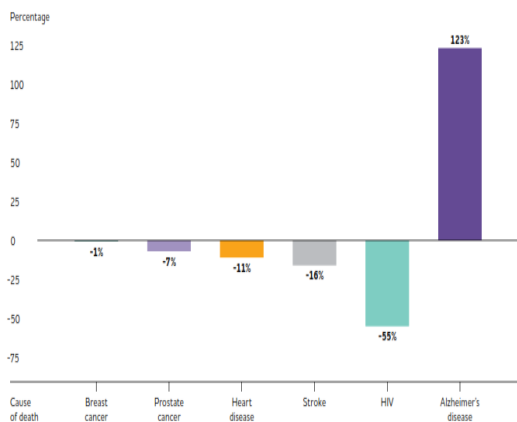
## Alzheimer Disease: A Global Epidemic



The Alzheimer's Association 2018 Report

## Alzheimer Disease: Major Cause of Mortality

Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2015

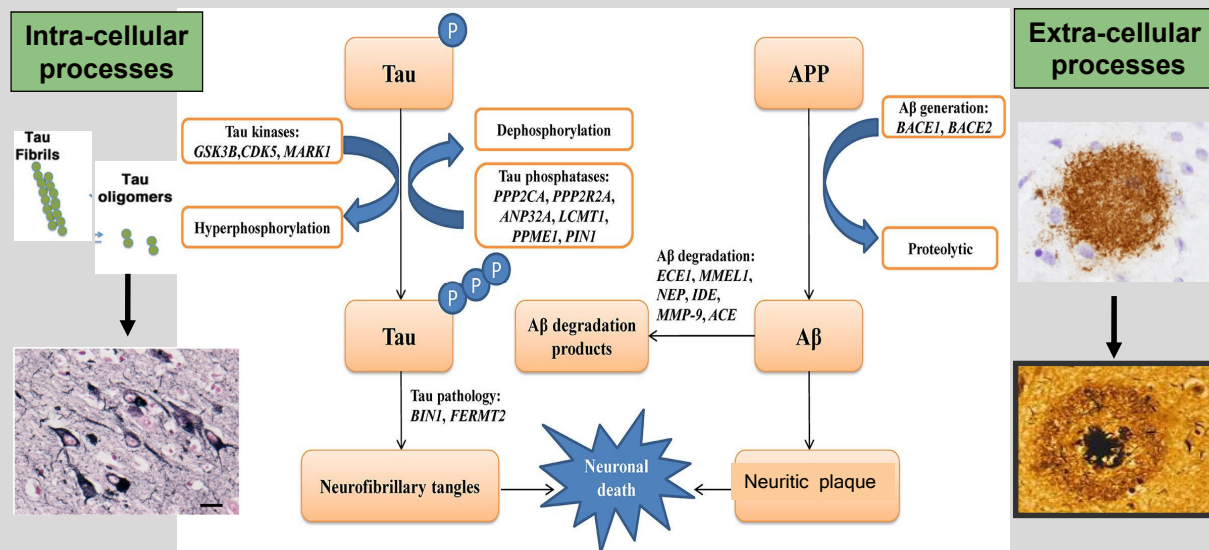


Created from data from the National Center for Health Statistics.<sup>22,24</sup>



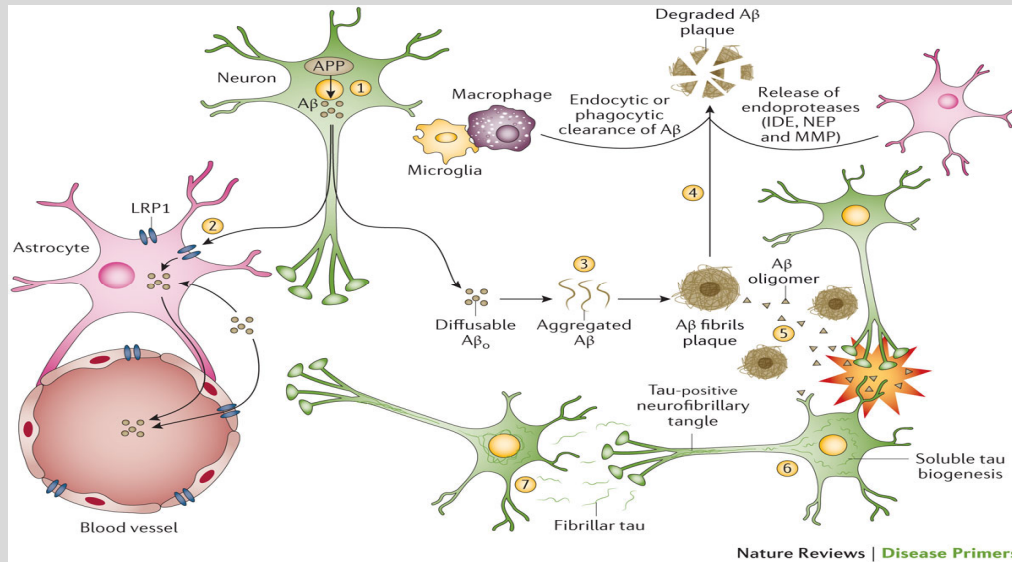
The Alzheimer's Association 2018 Report

## Amyloid and Tau Cascades in Alzheimer Disease



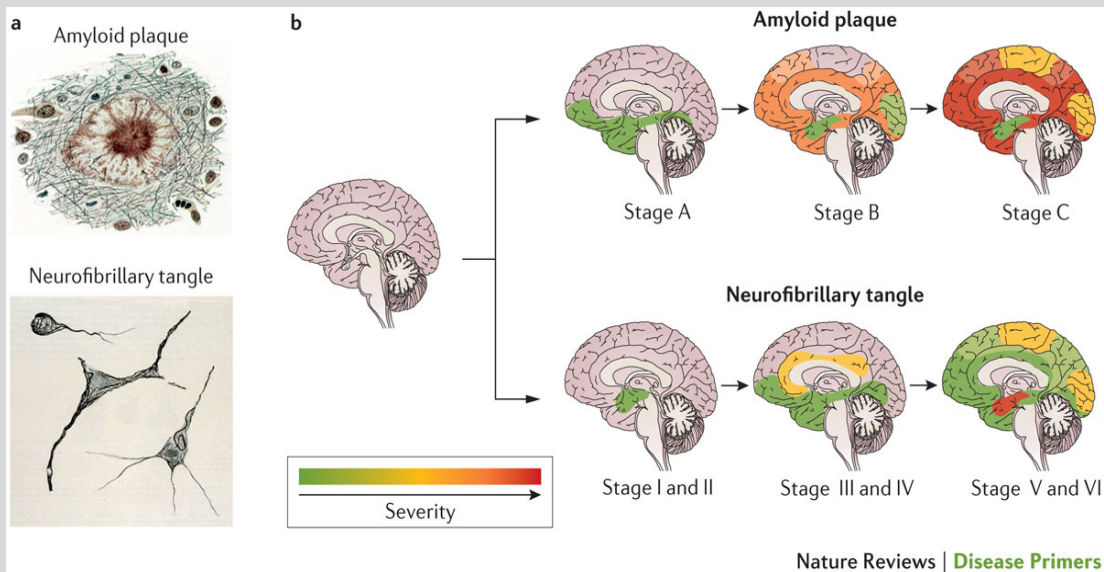
Xiao et al, Front. Aging Neurosci., 06 November 2020 with permission (Open Access)  
| <https://doi.org/10.3389/fnagi.2020.584801>

