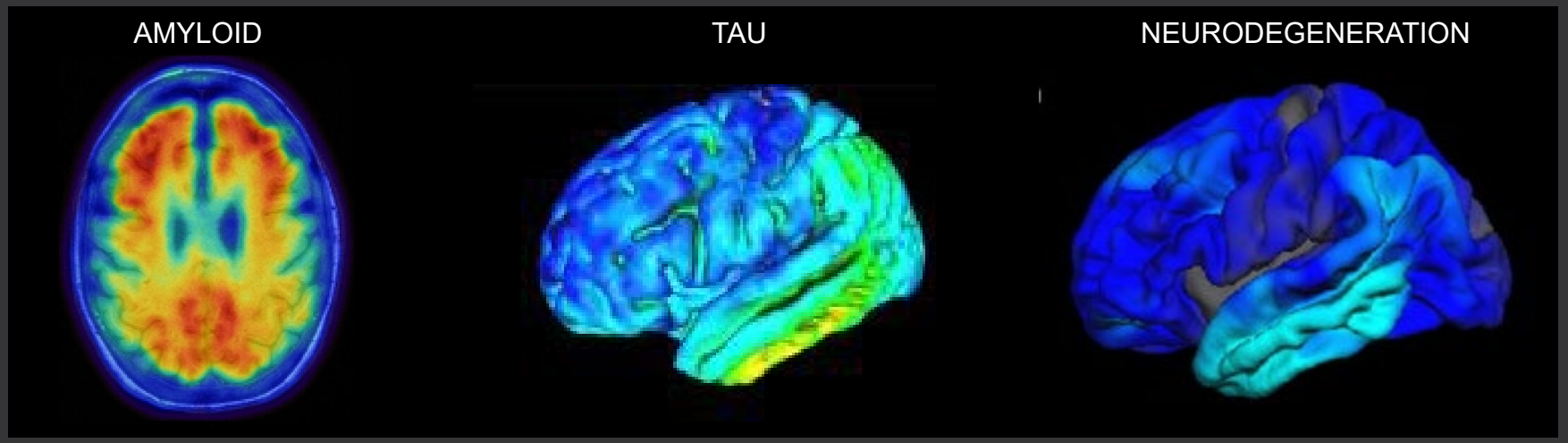
“ATN” triple brain imaging to better understand and detect Alzheimer’s disease



UC San Diego
SCHOOL OF MEDICINE
SHILEY-MARCOS ALZHEIMER'S DISEASE RESEARCH CENTER

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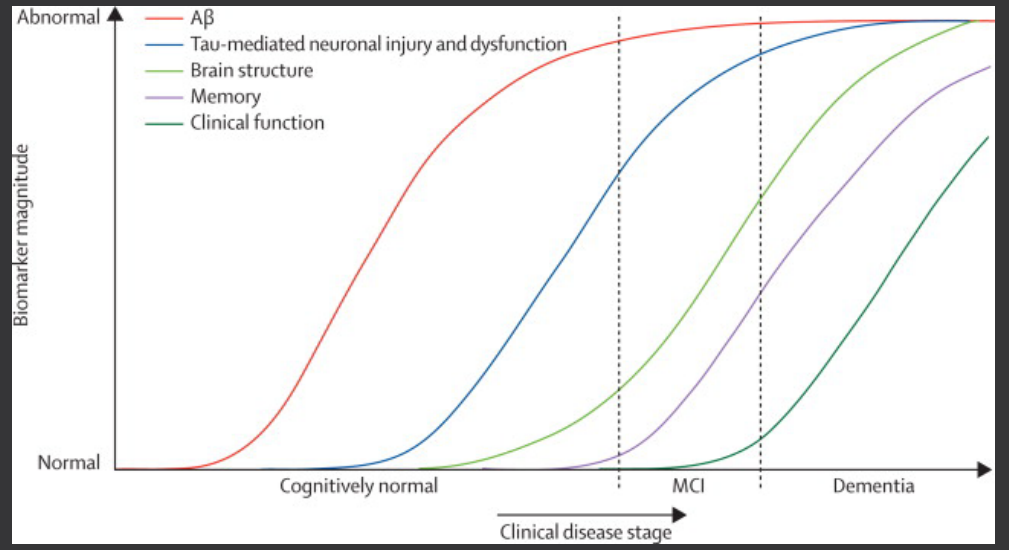
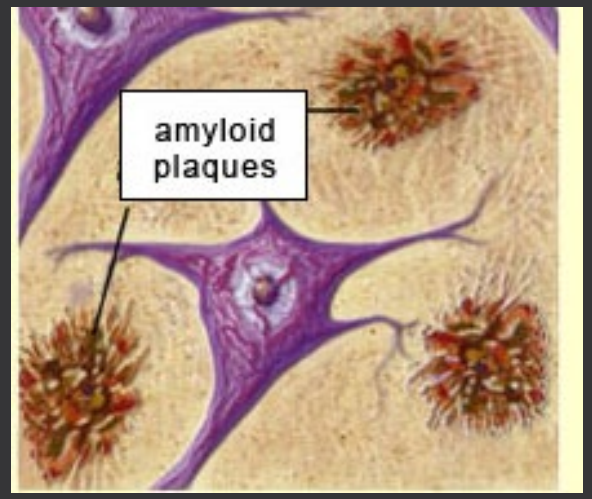
Alzheimer's disease

