# Alzheimer's Disease Biomarkers: Transforming Care and Drug Development

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**Health Research Alliance Members Meeting**
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# Disclosures

- Research support
  - Avid Radiopharmaceuticals, Eli Lilly, GE Healthcare, Piramal Imaging
  - NIH, American College of Radiology, Alzheimer's Association, Tau Consortium, Association for Frontotemporal Degeneration, Michael J Fox Foundation
- Consulting/honoraria
  - Eisai, Genentech, Lundbeck, Merck, Putnam, Roche
  - Associate editor, JAMA Neurology

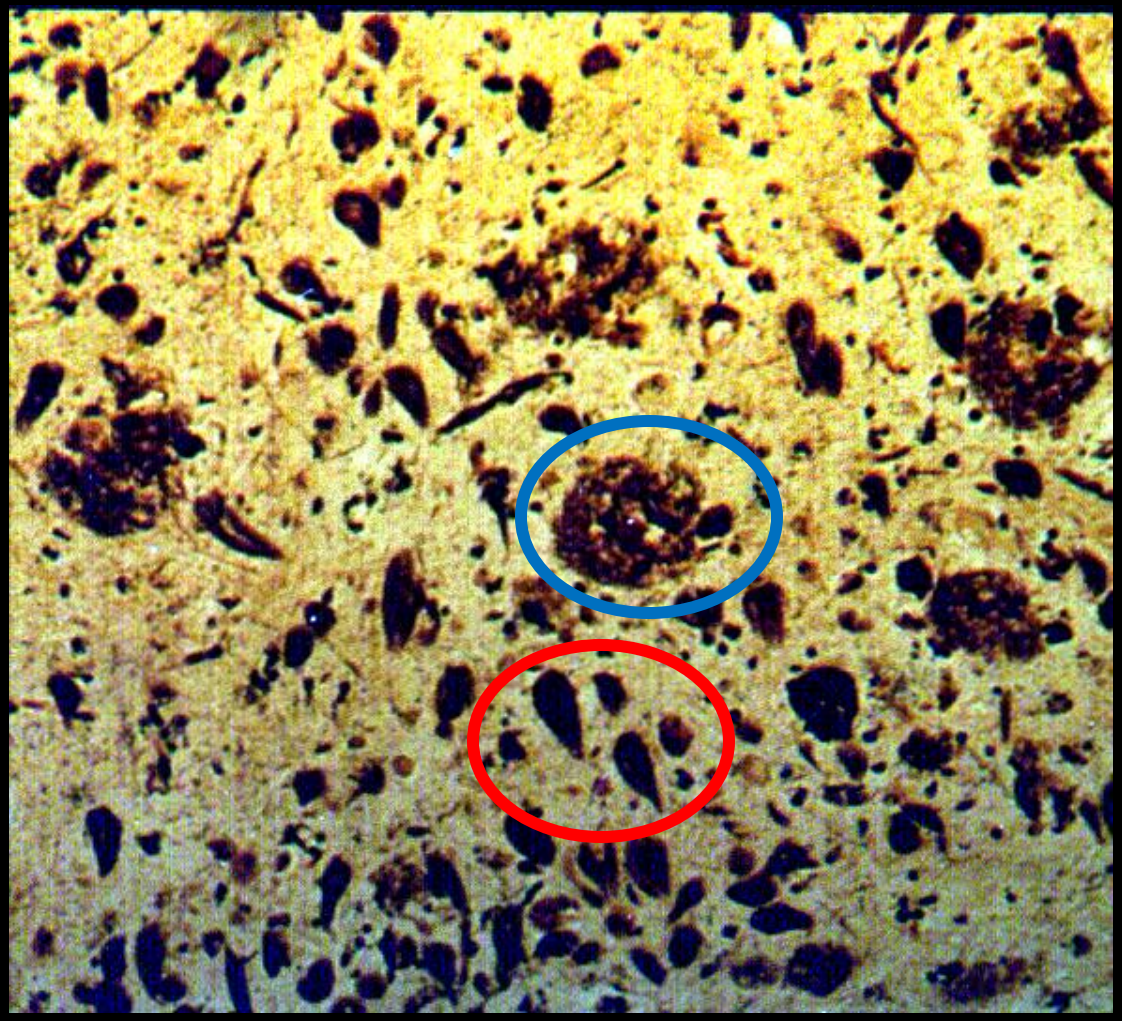
# Alzheimer's Disease (AD)

**Amyloid plaques**

- Extra-cellular
- Amyloid-β (Aβ)

**Neurofibrillary tangles**

- Intra-cellular
- Tau



# Importance of Measuring Plaques and Tangles During Life

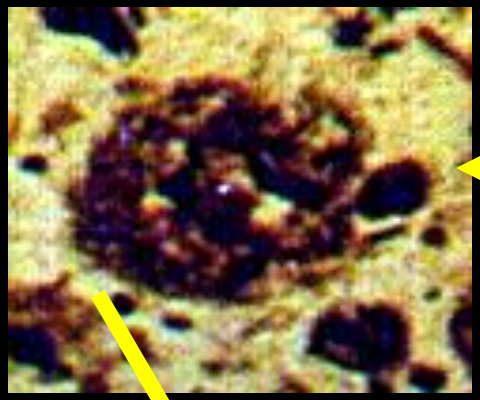
- Enable study of disease dynamics in humans
  - No single animal model recapitulates all elements of human disease
- Better diagnosis
  - Clinical diagnosis of AD only ~70%-80% accurate compared to autopsy
- Early detection and intervention
  - Pathology begins 15 years or more before symptoms
- Improve drug trials
  - Require biomarkers for subject inclusion
  - Determine if drugs engaging target

# Outline

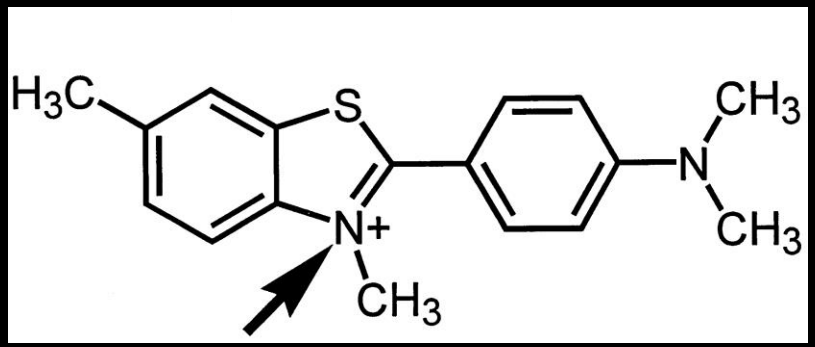
- Amyloid PET: the molecular imaging revolution
  - Early detection, preclinical disease
  - FDA approval, reimbursement: IDEAS Study
  - Biomarker-oriented clinical trials
- Tau PET: an emerging tool
  - Aging to AD continuum
  - Non-AD tauopathies
- Fluid-based biomarkers (Dr. Jim Hendrix)
  - CSF
  - Blood

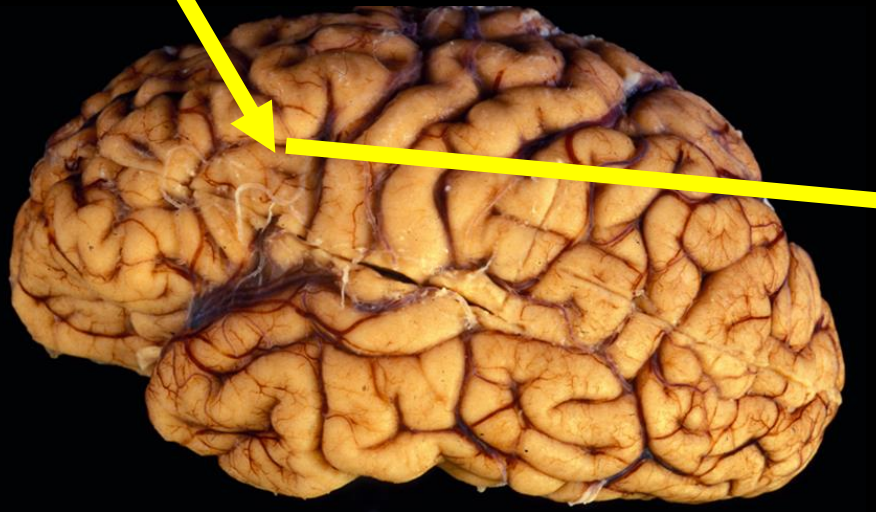
# Imaging Amyloid Plaques (PIB-PET)