## Other Disease Mechanisms and Pathways



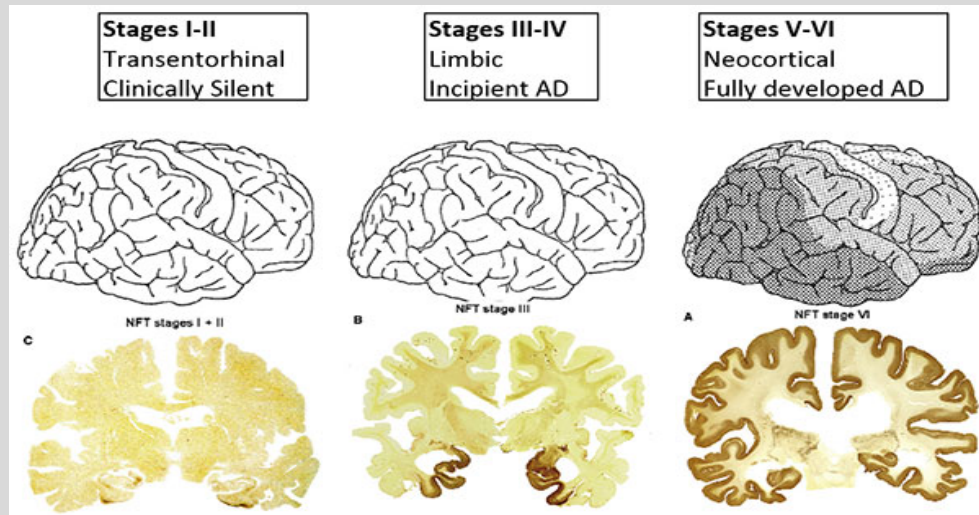
Masters, C. L. *et al.* (2015) Alzheimer's disease *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.56 with permission

## The pathological evolution of Alzheimer's disease



Masters, C. L. *et al.* (2015) Alzheimer's disease *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.56 with permission

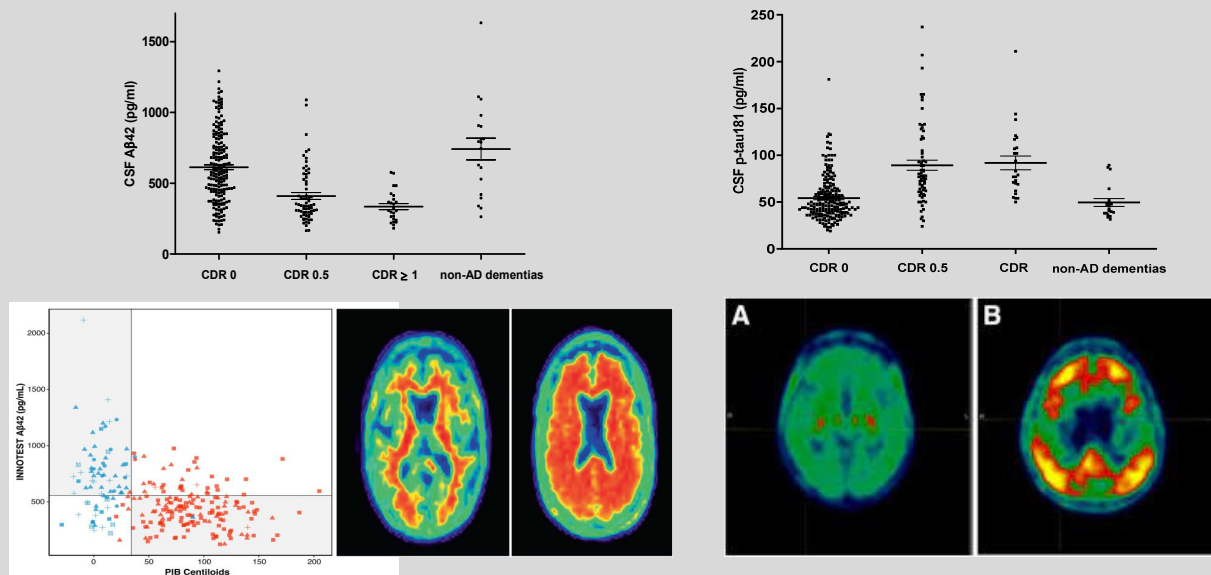
# Stages of Neurodegeneration



Braak and Braak 1991

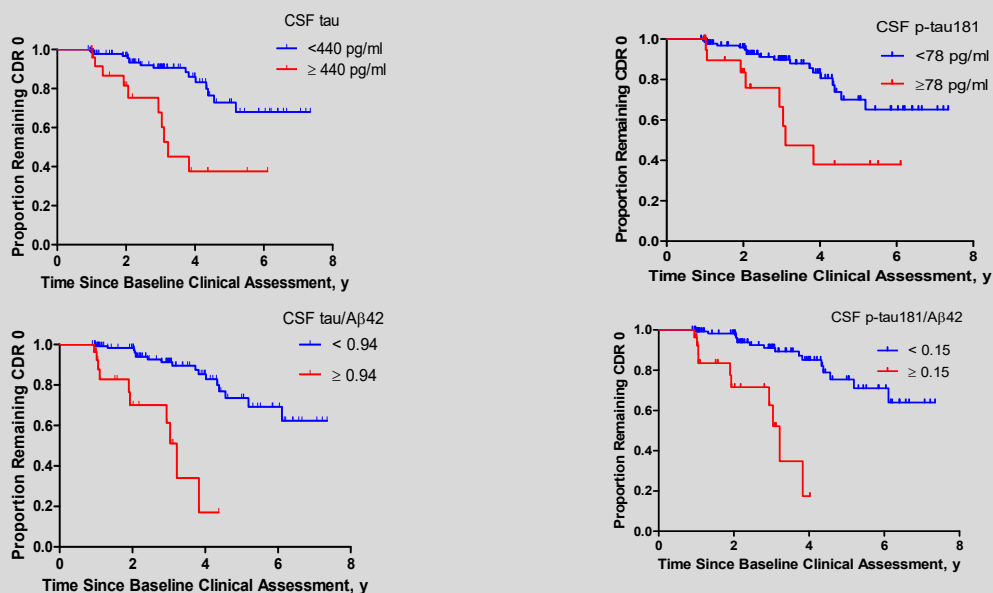
Vies, Saskia M. van der. "Protein kinases orchestrate early pathological events in Alzheimer 's disease." (2016).

## AD Biomarker Profile: High CSF tau and p-tau181 and low CSF A $\beta$ 42

Leuzy et al. *Brain*. 2016 Sep; 139(9): 2540–2553 (with permission-Open Access)Tarawneh et al. *Annals of Neurology*, 2011 Aug;70(2):274-85.2011 with permission



## CSF tau/A $\beta$ 42 and p-tau181/A $\beta$ 42 detect preclinical AD

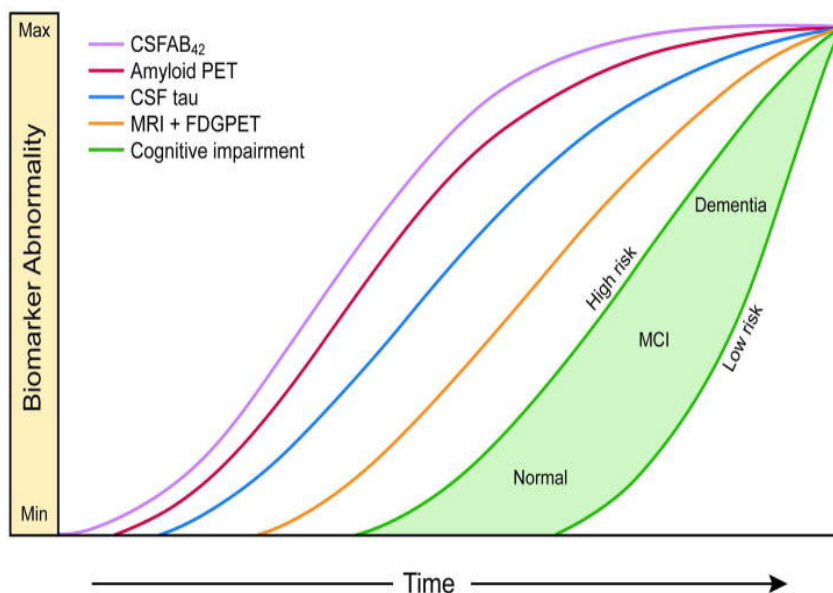


Tarawneh et al. Annals of Neurology, 2011 Aug;70(2):274-85.2011 with permission

## I. UPDATED RESEARCH FRAMEWORK FOR AD

TOWARDS BIOMARKER-BASED DEFINITIONS OF AD

## Theoretical Model of Disease Progression



Jack et al. Update on hypothetical models of Alzheimer's disease *Biomarkers Lancet Neurol.* 2013 Feb; 12(2): 207–216. 2014 with permission