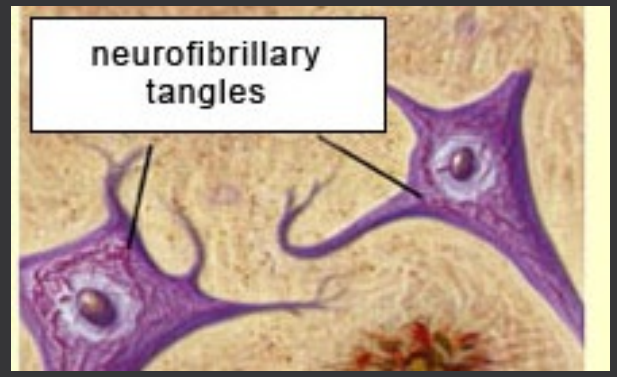
- Alzheimer's disease (AD) is characterized *clinically* by decline in memory and other cognitive functions.
- AD is defined *biologically* by amyloid plaques (A), tau tangles (T), and neurodegeneration (N).
- Because biological changes precede clinical symptoms, detecting "ATN" is crucial for early diagnosis and effective treatment.



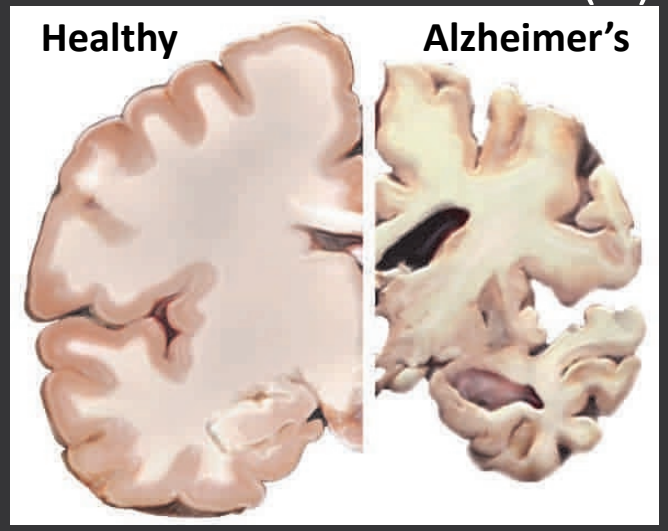
AMYLOID (**A**)



TAU (**T**)



NEURODEGENERATION (**N**)



Decades *Years* *Symptoms*

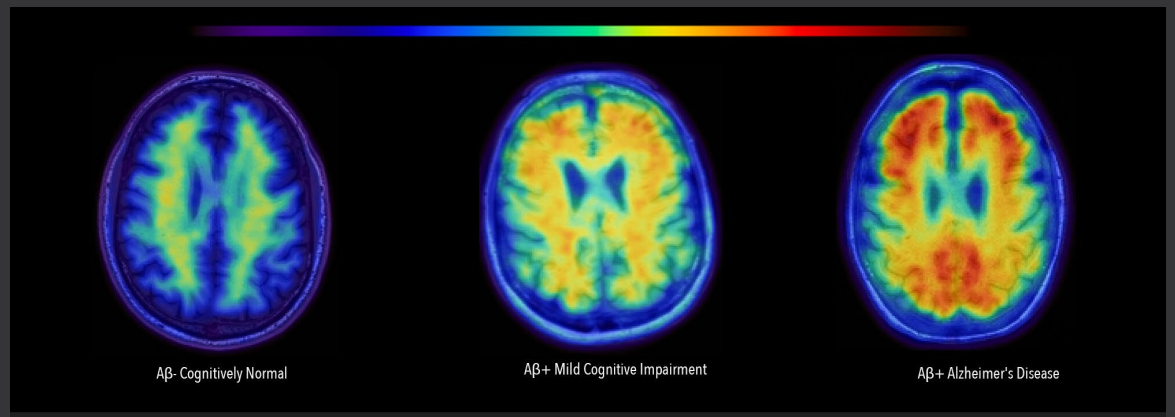
Measuring “ATN”