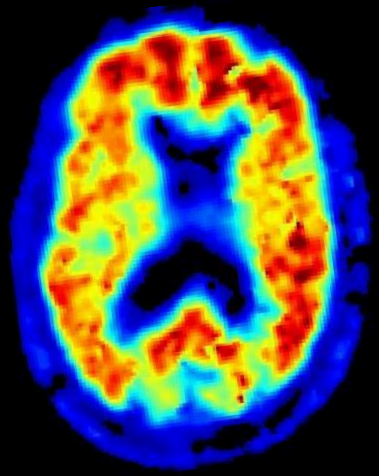
**Amyloid plaques**



**Pittsburgh Compound B (PIB)**

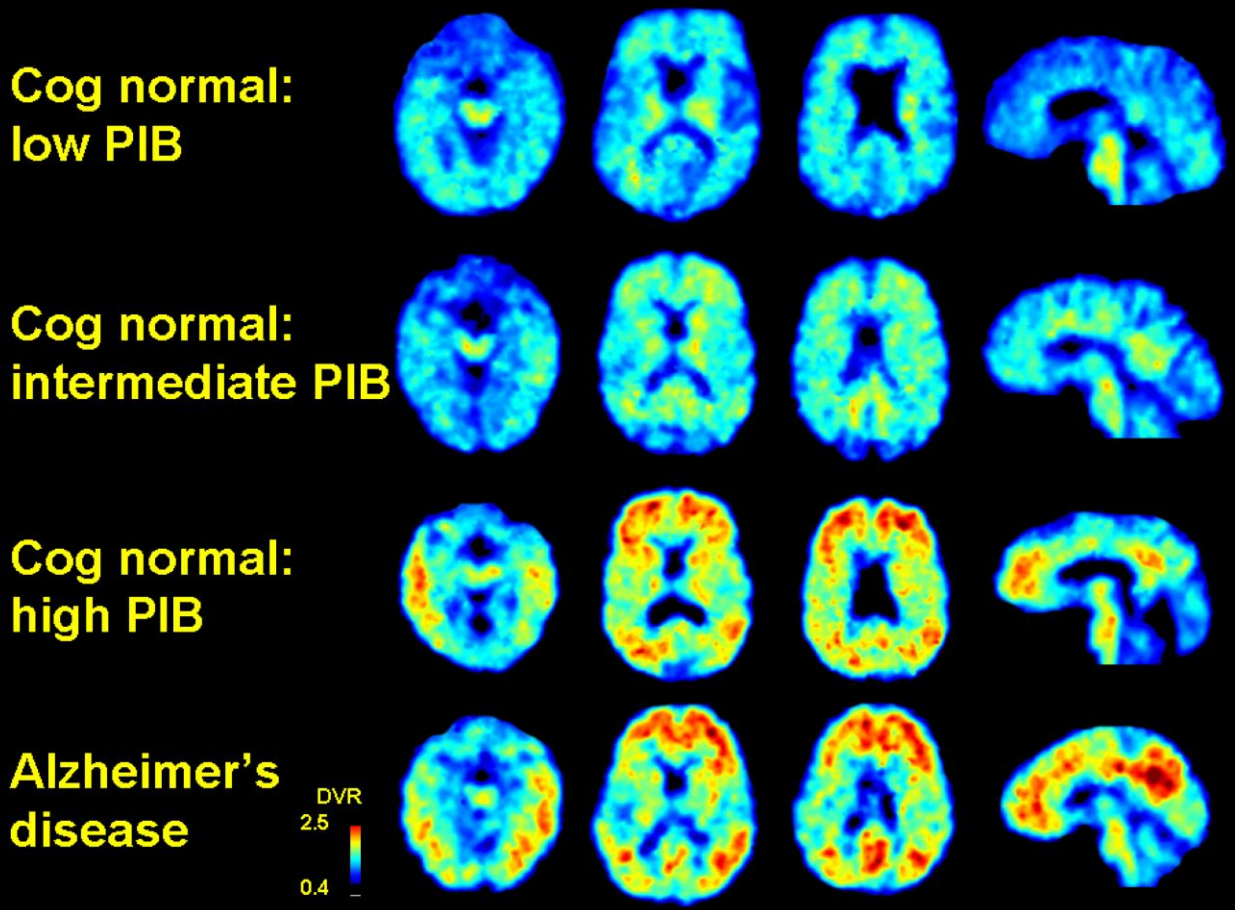




Klunk et al. Ann Neurol 2004

# Amyloid Positivity in Normal Older Adults: Concept of Preclinical AD




15%-30% of cognitively normal older adults are Aβ+

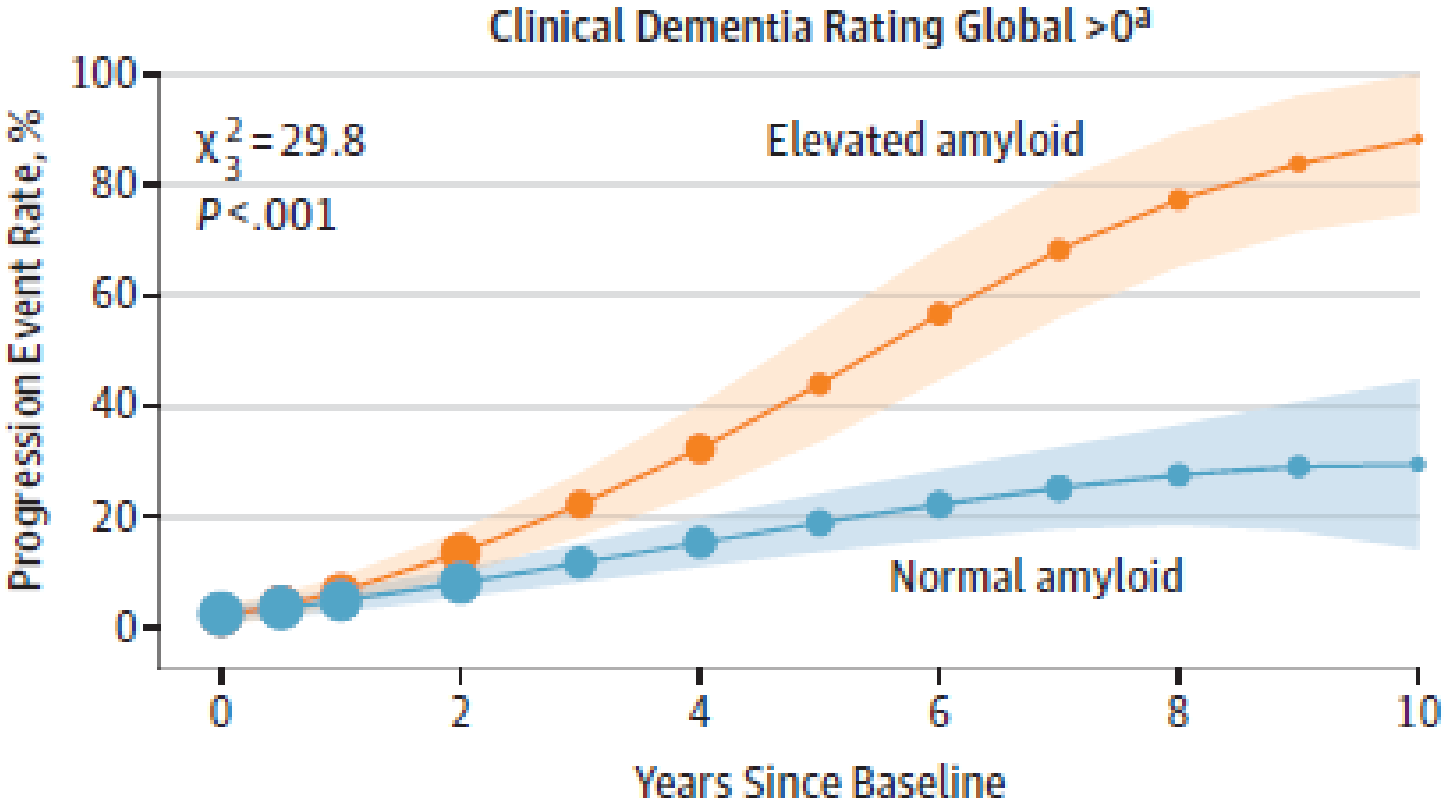
- More common in ApoE4+ and older age

Aβ+ "controls"