## Biomarkers: Central Concept in the Updated Research Framework of AD: AT(N)



Alzheimer's & Dementia 14 (2018) 535–562

Alzheimer's  
&  
Dementia

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

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

### AT(N) biomarker grouping

A: Aggregated Aβ or associated pathologic state

CSF Aβ<sub>42</sub>, or Aβ<sub>42</sub>/Aβ<sub>40</sub> ratio

Amyloid PET

T: Aggregated tau (neurofibrillary tangles) or associated pathologic state

CSF phosphorylated tau

Tau PET

(N): Neurodegeneration or neuronal injury

Anatomic MRI

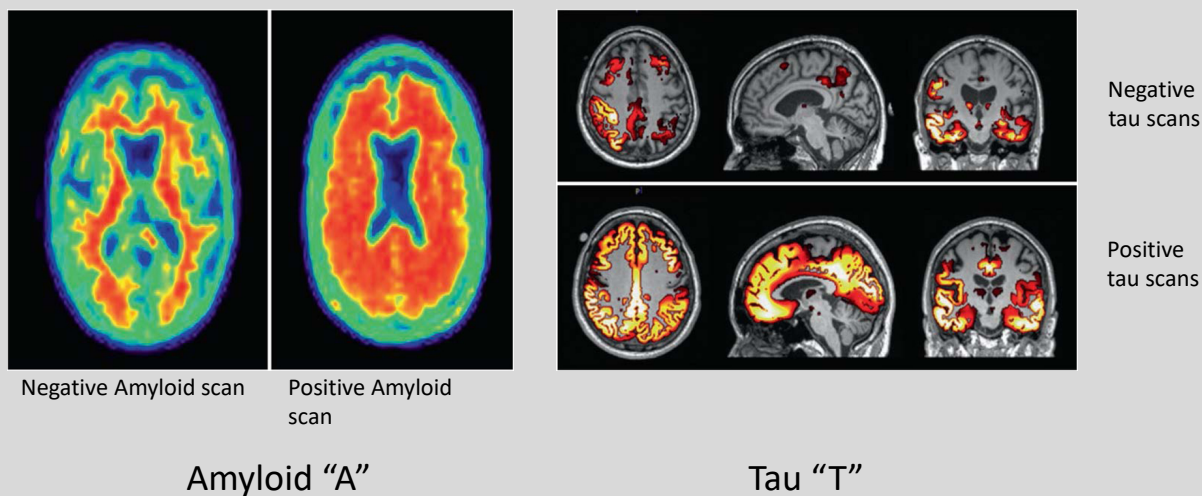
FDG PET

CSF total tau

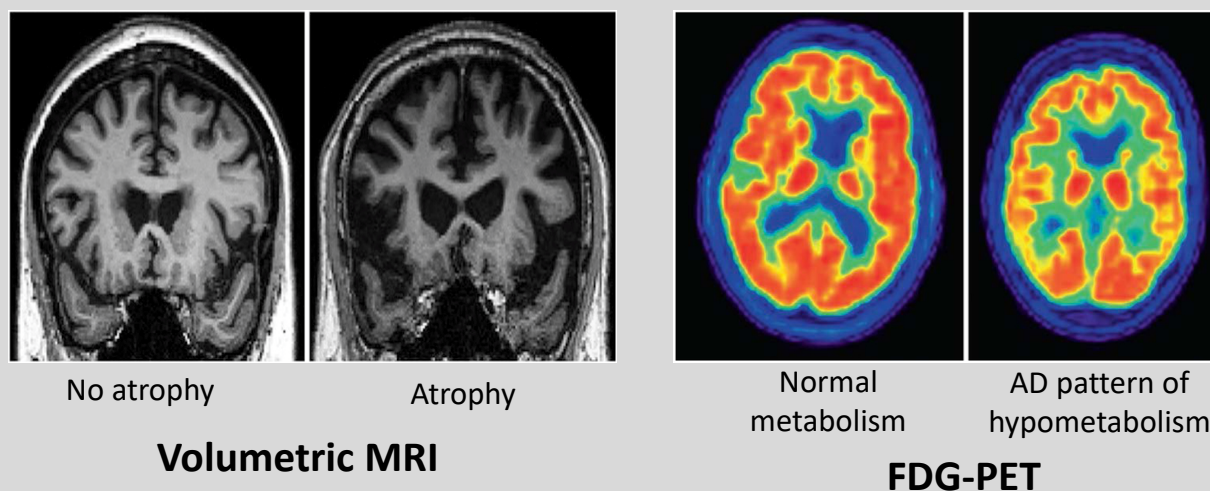
AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change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

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease, *Alzheimer's & Dementia*, 2018. 14 (4); 535–562, <https://doi.org/10.1016/j.jalz.2018.02.018> with permission .

## The ATN Framework for Alzheimer Disease Diagnosis and Characterization



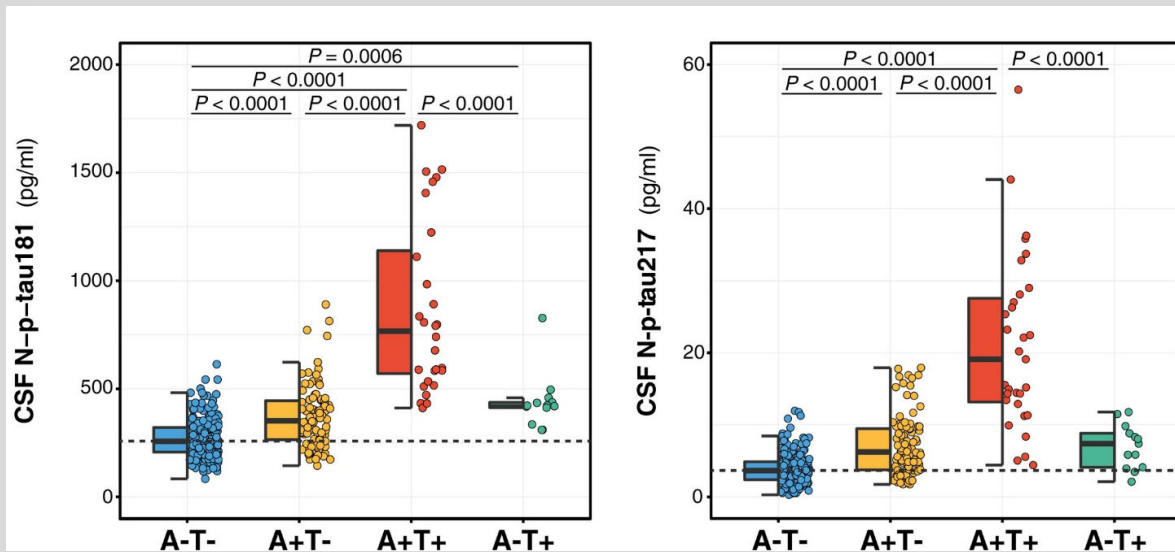
## Imaging Biomarkers of Neurodegeneration "N"



