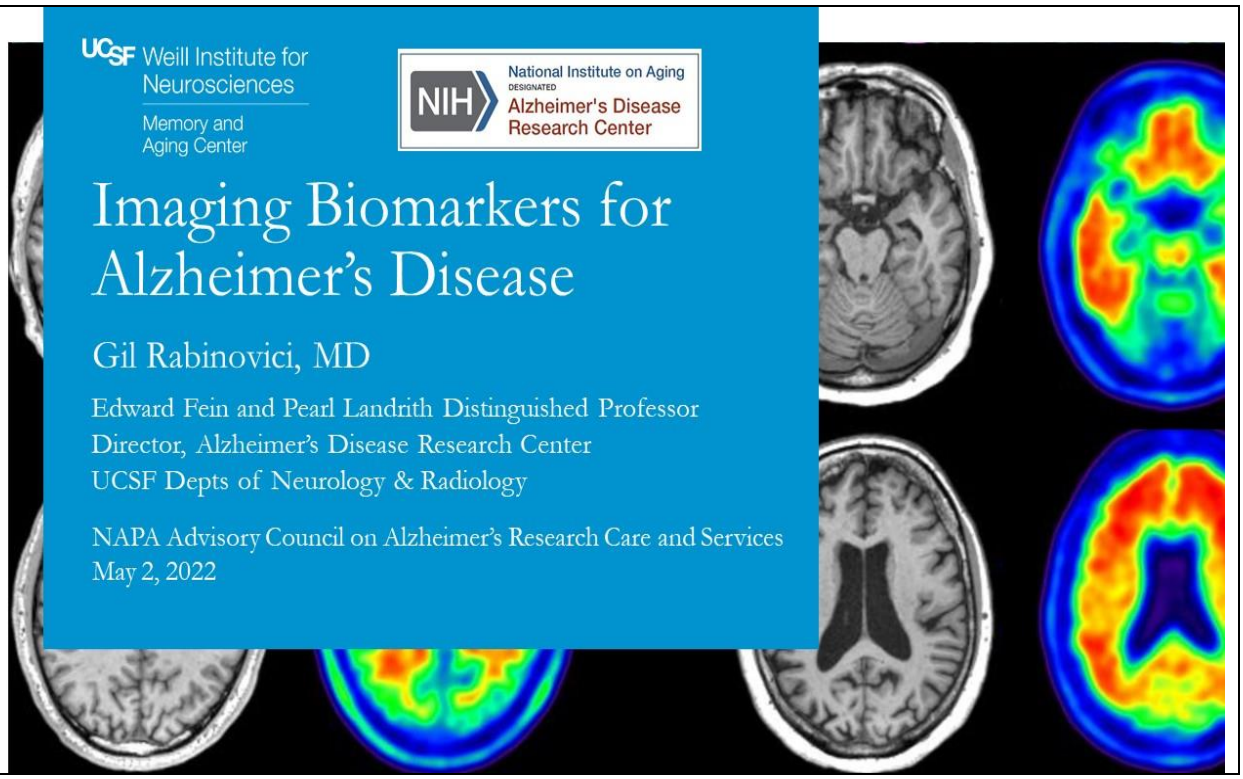

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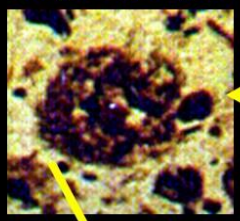
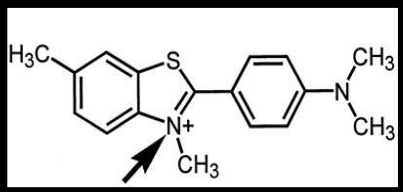
- Consulting/honoraria
  - Eli Lilly, GE Healthcare, Genentech, Johnson & Johnson, Roche

PET Imaging of Amyloid Plaques

Amyloid plaques

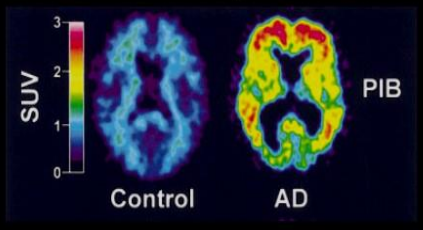


Radiotracer (PIB)