- AD-like structural and functional brain changes
- Longitudinal cognitive decline
- Elevated risk of incident cognitive impairment

**Mintun 2006; Pike 2007; Mormino 2009 & 2011; Sperling 2011; Chételat 2012; Petersen 2015**

# Aβ PET+ Predicts Cognitive Decline in Aging

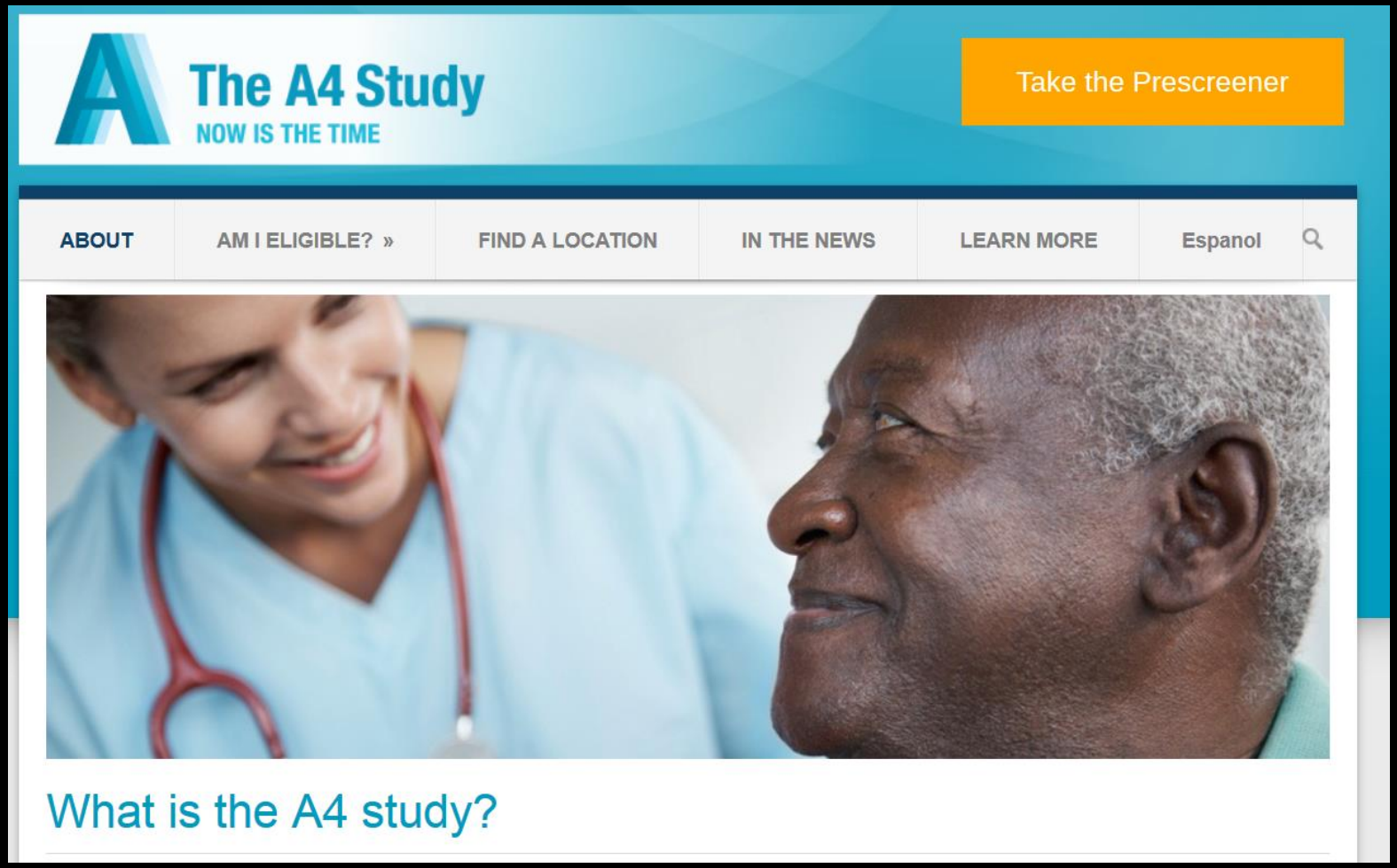



No. of patients, by amyloid level

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Elevated | 196 | 148 | 169 | 66 | 79 | 32 | 38 | 30 | 26 | 16 | 8 |
| Normal | 239 | 194 | 199 | 98 | 99 | 58 | 61 | 55 | 39 | 30 | 10 |

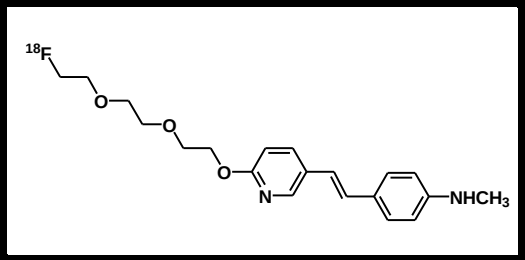
**Donohue et al., et al., JAMA 2017**

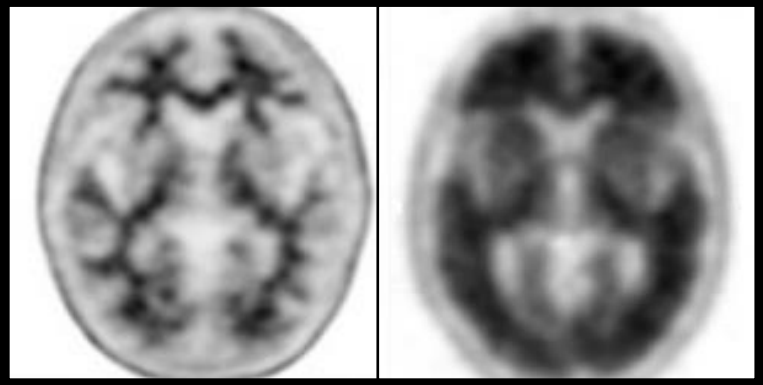
# Amyloid PET in Drug Development: Subject Selection and Early Intervention



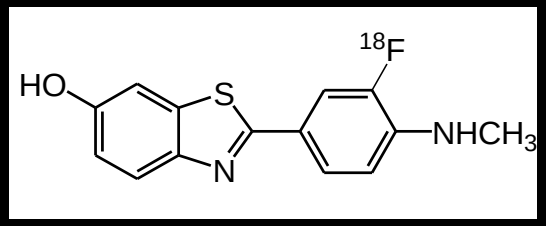

a4study.org

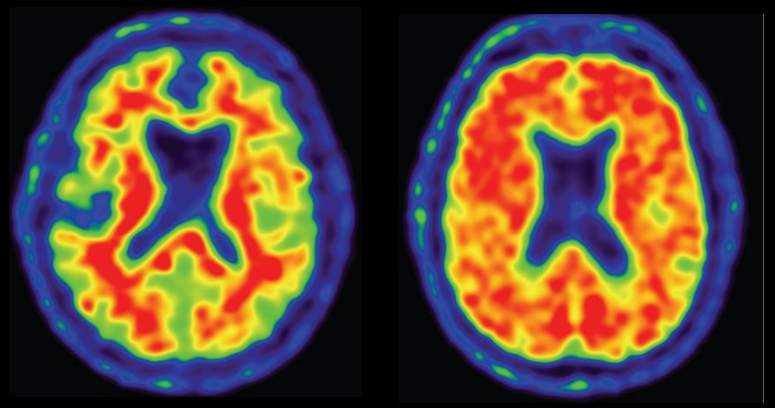
## $^{18}$F-florbetapir (Amyvid™)
## FDA approved April 2012