# Advances in AD Diagnosis:

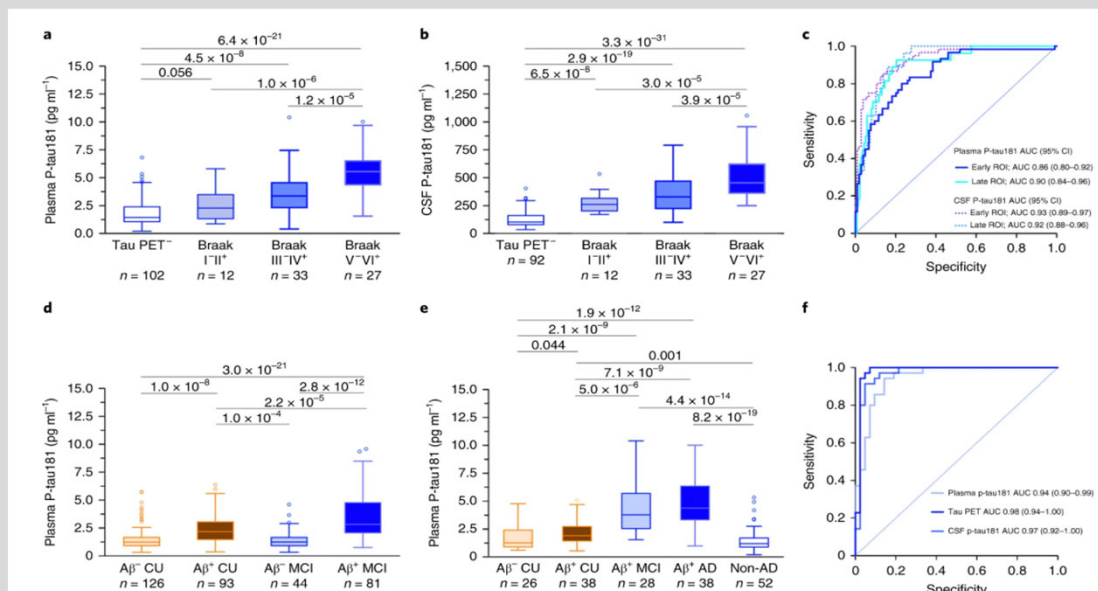
## Blood Biomarkers and Emerging Markers of Other Pathologies

### CSF p-tau217 outperforms CSF p-tau181



Suarez-Calvet, et al. EMBO Mol Med (2020) 12: 12: e12921 with permission

## Plasma p-tau181: New AD-Specific Blood Marker



Janelidze et al. *Nat Med* 26, 379–386 (2020). <https://doi.org/10.1038/s41591-020-0755-1> with permission

## Plasma p-tau217: Great Promise as Most Sensitive and Specific Blood Test for AD

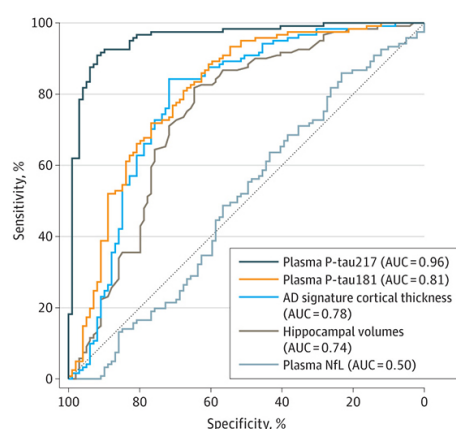


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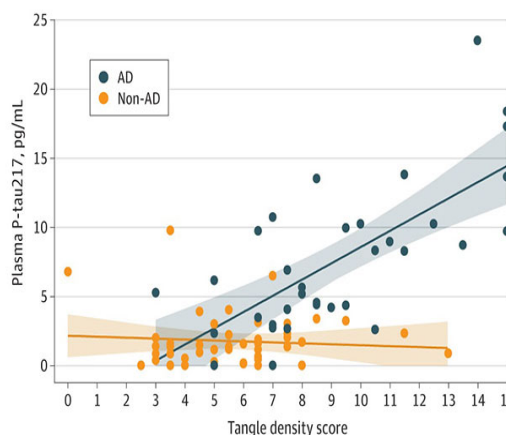
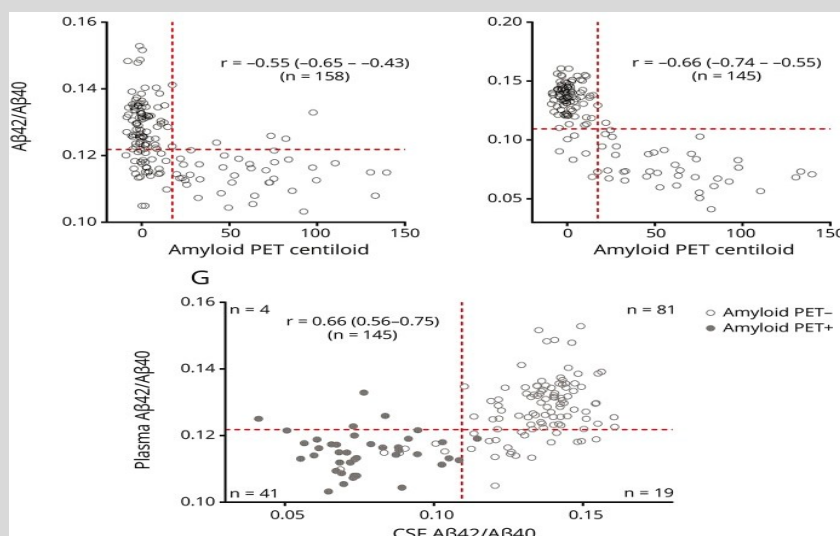


Image courtesy of JAMA Network®  
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Palmqvist et al. *JAMA*. 2020;324(8):772–781. doi:10.1001/jama.2020.12134 with permission

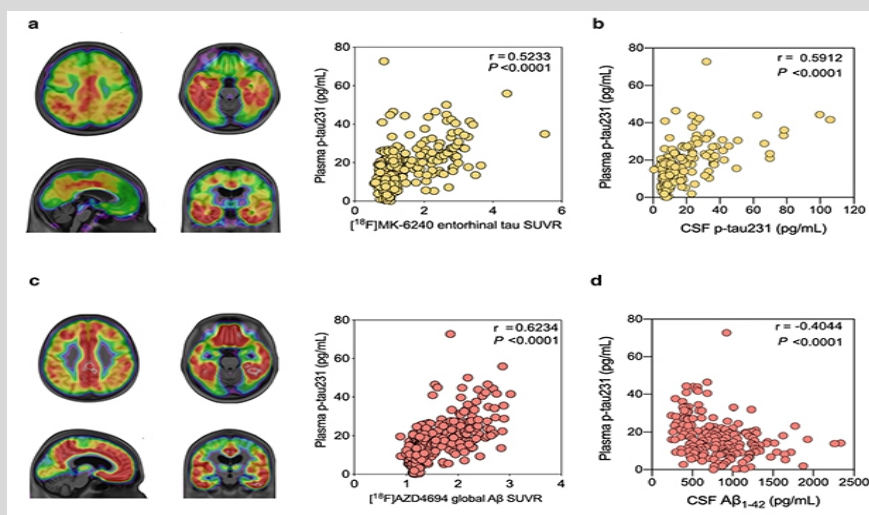


## Plasma Markers Can Detect Brain Amyloid



Schinder SE, et al. *Neurology*. 2019;93(17):e1647-e1659 (with permission)