	Measure	Method	Pro	Con
Cerebrospinal fluid	**A**: amyloid-β 42/40 **T**: phosphorylated tau **N**: neurofilament light	Lumbar puncture	Directly measures brain proteins	Requires lumbar puncture
Plasma	**A**: phosphorylated tau-217; amyloid-β 42/40 **T**: MTBR-tau243 **N**: neurofilament light	Blood draw	Inexpensive Non-invasive	Indirect
Brain imaging	**A**: Amyloid PET **T**: Tau PET **N**: MRI	*MRI*: Strong magnetic field creates pictures of brain *PET*: Radioactive tracer binds to protein of interest	Directly measures brain structure & proteins Shows where in the brain	Expensive PET involves radiation

- MRI (magnetic resonance imaging) and PET (positron emission tomography) provide a *direct* picture of *regional* brain changes.

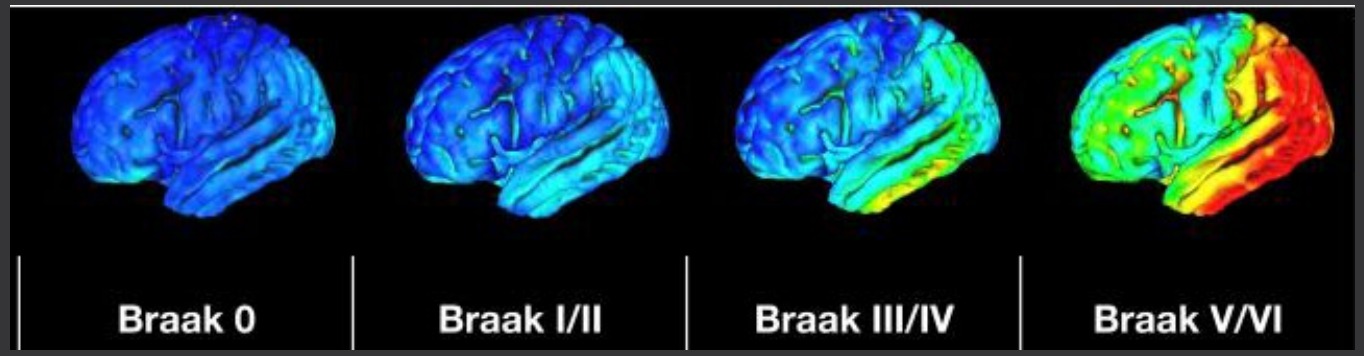