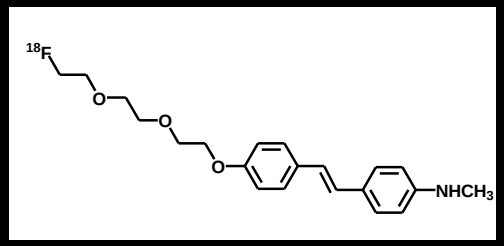



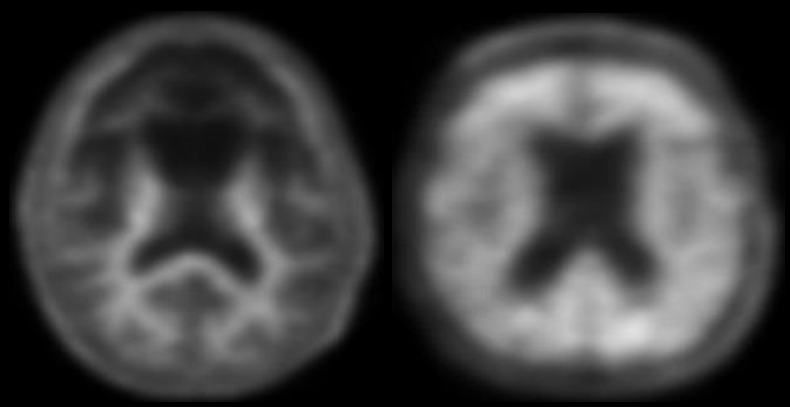
## $^{18}$F-flutemetamol (Vizamyl™)
## FDA approved October 2013



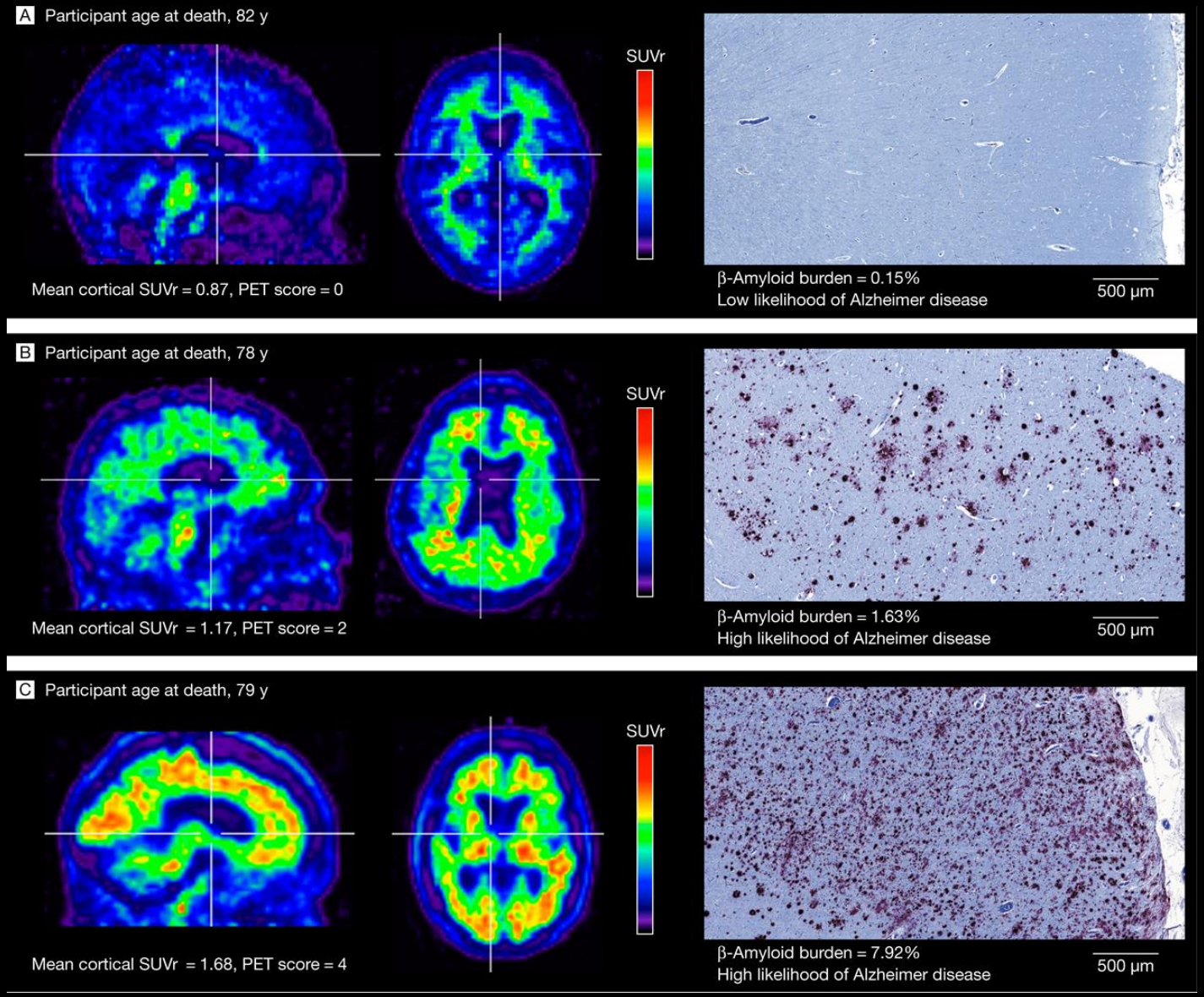



## $^{18}$F-florbetaben (Neuraceq™)
## FDA approved March 2014



# Pathology Validation: Florbetapir PET




Radiologist reads

92% positive when amyloid was present at autopsy

95% negative when amyloid was absent at autopsy

**Clark et al. JAMA 2011, Lancet Neurol 2012**

# 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% |

**Gold standard: moderate- frequent neuritic plauques (CERAD)**


**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**

# Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N)

- **Insufficient evidence of clinical utility to justify coverage of Aβ PET**
- **Reimbursement would be considered under coverage with evidence development (CED) in clinical studies designed to:**
  - *Develop better treatments or prevention strategies for AD*
  - *Identify subpopulations at risk for developing AD*
  - *Resolve clinically difficult differential diagnoses (e.g., frontotemporal dementia versus AD)*
- **Must demonstrate Aβ PET improves health outcomes (short-term outcomes related to changes in management as well as longer-term dementia outcomes)**