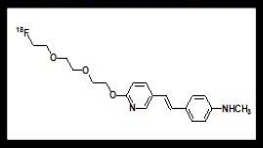
Cyclotron

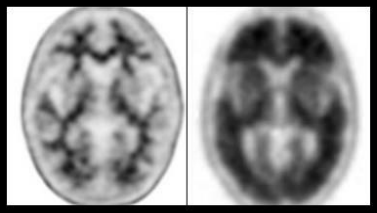
PET Scan



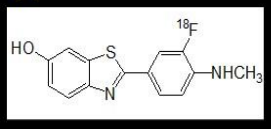
Klunk et al., Ann Neurol 2004

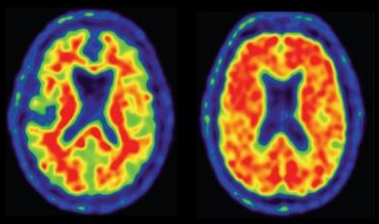
^{18}F-florbetapir (Amyvid™)
FDA approved April 2012



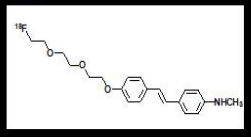


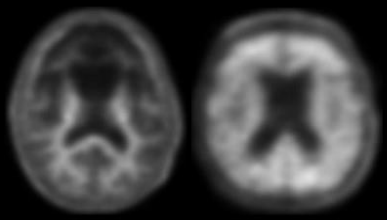
^{18}F-flutemetamol (Vizamyl™)
FDA approved October 2013





^{18}F-florbetaben (Neuraceq™)
FDA approved March 2014





Amyloid PET Visual Reads
PET vs. Autopsy Studies

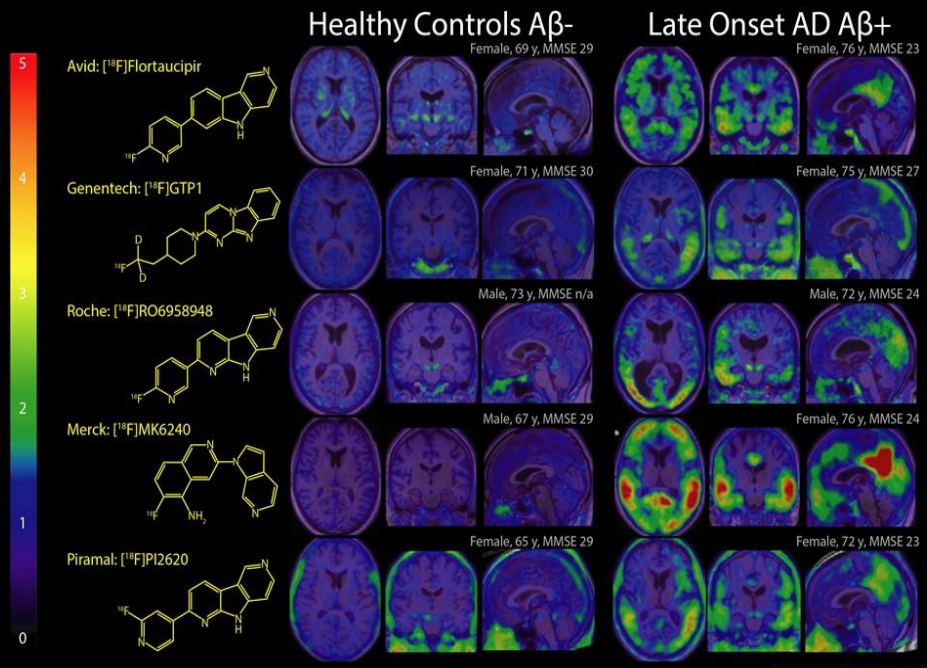
Tracer	N	Report	Sensitivity	Specificity
Florbetapir (Amyvid)[1]	59	Median	92%	95%
Flutemetamol (Vizamyl)[2]	68	Median	88%	88%
Florbetaben (Neuraceq)[3]	82	Median	98%	80%

Sensitivity: Proportion of patients with high amyloid pathology who had a positive PET scan

Specificity: Proportion of patients with low amyloid pathology who had a negative PET scan