ATN neuroimaging

Amyloid PET



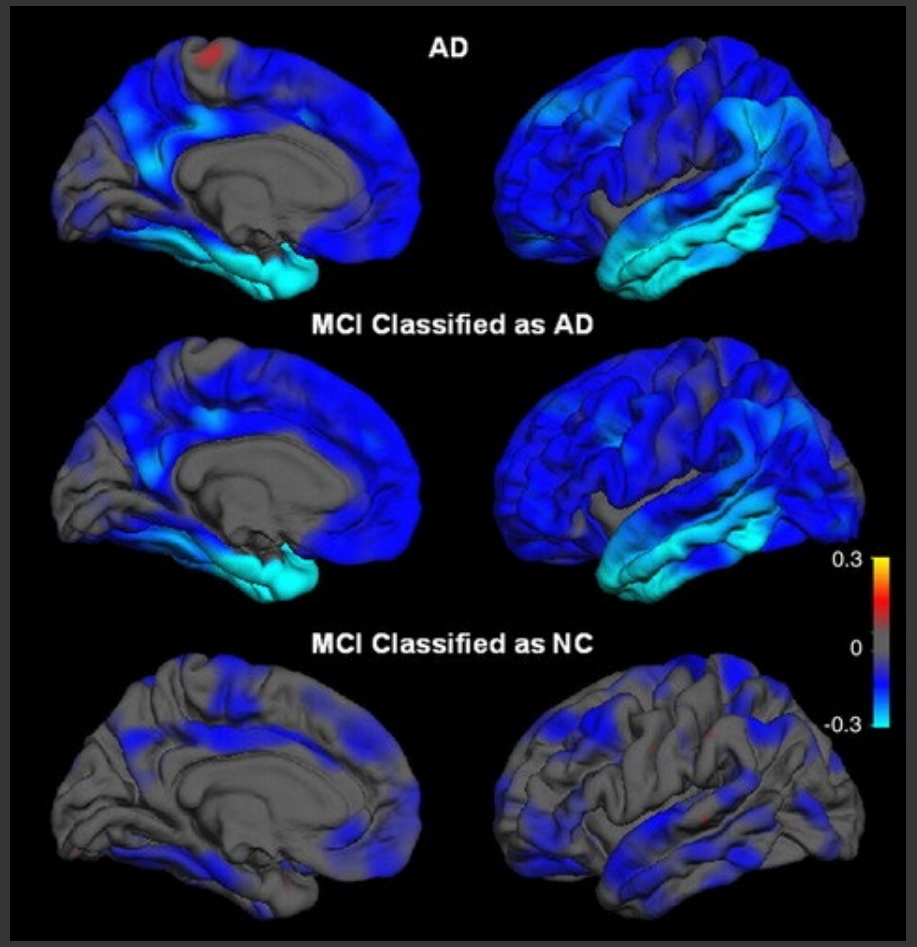
Courtesy Bill Jagust lab, UC Berkeley

Tau PET



Scholl et al. (2016) *Neuron*

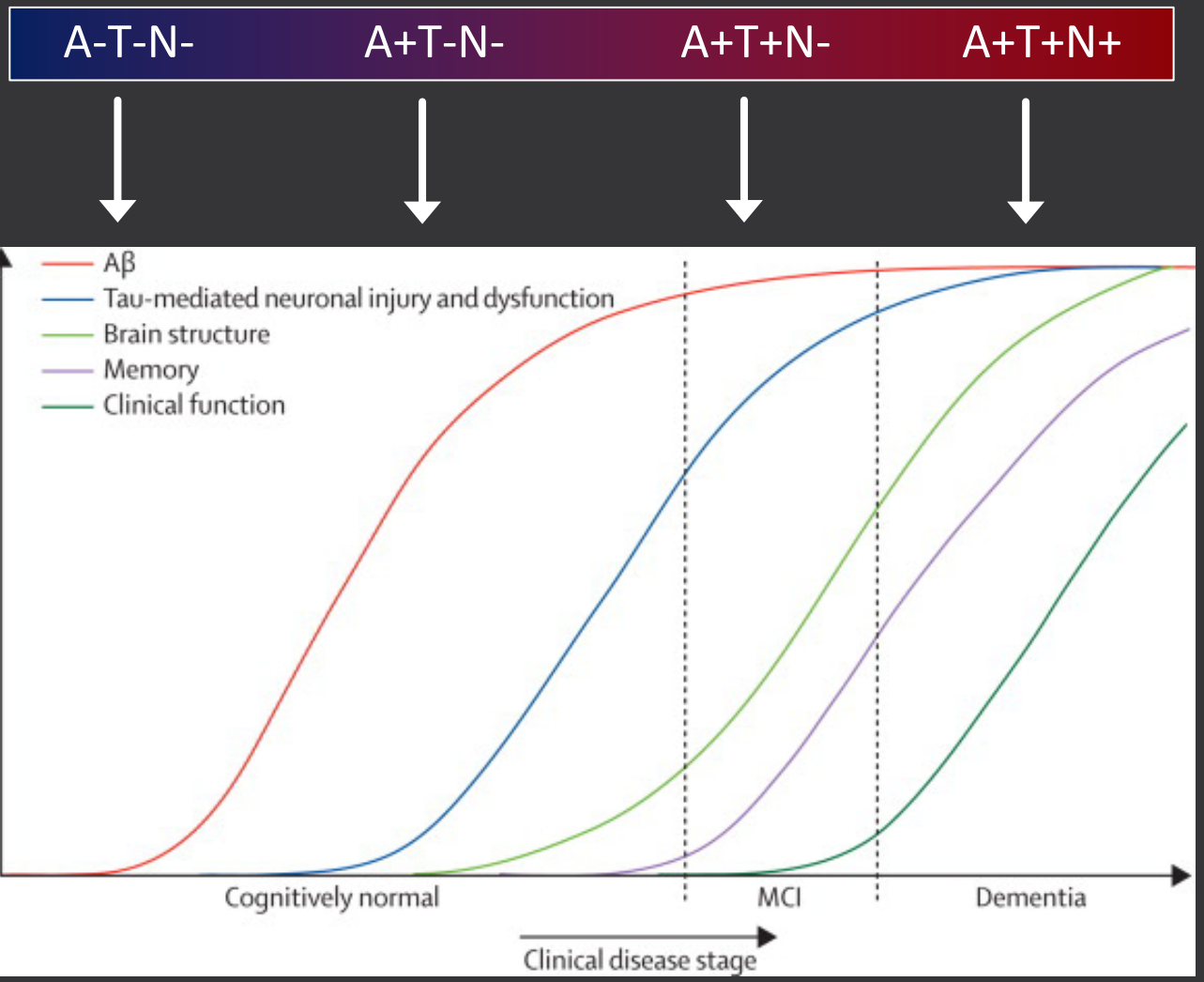
MRI



McEvoy et al. (2009) *Radiology*

ATN neuroimaging applications:

Detecting and staging Alzheimer's disease



ATN neuroimaging applications:
Understanding Alzheimer's disease

Comparing ATN markers to other measures (cognitive, clinical, fluid, imaging, post-mortem) helps us better understand:

Risk factors:

- How do modifiable or non-modifiable factors influence AD risk?
  - *APOE4*, sex, race/ethnicity, vascular and cardiometabolic disorders, sleep, physical activity, hearing loss, etc

Copathologies:

- Do other neuropathological changes interact with amyloid or tau to influence dementia risk?