IDEAS

Imaging Dementia—Evidence For Amyloid Scanning

IDEAS-Study@acr.org

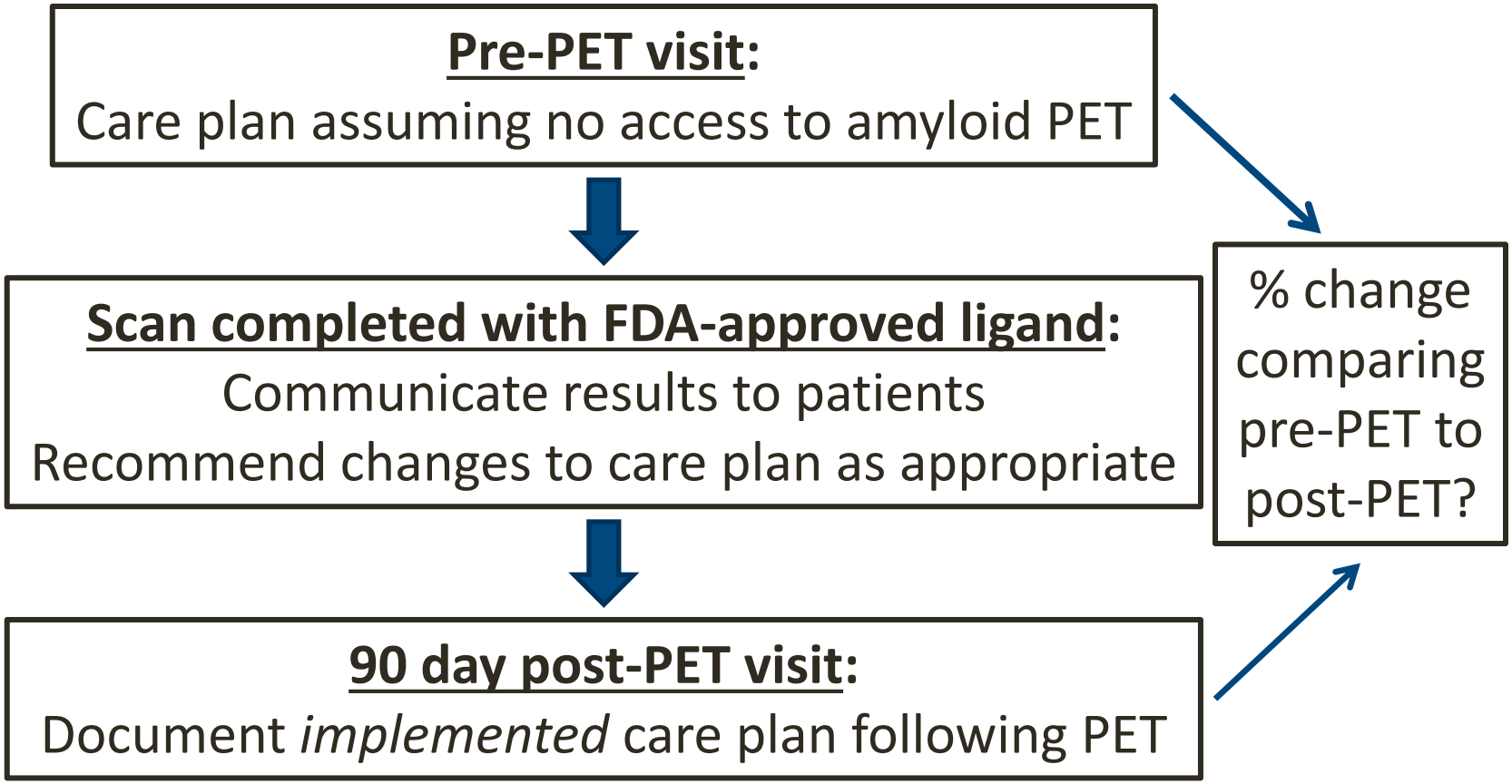
IDEAS-Study.org

- National, open-label study on utility of amyloid PET in ~18,500 Medicare beneficiaries with mild cognitive impairment (MCI) or dementia of uncertain etiology
  - Eligible patients referred for PET by dementia experts
  - Scans covered by CMS, performed and interpreted locally
- Aim 1: Impact of scan on 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*

# Interim Analysis: Objective

- To report early results assessing changes in patient management in the first 3,979 participants in whom case report forms were completed before and ~90 days after PET
- This represents a pre-specified analysis to assess the feasibility of detecting a ≥ 30% change in management based on observed results in the first 1/3 of the Aim 1 cohort

# Aim 1 Study Flow






IDEAS
Imaging Dementia—Evidence For Amyloid Scanning

# Methods: Analysis

- **Primary outcome: change in composite score:**
  - Change in AD drugs (cholinesterase inhibitors or memantine)
  - Change in non-AD drugs
  - Change in counseling and planning
- **Interim analysis sample size: N=3,979 completed post-PET**
  - 1/3 of total Aim 1 accrual (N=11,050, 80% power to detect ≥ 30% change in MCI and dementia)

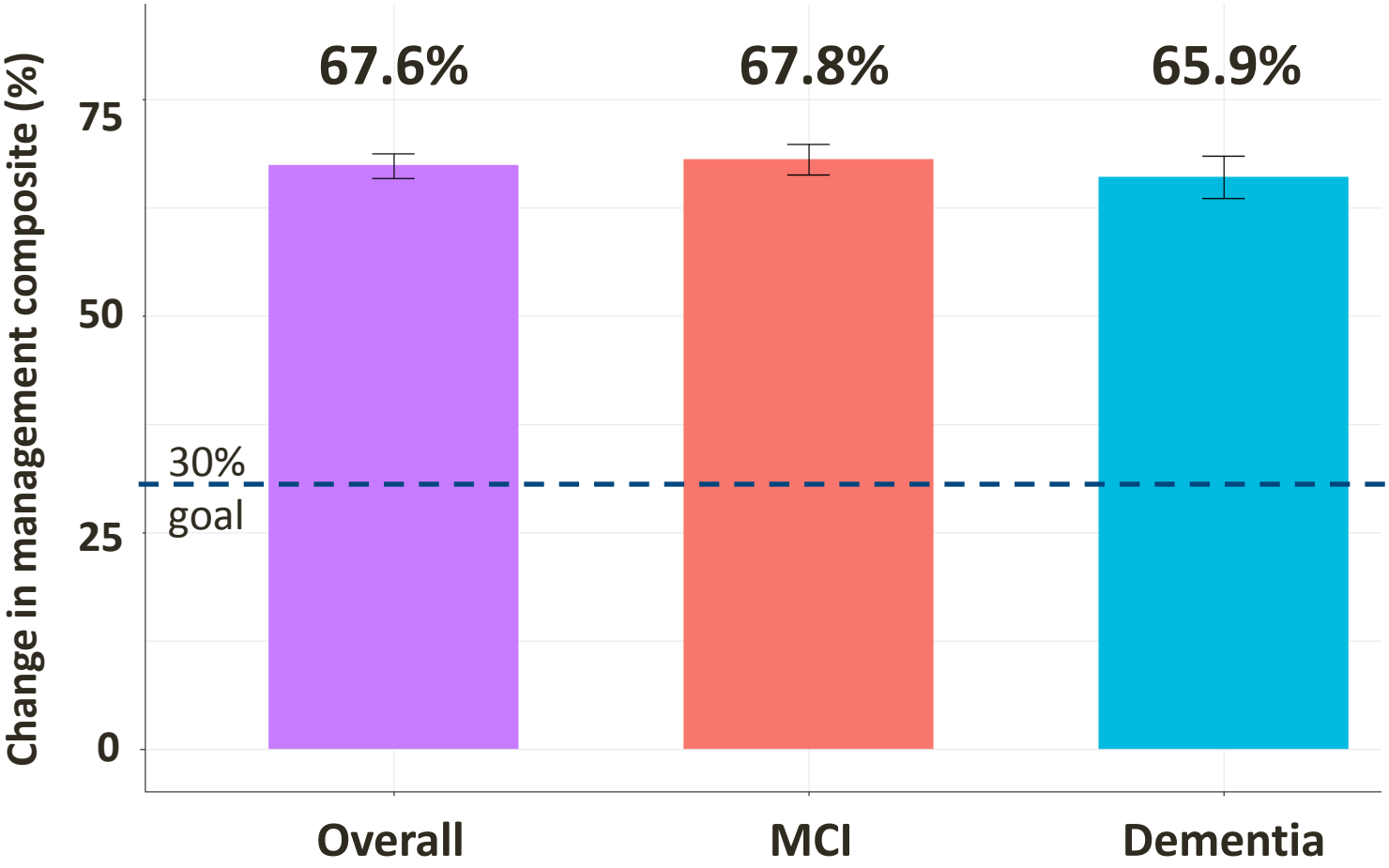
# Demographics, N=3,979

## 64.3% MCI, 35.7% dementia

| *Characteristic* | *MCI* | *Dementia* | *All* |
|---|---|---|---|
| Age, mean (s.d.) | 75(6.1) | 77(6.5) | 75(6.3) |
| Sex, n female (%) | 1,281(50.0) | 736(51.9) | 2,017(50.7) |
| Caucasian, n (%) | 2,349(91.7) | 1,248(88.0) | 3,597(90.4) |
| MMSE, mean (s.d.) | 26(3.3) | 20(5.5) | 24(5.0) |
| MoCA, mean (s.d.) | 22(3.8) | 17(5.8) | 20(5.1) |
| Leading suspected etiology AD, n (%) | 1,895(74.0) | 1,141(80.5) | 3,036(76.3) |
| Taking AD drugs at enrollment, n (%) | 951(37.1) | 919(64.8) | 1,870(47.0) |
| PET results, n (% positive for β-amyloid) | 1,391(54.3) | 999(70.5) | 2,390(60.1) |