1 – Clark et al., Lancet Neurol 2012
2 – Curtis et al., JAMA Neurol 2015
3 – http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204677s000lbl.pdf

Tau PET Ligands

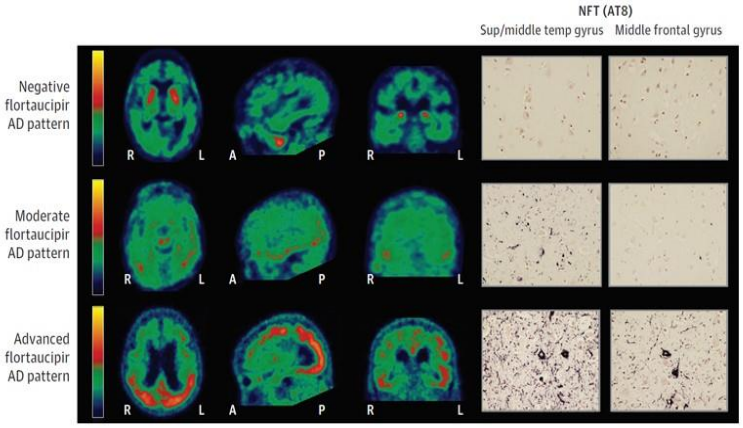


Schöll et al. Mol Cell Neurosci 2019

^{18}F-FTP: PET-to-Autopsy Validation

Patients underwent FTP-PET and autopsy (N=64)
- Mean age 82.5
- PET-to-autopsy 2.6 months
- Visual reads vs. Braak V/VI tau neuropathology

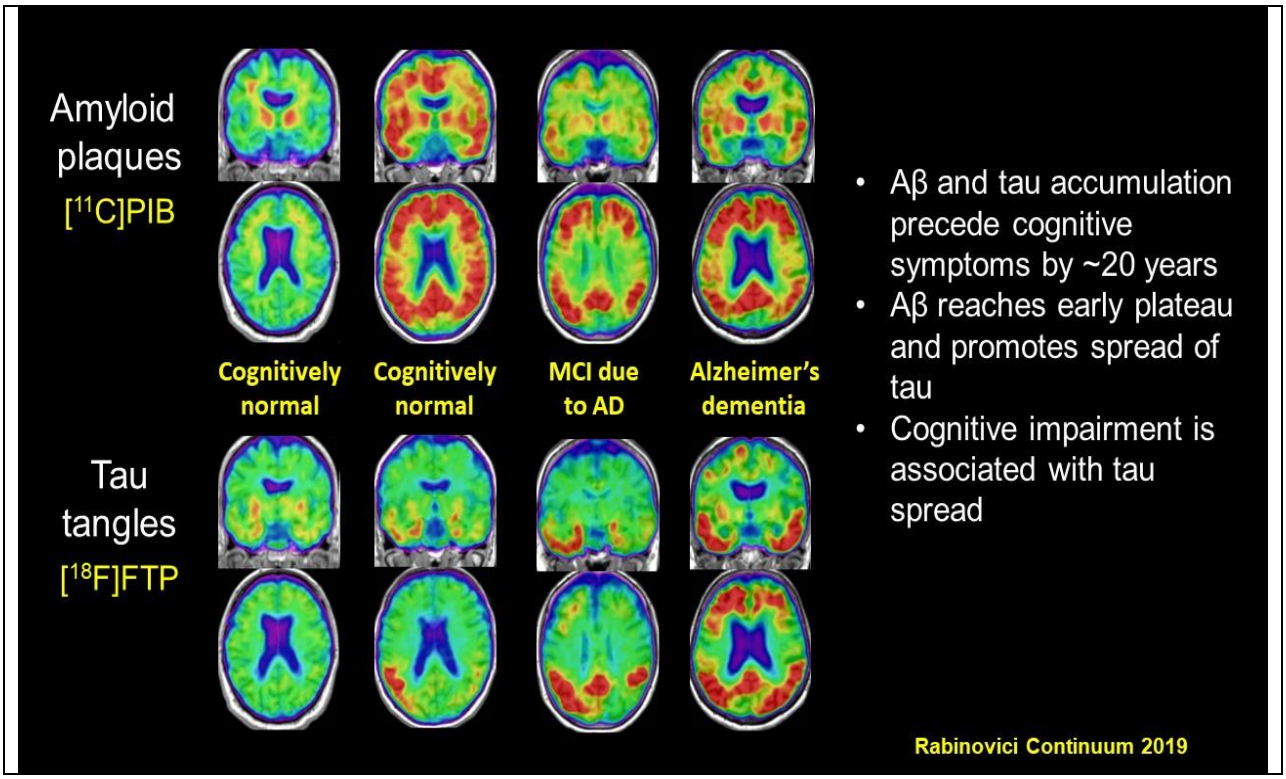
Majority reads (5 raters)
- Sensitivity 92%
- Specificity 80%