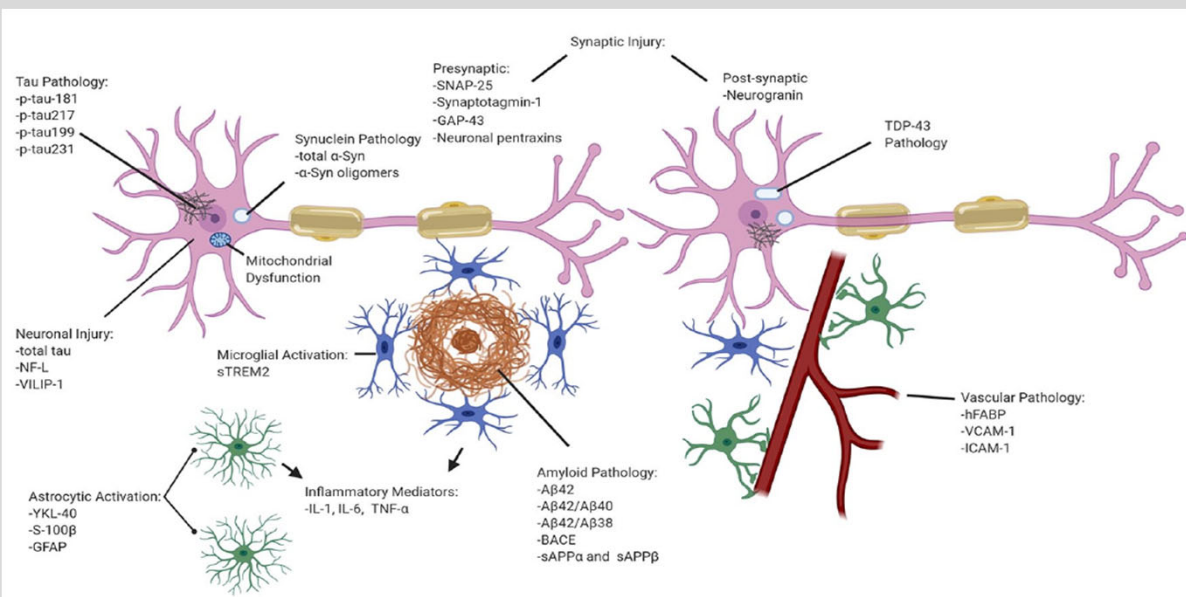
## P-tau231 May Precede Amyloid in AD Brains



Ashton et al. *Acta Neuropathol* 141, 709–724 (2021). <https://doi.org/10.1007/s00401-021-02275-6> with permission (Open Access)

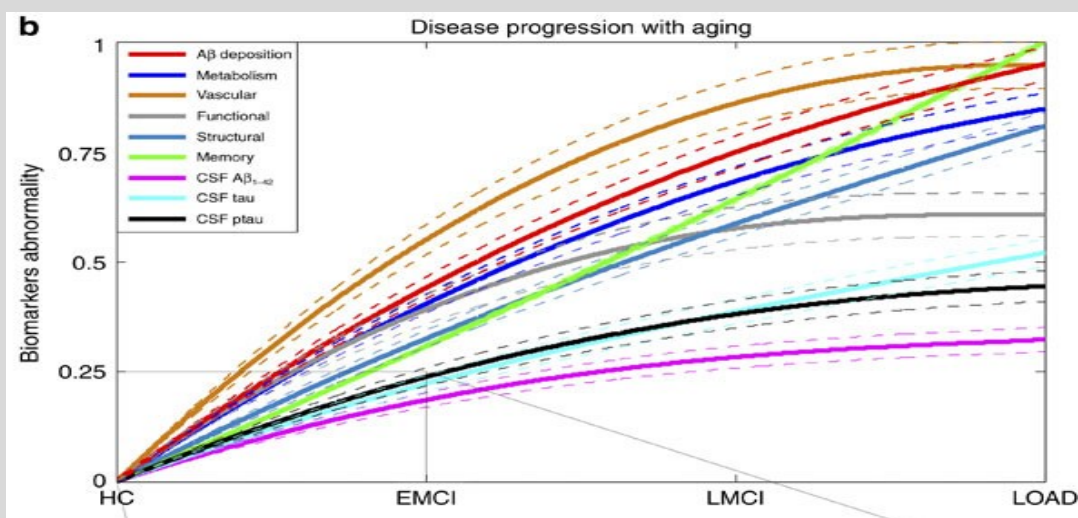
# Understanding the Clinicopathological and Molecular Heterogeneity of AD

## Biomarkers of AD Pathologies: Beyond Amyloid and Tau



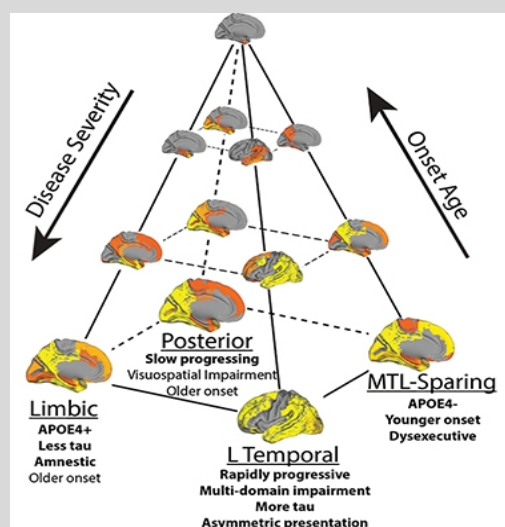
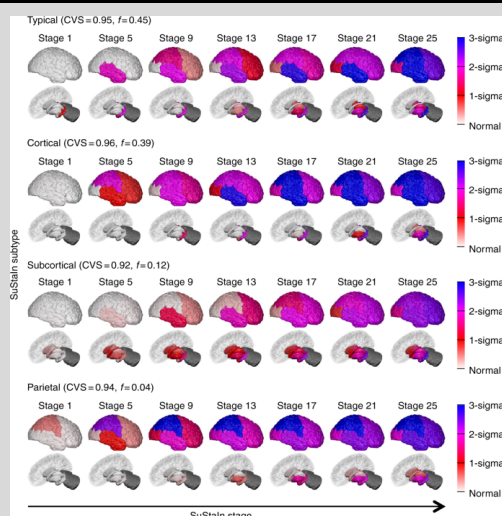
Tarawneh, R. Biomarker Insights, 2020 (with permission)

## New Biomarkers And Big Data Analytics: Data-Driven Disease Models



Iturria-Medina et al. *Nat Commun* 7, 11934 (2016) with permission (Open Access)

## AI Algorithms Identify 4 AD Subtypes



Young et al. *Nat Commun* 9, 4273 (2018) with permission (Open Access)

Vogel et al. *Nat Med.* 2021 May;27(5):871-881 with permission

# Update on Investigational AD Therapies

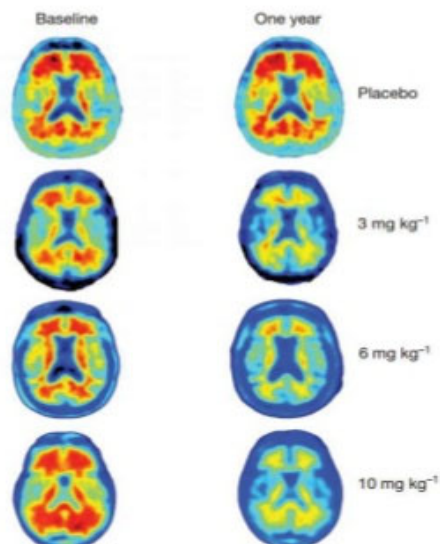
## Anti-amyloid immunotherapies: Effectively Remove Amyloid And May Slow Down Disease Progression

### Results

#### Amyloid Plaque Reduction with Aducanumab

Amyloid PET Images at Baseline and at Week 54

- › Actually shown to penetrate the brain and decrease A $\beta$  in patients with AD in a time- and dose- dependent manner
- › Mean PET SUVR composite score at baseline was 1.44
- › After 54 wks of treatment, this decreased significantly ( $P < 0.001$ ) in the 3, 6, and 10 mg/kg dose groups
- › Change in placebo group was minimal