MMSE – Mini-Mental State Exam; MoCA – Montreal Cognitive Assessment

# High Rate of Management Changes After PET




IDEAS-Study.org

Rabinovici et al., AAIC 2017

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# Change by Management Domain

| Domain | MCI | Dementia |
|---|---|---|
| AD drugs | 47.8% | 47.7% |
| Non-AD drugs | 36.0% | 32.2% |
| Counseling | 23.9% | 15.9% |
| Overall | 67.8% | 65.9% |

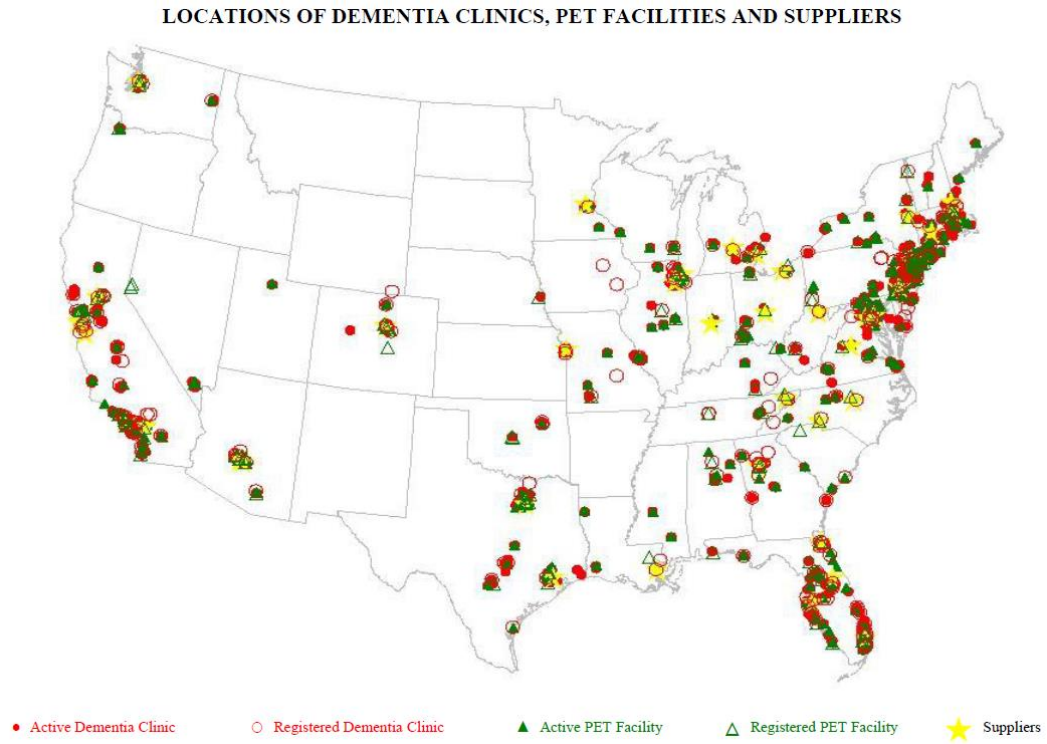


Rabinovici et al., AAIC 2017

# More Precise Diagnosis and Treatment Post-PET

- **Concordance between diagnosis and PET results**
  - Pre-PET diagnosis AD: 61.2% amyloid PET+
  - Pre-PET diagnosis non-AD: 54.5% amyloid PET+
- **PET led to changes in diagnosis**
  - In patients with *positive* scan, rate of AD diagnosis *increased* from 78.5% pre-PET to 95.2% post-PET
  - In patients with *negative* scan, rate of AD diagnosis *decreased* from 73.0% pre-PET to 14.5% post-PET
- **PET modified use of AD drugs**
  - In patients with *positive* scan, use of AD drugs *increased* from 50.9% pre-PET to 83.8% post-PET
  - In patients with *negative* scan, use of AD drugs *decreased* from 39.1% pre-PET to 30.8% post-PET

## 673 active dementia practices
## 1,142 dementia experts




## 394 active PET facilities

**14,514** patients registered

**13,733** scans completed

Median age 75 (range: 65-105)

59.7% MCI, 40.3% dementia

Aβ-PET positive:

MCI 54.6%, dementia 69.2%

**95.5%** consent to use images

**82.5%** consent to be contacted about other research

**BHR (web-based cognitive)**

**ANGI (DNA collection)**

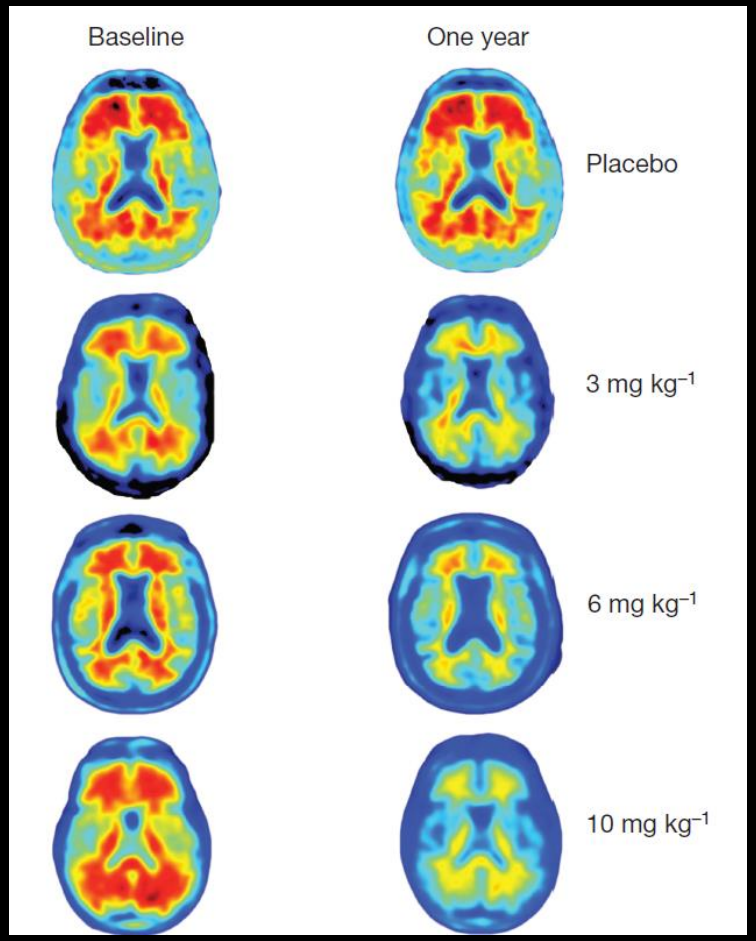
**CARE-IDEAS**

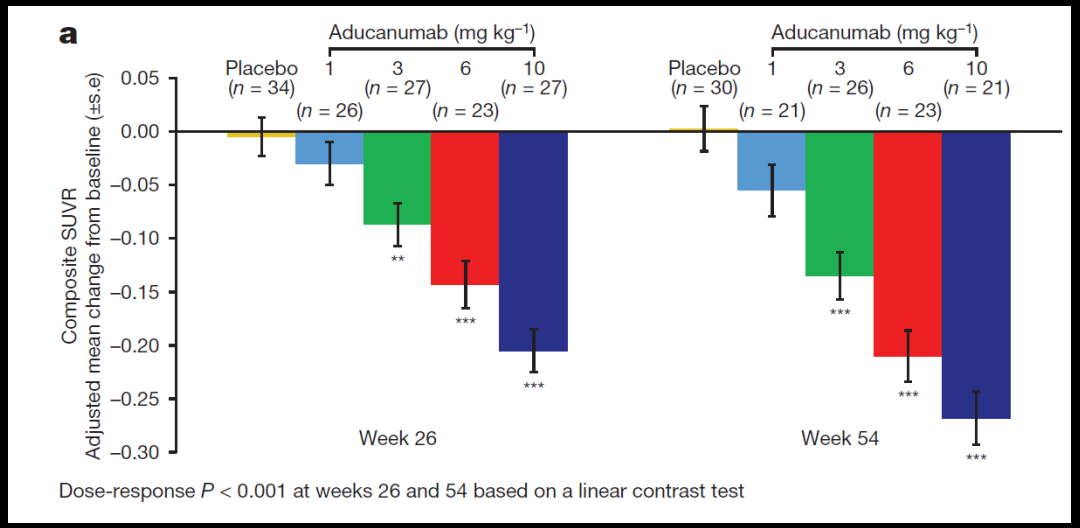
**Anticipate completing recruitment ~Jan-Feb 2018**

**IDEAS-Study.org**

IDEAS
Imaging Dementia—Evidence For Amyloid Scanning

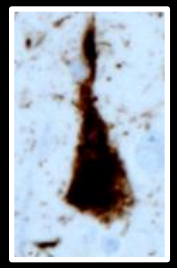
# Amyloid PET in Drug Development: Assessing Target Engagement




Aducanumab (humanized monoclonal Anti-Aβ antibody) Phase Ib RCT

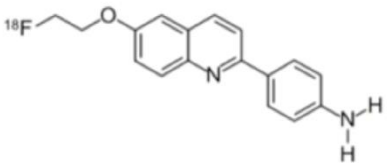
**Sevigny et al., Nature 2016**



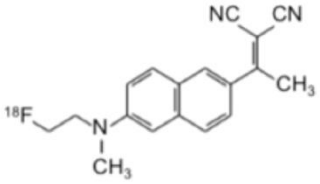
# Tau as an Imaging Target

- Study *in vivo* relationships between Aβ, Tau and aging brain
- Disease staging and progression
  - Autopsy studies suggest symptoms correlate better with tangles than plaques
- Biomarker for non-AD tauopathies
  - Chronic Traumatic Encephalopathy
  - Frontotemporal dementia
  - Atypical parkinsonian disorders (PSP, CBD)
- Evidence of target engagement and disease modification

# Landscape of Tau Tracers




$^{18}$F-THK-523

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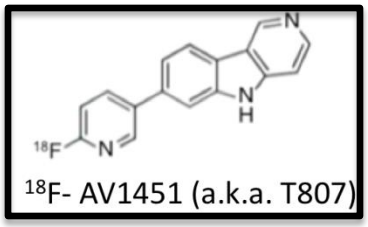
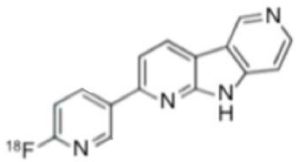



$^{18}$F- AV1451 (a.k.a. T807)

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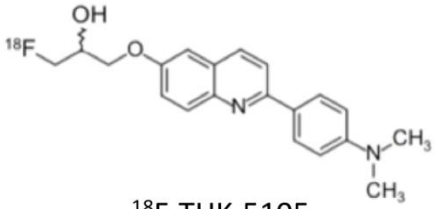


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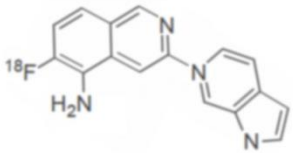


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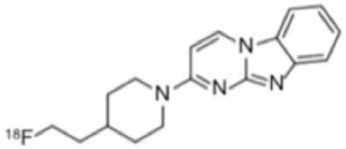


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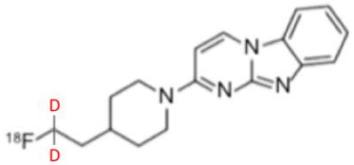


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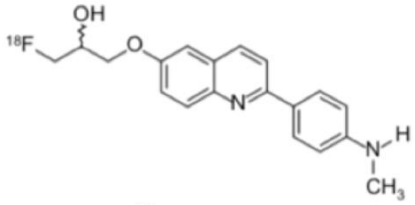


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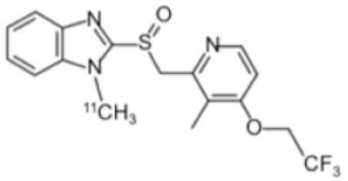
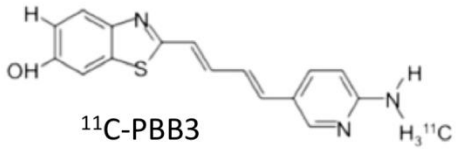



$^{11}$C-N-Methyl Lansoprazole




$^{11}$C-PBB3

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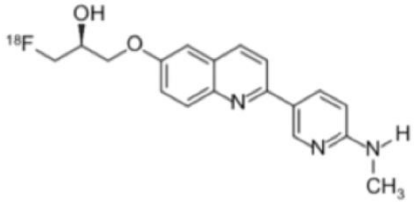
$^{18}$F-PI-2620

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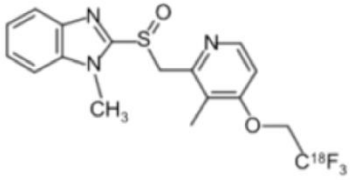


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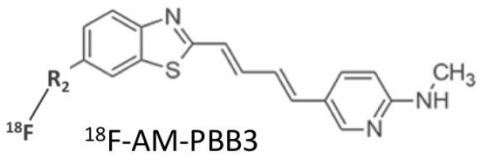


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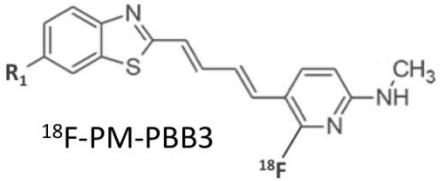
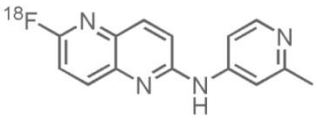