FDA approval May 28, 2020

"To estimate the density and distribution of NFTs in adult patients with cognitive impairment being evaluated for AD"

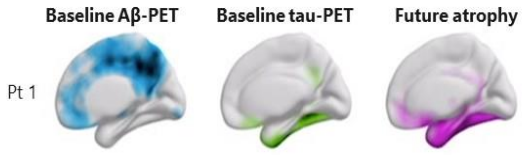
Fleisher et al. JAMA Neuro 2020



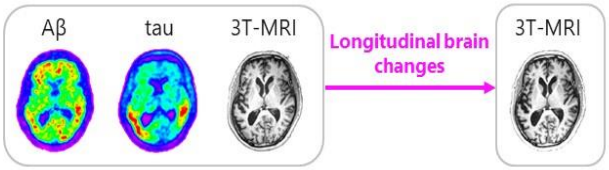
- Aβ and tau accumulation precede cognitive symptoms by ~20 years
- Aβ reaches early plateau and promotes spread of tau
- Cognitive impairment is associated with tau spread

Rabinovici Continuum 2019

Baseline Tau Predicts Future Brain Atrophy



32 patients with MCI/AD dementia



15 ± 3 months

La Joie et al. Sci Trans Med 2020

IDEAS
Imaging Dementia—Evidence For Amyloid Scanning

Co-Chairs:
Rabinovici, Carrillo, Gatsonis, Hillner, Siegel, Whitmer

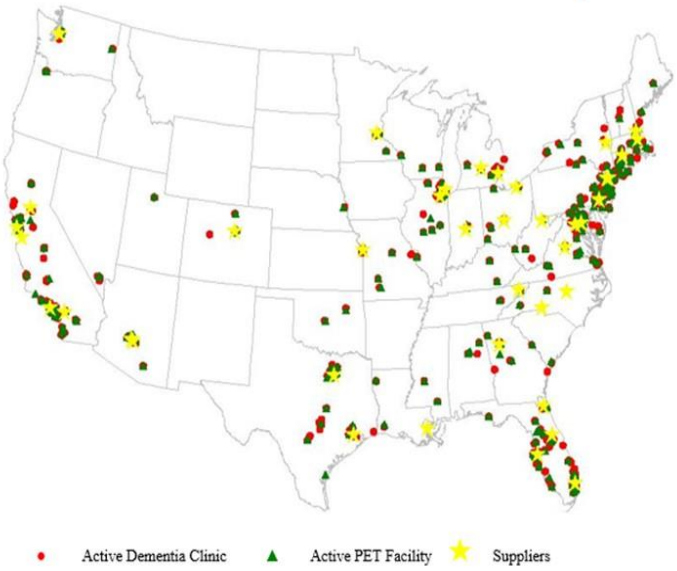
IDEAS-Study@acr.org
IDEAS-Study.org

U.S-wide, longitudinal study on utility of amyloid PET in ~18,000 U.S. adults over age 65 with mild cognitive impairment (MCI) or dementia of uncertain cause

- Eligible patients referred for PET by dementia specialists
- Scans covered by Medicare, performed and interpreted locally

- Aim 1: Impact of scan on patient management plan at 3 months
- Aim 2: Impact on major medical outcomes at 12 months
- *The primary hypothesis is that, in diagnostically uncertain cases, amyloid PET will lead to significant changes in patient management, and this will translate into improved medical outcomes*