  - alpha-synuclein, TDP-43, cerebrovascular disease

Disease heterogeneity:

- Spatial patterns of amyloid, tau, and neurodegeneration can reveal AD subtypes, that differ in clinical time-course, and relationships with risk factors and clinical outcomes.
  - Women sustain more tau before showing cognitive decline (*Digma et al, Brain, 2020*)
  - Black, Hispanic, and Asian individuals have greater cognitive impairment at lower levels of AD pathology (*Wilkens et al, JAMA Neurology, 2022*)
  - Different spatial patterns of tau and neurodegeneration correspond with different symptoms (*Vogel et al, Nature Medicine, 2021; ten Kate et al, Brain, 2018*)

ATN neuroimaging applications:

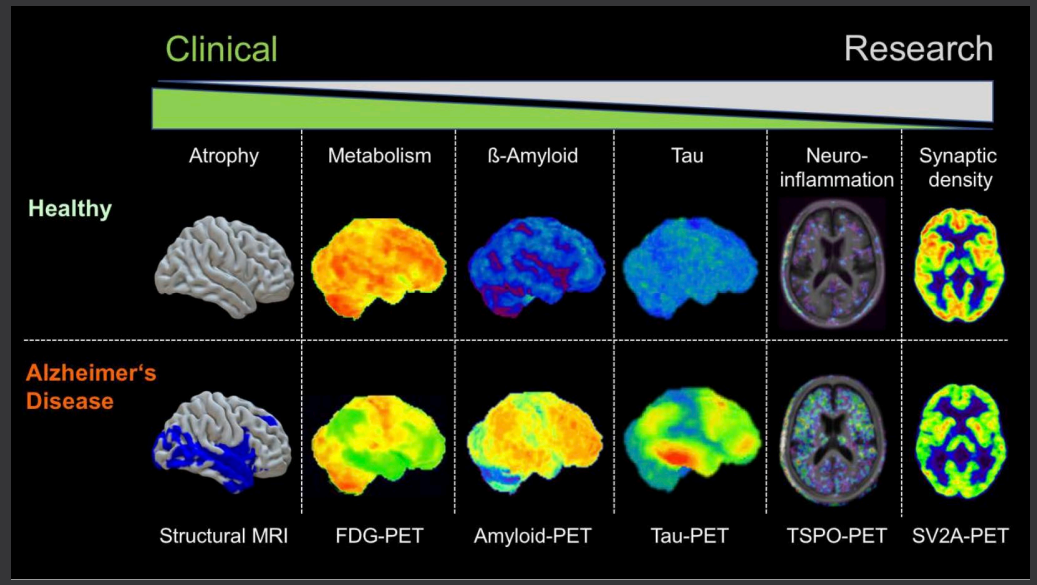
Developing new Alzheimer's disease biomarkers