Sevigny, J., Chiao, P., Bussière, T. *et al.* *Nature* **537**, 50–56 (2016) with permission

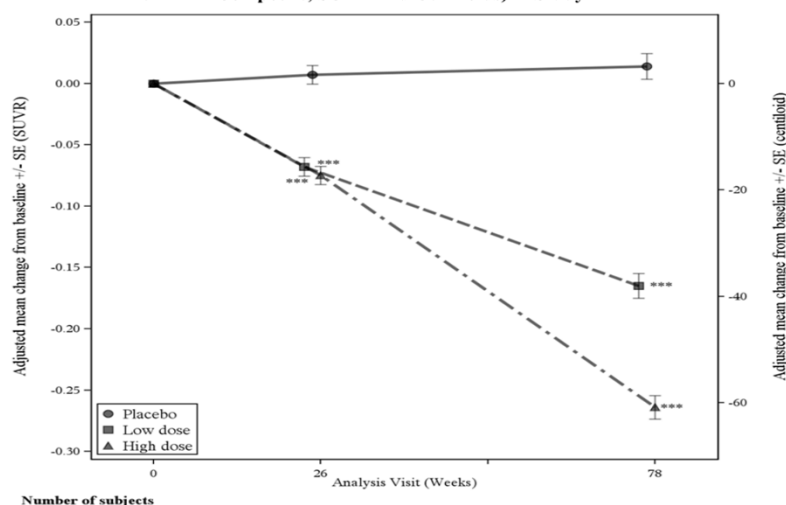
## NEWS: Aducanumab FDA-Approved June 7, 2021 As First Disease-Modifying Treatments for AD

- Aducanumab is an amyloid beta-directed antibody indicated for the treatment of early symptomatic Alzheimer's disease.
- This targets soluble and insoluble (aggregated) A $\beta$  peptides
- This indication was just recently approved under accelerated approval based on reduction in amyloid beta plaques observed in treated patients.
- Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
- Both Phase 3 clinical trials includes patients with:
  - Clinical Dementia Rating (CDR) score of 0.5 (equivalent to MCI)
  - MMSE 24-30
  - RBANS (Repeatable Battery for Assessment of Neuropsychological Status) delayed memory index of  $\leq 85$

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)

## Aducanumab reduces amyloid burden

**Figure 1: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1**

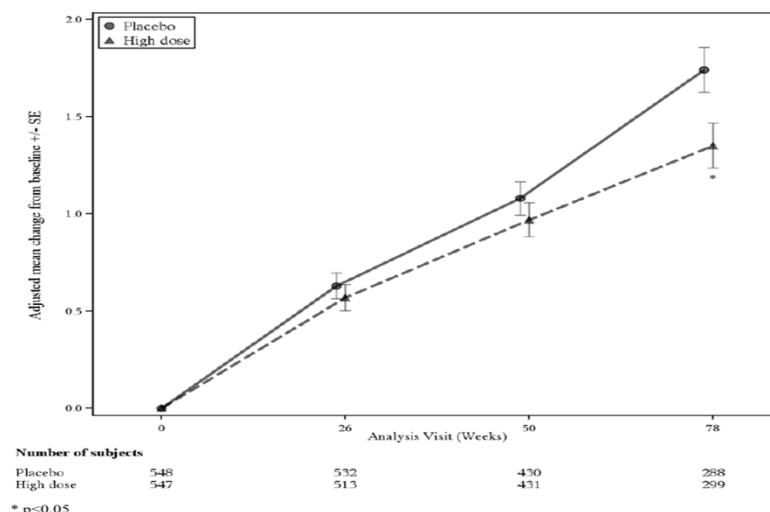


[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)



## Clinical Endpoints

**Figure 2: Line Plot of Primary Efficacy Endpoint (Change From Baseline in CDR Sum of Boxes) in Study 1**



[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)

## Clinical Endpoints-Continued

Clinical Endpoint at Week 78	ADUHELM High dose (N=547)	Placebo (N=548)
<b>CDR-SB</b>		
Mean baseline	2.51	2.47
Change from baseline	1.35	1.74
Difference from placebo (%)	-0.39 (-22%) p=0.0120	
<b>MMSE</b>		
Mean baseline	26.3	26.4
Change from baseline	-2.7	-3.3
Difference from placebo (%)	0.6 (-18%) p=0.0493	
<b>ADAS-Cog 13</b>		
Mean baseline	22.246	21.867
Change from baseline	3.763	5.162
Difference from placebo (%)	-1.400 (-27%) p=0.0097	
<b>ADCS-ADL-MCI</b>		
Mean baseline	42.5	42.6
Change from baseline	-2.5	-4.3
Difference from placebo (%)	1.7 (-40%) p=0.0006	
<b>NPI-10<sup>1</sup></b>		
Mean baseline	4.5	4.3
Change from baseline	0.2	1.5
Difference from placebo (%)	-1.3 (-87%) p=0.0215	

<sup>1</sup>P-value was not statistically controlled for multiple comparisons.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)

## Biomarker End-points

Biomarker Endpoint at Week 78 <sup>1</sup>	ADUHELM High dose	Placebo
<b>Amyloid Beta PET Composite SUVR</b>	N=170	N=159
Mean baseline	1.383	1.375
Change from baseline	-0.264	0.014
Difference from placebo	-0.278, p<0.0001	
<b>Amyloid Beta PET Centiloid</b>	N=170	N=159
Mean baseline	85.3	83.5
Change from baseline (%)	-60.8 (-71%)	3.4
Difference from placebo	-64.2, p<0.0001	
<b>CSF p-Tau (pg/mL)</b>	N=17	N=28
Mean baseline	100.11	72.55
Change from baseline	-22.93	-0.49
Difference from placebo	-22.44, p=0.0005	
<b>CSF t-Tau (pg/mL)</b>	N=17	N=28
Mean baseline	686.65	484.00
Change from baseline	-112.44	-0.39
Difference from placebo	-112.05, p=0.0088	

<sup>1</sup>P-values were not statistically controlled for multiple comparisons.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)

## Aducanumab –in the clinic

- Is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.
- Patients with mild cognitive impairment due to Alzheimer disease
- Evidence of Amyloid on Amyloid-PET scans
- Brain MRI within a year prior to starting the infusion as a baseline
- Safety has not been assessed in patients who have pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)

## ARIA-E and ARIA-H

- ARIA-E or ARIA-H were observed in 41% of treatment compared to 10% of placebo groups
- ARIA-E was observed in 35% of treated patients compared to 3% of placebo
- ARIA-E was more common in APOE4 carriers (42%) vs APOE4 noncarriers (20%)
- Most ARIAs occurred within the first 8 doses but can occur any time
- ARIAs were mild in 30%, moderate in 58% and severe in 13%
- Resolution occurred in 68% of ARIA-E patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection
- 10% of patients on the full dose had more than one episode of ARIA
- Besides ARIA, angioedema and hypersensitivity have been reported

## Amyloid Related Imaging Abnormalities (ARIAs)

**Table 2: ARIA MRI Classification Criteria**

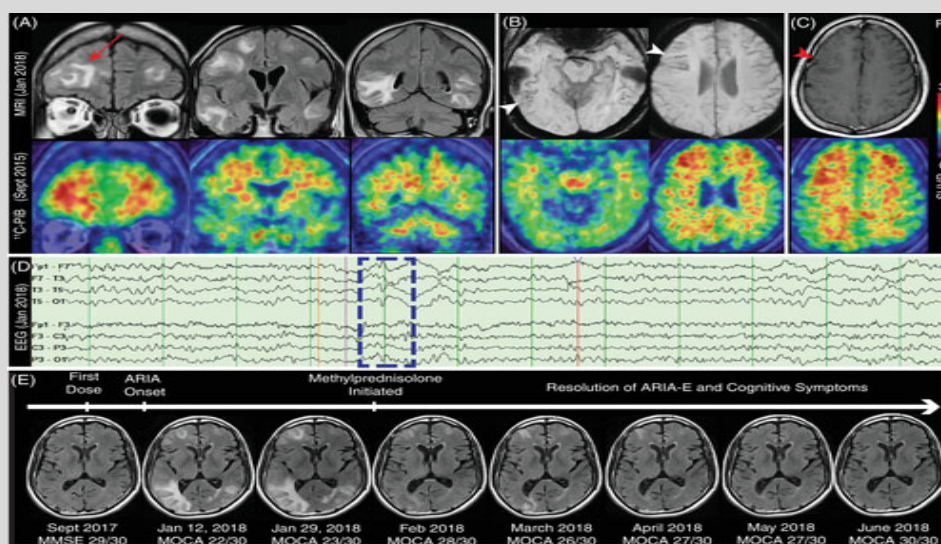
ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often 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