IDEAS Study Network



595 dementia practices
- 79% private/group practice
- 946 dementia specialists

343 PET facilities
- 733 imaging specialists

18,295 scans completed

Median age 75 (65-105)
- 60.4% MCI
- 39.6% dementia

PET Aβ+:
- MCI 55.2%
- Dementia 69.6%

IDEAS-Study.org

Rabinovici et al. JAMA 2019

IDEAS Imaging Dementia–Evidence For Amyloid Scanning

Primary Results of IDEAS Study

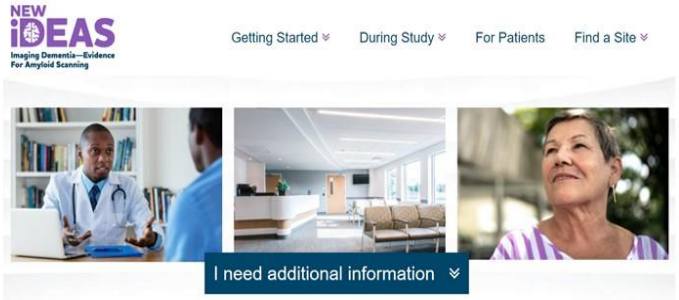
- **Amyloid PET had a profound impact on diagnosis and care plan**
  - Diagnosis changed from AD to non-AD in 25%, non-AD to AD in 11%
  - Patient management changed after PET in 60% of MCI and 64% of dementia
- **Amyloid PET had a modest impact on major medical outcomes**
  - 4.5% relative reduction in 12-months hospitalizations, no impact on12-months emergency room visits
  - Aβ PET-positive patients had *lower* hospitalization rates than Aβ PET-negative
- **Amyloid PET results were disclosed safely to impaired participants**
  - No reports of psychological harm at post-PET visits; no known suicides
- **Low rate of referrals of minoritized groups**
  - 3.7% Black/African-American, 4.8% Hispanic/Latino

IDEAS-Study.org

Rabinovici et al. JAMA 2019, AAIC 2020, CTAD 2020, AD/PD 2021

IDEAS Imaging Dementia–Evidence For Amyloid Scanning

New IDEAS: A Study to Improve Precision in Amyloid PET Coverage and Patient Care



- **Recruit diverse cohort of 7,000 Medicare beneficiaries**
  - At least 2,000 African-Americans/Blacks and 2,000 Latinx/Hispanics
  - Typical and atypical clinical presentations of AD
  - Early-onset and late-onset dementia
  - Biorepository (DNA and plasma) and image archive

IDEAS-Study.org

NEW iDEAS

Underrepresented Community Recruitment

NEW iDEAS
Imaging Dementia—Evidence For Amyloid Scanning

Metro Area Community Engagement

- Washington D.C., Chicago, Dallas, Houston, Los Angeles, Miami, Philadelphia, San Diego
- Partnership with ALZ on community engagement activities

National Engagement

- National awareness campaigns
- New IDEAS Advisory boards
- Culturally adapted recruitment materials

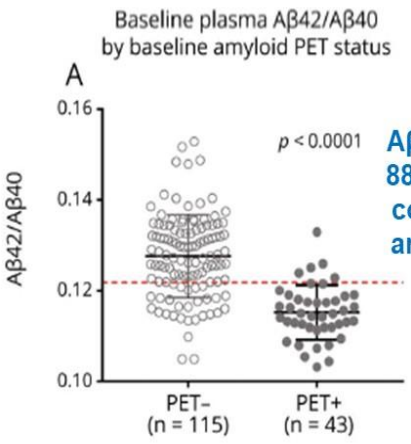
Support Dementia Experts & Facilities

- Identify experts with capacity to enroll underrepresented community volunteers
- Support training and materials for experts and facilities