Using MRI and PET as the gold standard supports development of *less expensive, more convenient* ATN biomarkers.

e.g.. Plasma phosphorylated tau and neurofilament light

ATN neuroimaging can help develop biomarkers of other processes that contribute to, or interact with, amyloid, tau and neurodegeneration.

- Blood-brain barrier dysfunction (dynamic contrast-enhanced MRI)
- Brain blood flow (arterial spin labeling)
- White matter lesions (FLAIR MRI)
- Microstructural damage (diffusion MRI)
- Brain clearance (glymphatic MRI)
- Brain metabolism (FDG PET)
- Brain inflammation (GFAP, TSPO PET)
- Synapse loss (CSF markers, SV2A PET)



Chetelat et al. (2020) *The Lancet Neurology*

ATN neuroimaging applications:
Developing Alzheimer's disease treatments

ATN neuroimaging is critical in AD clinical trials:

<u>Participant selection</u>:

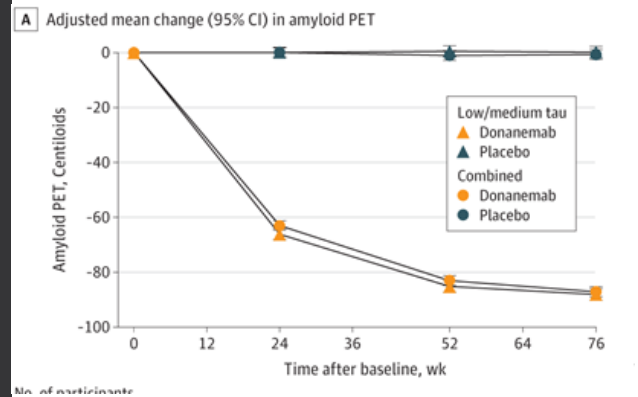
- For drugs targeting amyloid or tau, PET can identify individuals with increased levels.
- Some drugs work best at specific disease stages; ATN imaging can identify individuals at the right stage.

<u>Treatment efficacy</u>:

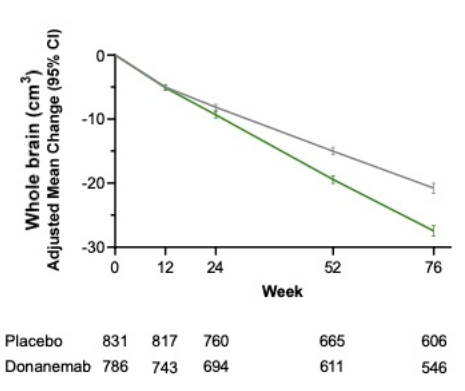
- Did the drug remove amyloid or tau, or slow neurodegeneration?

Donanemab (Kinsula)

Amyloid removal



Brain volume change



Sims et al. (2023) *JAMA*

Risks and contraindications of ATN neuroimaging

MRI

- Large magnetic field (no radiation)
- No metal implants / pacemakers
- Possible claustrophobia, anxiety, exposure to loud noise

PET

- Low levels of radiation equivalent to ~6 years natural environmental exposure
- Injection of radiotracer may be associated with mild pain, light-headedness, bruising, or headache

Will I find out my results?

If you choose, you can receive:

Test	Results shared
Amyloid and tau PET	Abnormally elevated proteins, or normal for age
MRI	Abnormal brain finding CD of brain images
Memory & thinking tests	Summary of results
Lumbar puncture	Abnormally elevated cerebrospinal fluid proteins

How do I participate?

For study questions, screening, and enrollment:

- Nichol Ferng (ADRC study coordinator; **nferng@health.ucsd.edu**)
- Christina Gigliotti (Manager of Clinical Operations; **cgigliotti@health.ucsd.edu**)
- Emilie Reas (ADRC Biomarker Core Co-leader; **ereas@health.ucsd.edu**)

THANK YOU!

UCSD Shiley-Marcos ADRC participants

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