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/761178s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf)

## ARIA Follow-up

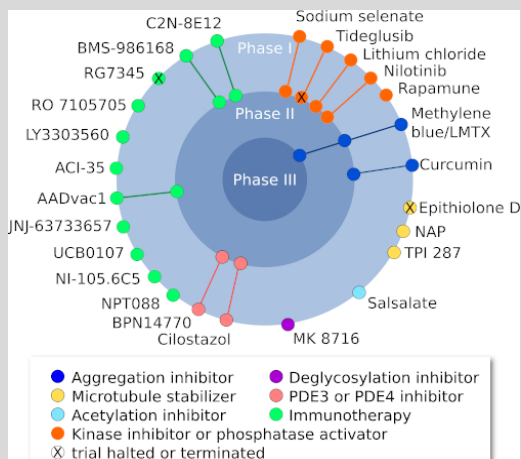
- Enhanced clinical vigilance for ARIA is recommended during the first 8 doses
- Clinical evaluation of symptomatic patients with suspected ARIA should include a brain MRI
- Brain MRIs should be obtained routinely prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg) to evaluate for the presence of asymptomatic ARIA.
- For patients with radiographic ARIA, enhanced clinical vigilance is recommended including possible need for additional MRIs
- For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may resume at that same dose and titration schedule.
- In Studies 1 and 2, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H.
- In Studies 1 and 2, permanent discontinuation of dosing was required for radiographically severe ARIA-H.

## ARIA-Case Report Outlining Suggested Treatment



VandeVrede, L, et al *Alzheimer's Dement.* 2020; 12:e12101. <https://doi.org/10.1002/dad2.12101>

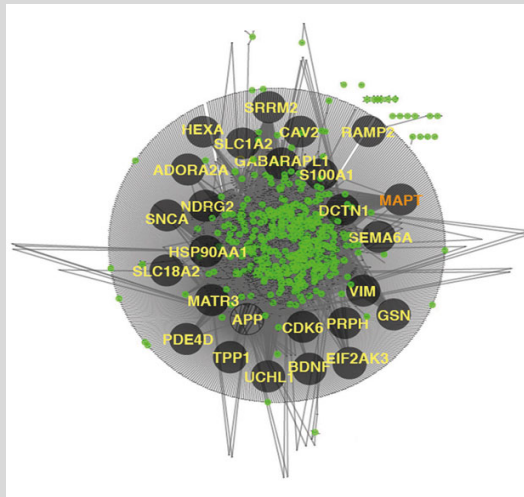
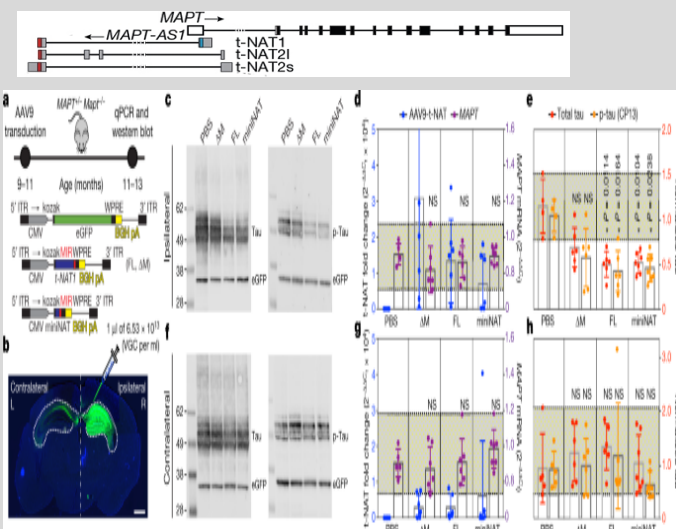
# Anti-Tau Trials



Semorinemab	Roche/AC Immune	Pan-tau mAb; N-terminal epitope	Phase II; failed in first phase II, more results due in 2021.
ABBV-8E12	AbbVie/C2N Diagnostics	mAb; N-terminal epitope	Phase II; results due in 2021. Failed in PSP.
Gosuranemab	Biogen/Bristol Myers Squibb	mAb; N-terminal epitope	Phase II; results due in 2021. Failed in PSP.
Zagotenemab	Eli Lilly	mAb; conformational epitope includes N-terminal site	Phase II; results due in 2021.
JNJ-63733657	Johnson & Johnson	Pathogenic tau mAb, targeting mid-region epitope	Phase II; started in 2020.
IONIS-MAPTRx	Biogen/Ionis	Antisense	Phase I/II; results due in 2021.
ACI-35	Johnson & Johnson/AC Immune	Vaccine	Phase I/II
AADvac1	AXON Neuroscience	Vaccine	Phase I
ACI-3024	Eli Lilly /AC Immune	Small-molecule aggregation inhibitor	Phase I
BIB076	Biogen	mAb	Phase I
E2814	Eisai	mAb	Phase I
Lu AF87908	H. Lundbeck	mAb	Phase I

Current clinical trials targeting tau (Adapted from Congdon and Sirgudsson, 2018)

## MIR-NATs: Noncoding RNAs That Regulate Tau Translation In Vivo



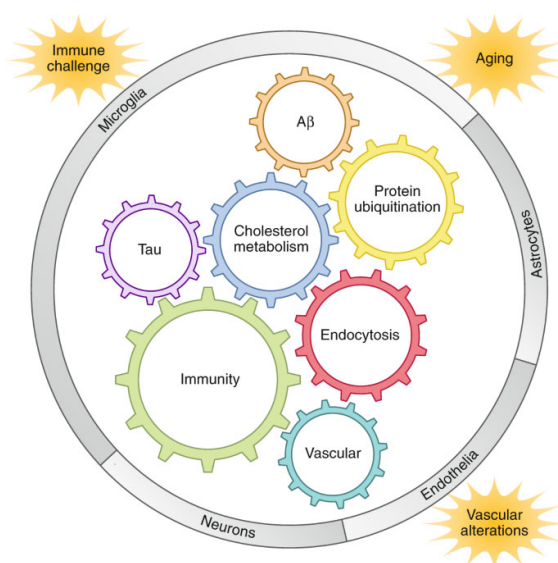
Simone, et al. *Nature* 594, 117–123 (2021). <https://doi.org/10.1038/s41586-021-03556-6> with permission



# Unraveling New Disease Mechanisms

Beyond Protein Aggregation:  
Immune Mechanisms and Vascular Disturbances are Key Players

## Immune Dysregulation as a Central Mechanism in AD



Sims, R., Hill, M. & Williams, J. The multiplex model of the genetics of Alzheimer's disease. *Nat Neurosci* **23**, 311–322 (2020). with permission