ALZHEIMER'S ASSOCIATION

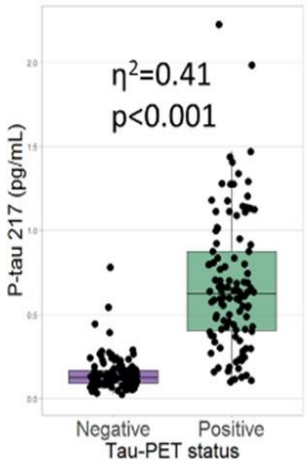
NewIDEAS@acr.org
IDEAS-Study.org

Validating Aβ and Tau Blood Tests Using PET



Aβ blood test 88% accurate compared to amyloid PET scan

Schindler et al. Neurology 2019



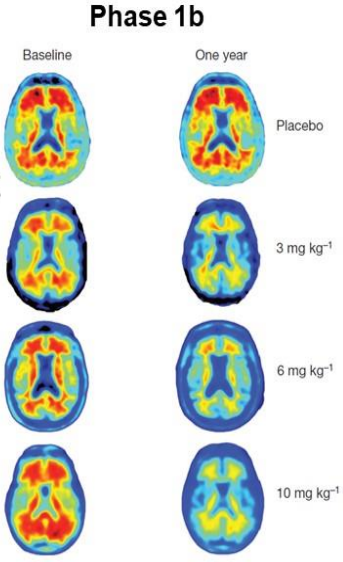
pTau217 blood test 96% accurate compared to tau PET scan

Thijssen et al. Lancet Neurol 2021

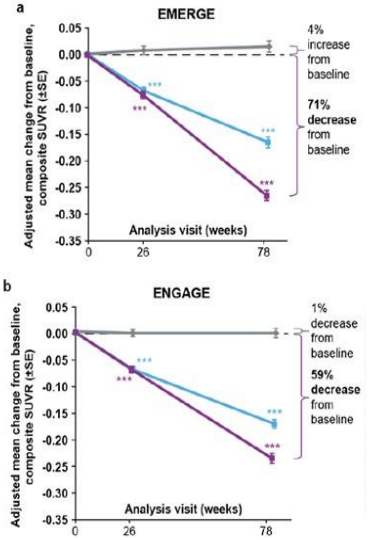
Aβ PET in AD Drug Development and Clinical Trials

- Patient Selection
- Early intervention
- Target engagement

Aducanumab
(humanized anti-Aβ monoclonal ab)



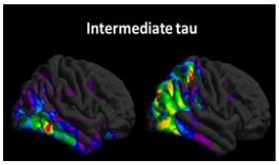
Sevigny et al. Nature. 2016



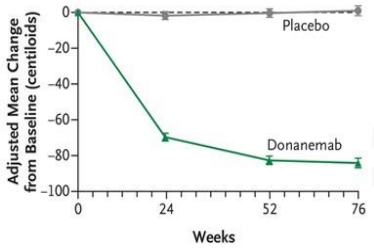
Haeberlein et al. JPAD 2022

Donanemab: "Next Generation" AD Clinical Trial

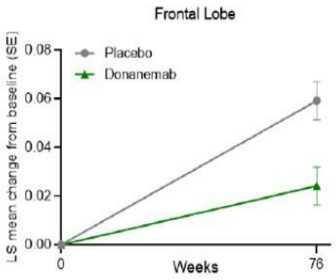
- Phase II trial of anti-Aβ antibody in MCI/early AD
- Only patients with intermediate tau PET uptake included
- Antibody dose titrated to PET response, switch to placebo when Aβ PET turned negative



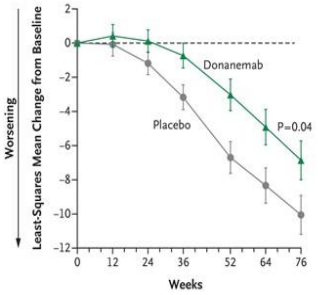
Aβ cleared on PET



Slowing of Regional Tau PET



Clinical benefit on iADRS



Mintun et al. NEJM 2021

Conclusions

- Amyloid and tau PET have accelerated AD research
  - Detect pathology and follow the evolution of AD in living people
  - Major impact on clinical trials and drug development
  - Accelerate development and validation of blood biomarkers
  - Improve diagnosis and care in clinical practice
- Advances in biomarkers will lead to novel therapies
  - Better designed clinical trials at earlier disease stages
  - PET will play a role in evaluating treatment eligibility and response
  - Paradigm shift from treating symptoms to early (pre-clinical) detection and disease prevention

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RAB LAB

NIH National Institute on Aging DESIGNATED Alzheimer's Disease Research Center