40

## Targeting Inflammation in AD; Anti-TREM2 Antibodies

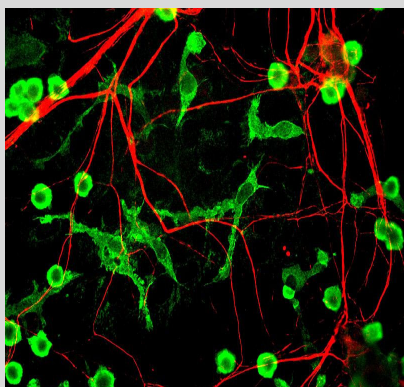
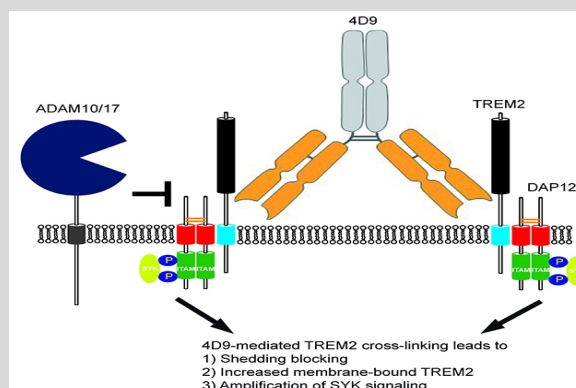
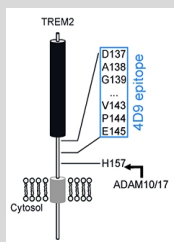
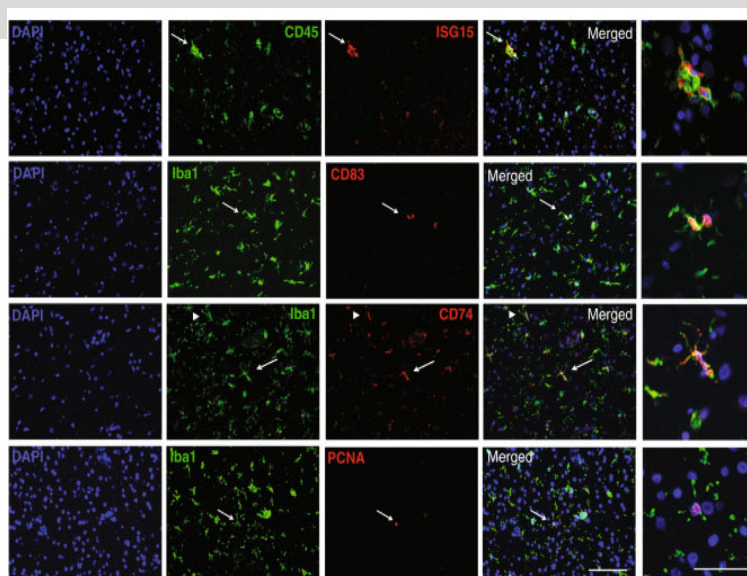
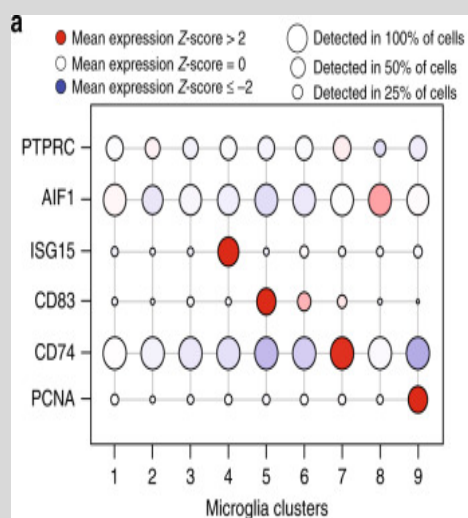


Image by Gerry Shaw. ikimediaCommons



Schelpckow et al. EMBO Mol Med (2020)12:e11227

## RNA-seq identifies different microglial subtypes in AD

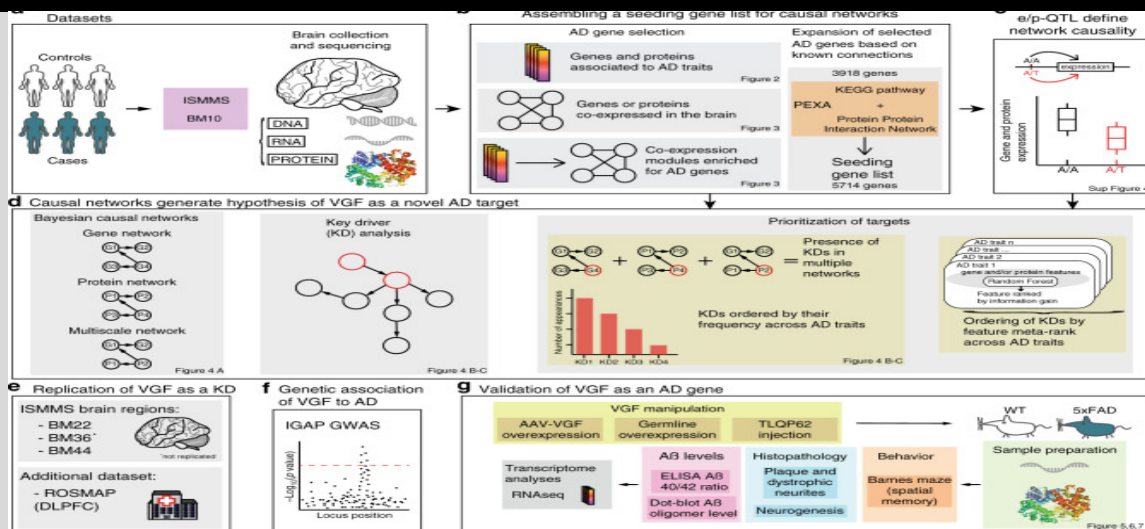


Olah, Marta et al. *Nature communications* vol. 11,1 6129. 30 Nov. 2020. doi:10.1038/s41467-020-19737-2 with permission (Open Access)

# Novel Therapeutic Targets

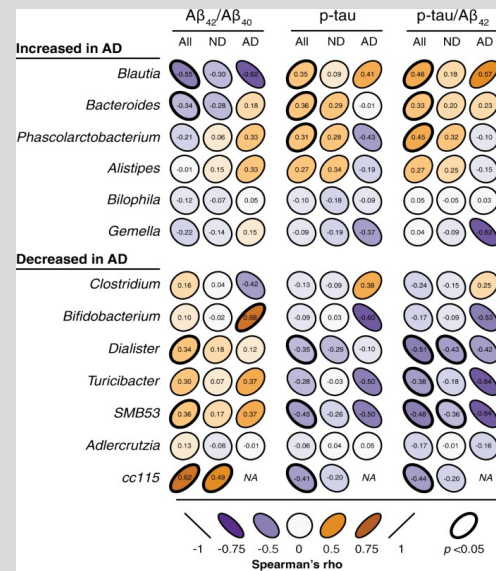
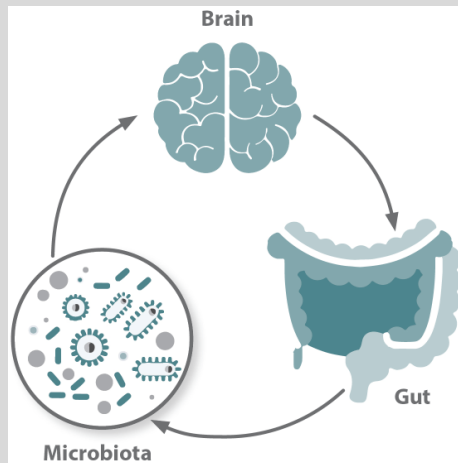
## Big Data Analytics at Forefront of AD Drug Discovery

### VGF Gene As A Key Regulator of AD



Beckman et al. *Nat Commun* 11, 3942 (2020) with permission

# AD and the Gut Microbiome



Vogt, N.M., Kerby, R.L., Dill-McFarland, K.A. *et al.* Gut microbiome alterations in Alzheimer's disease. *Sci Rep* 7, 13537 (2017) with permission