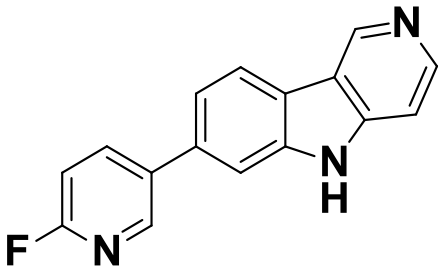

$^{18}$F-PM-PBB3

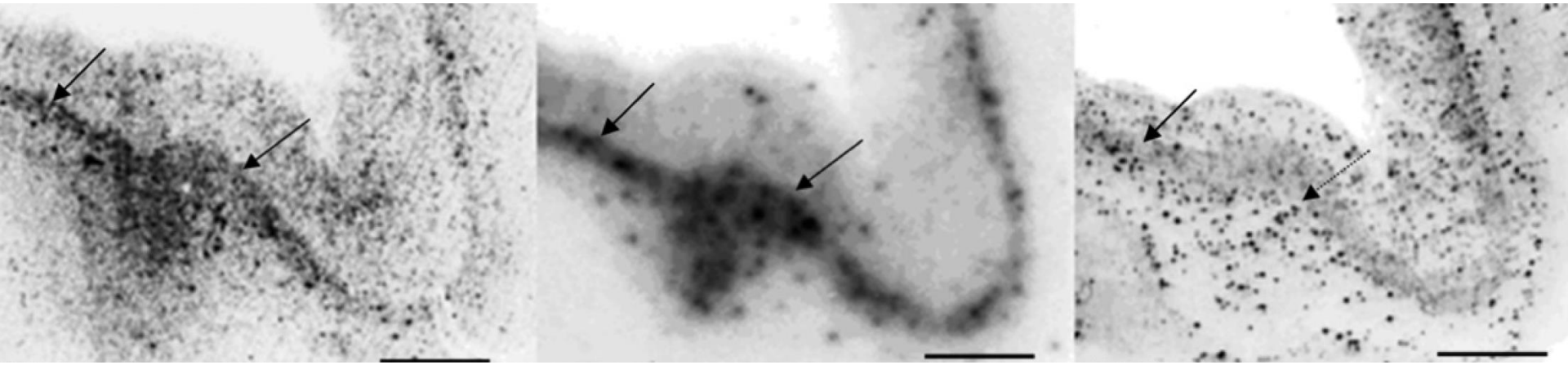



$^{18}$F-JNJ311

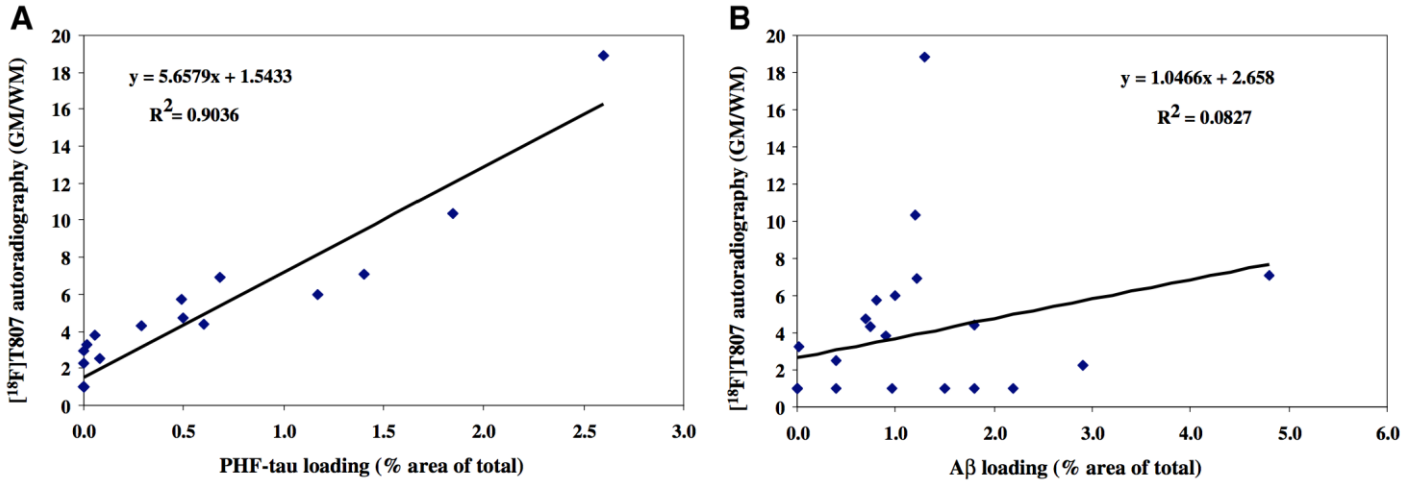
Slide courtesy of Victor Villemagne

# [$^{18}$F]AV1451/T807/FTC: PHF-Tau Tracer



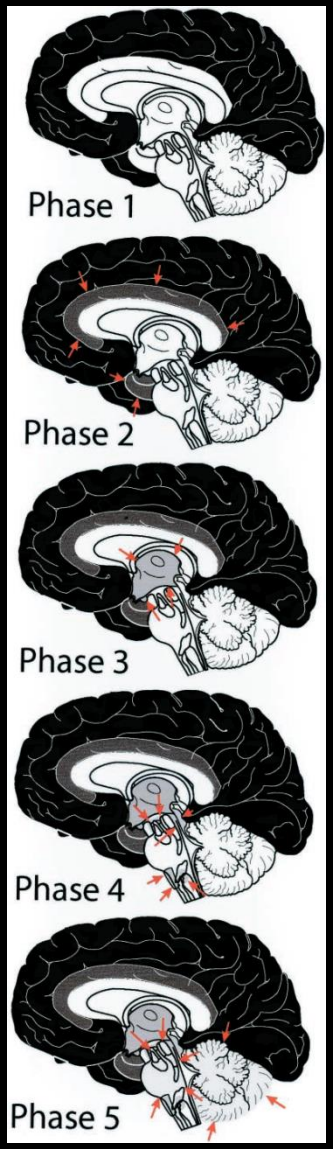
PHF tau IHC (AT8) [18F] T807 autoradiography Amyloid β IHC

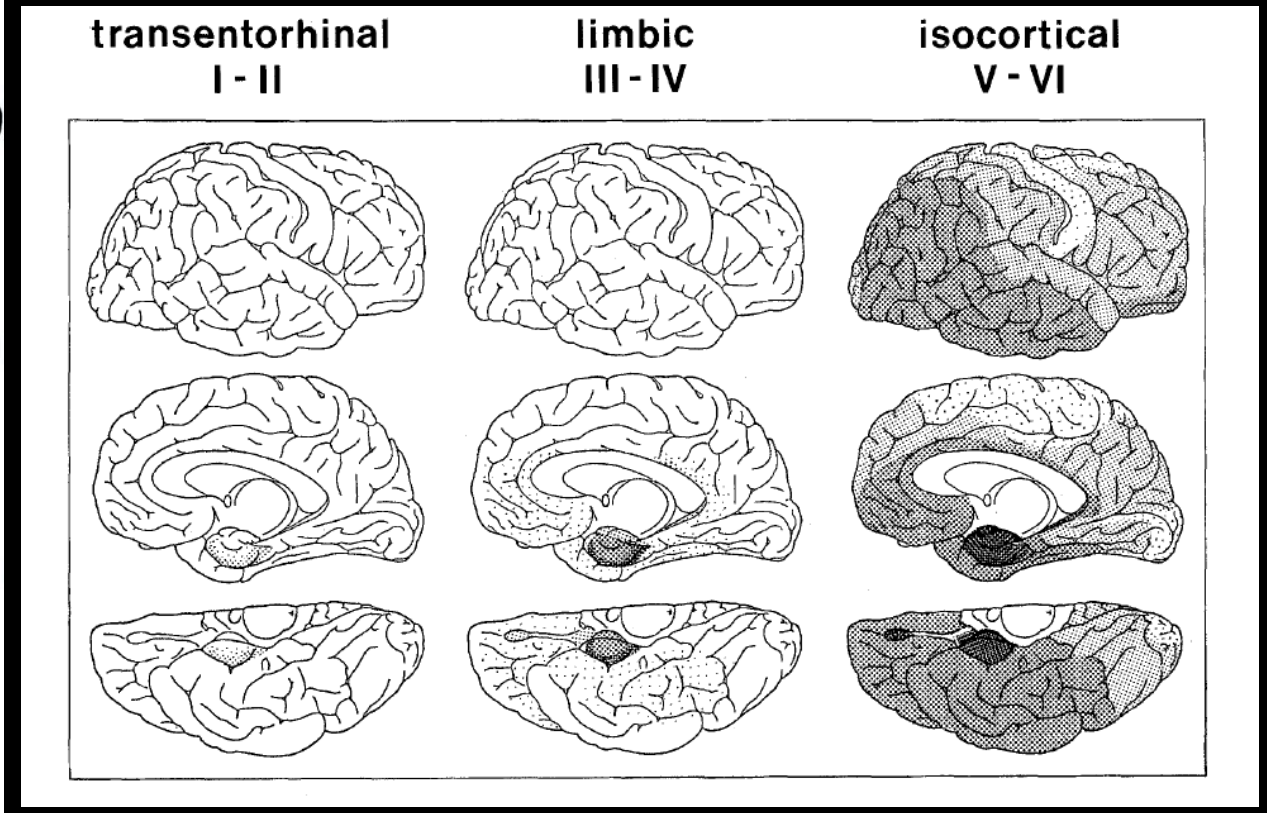



Xia et al., Alz and Dem 2013

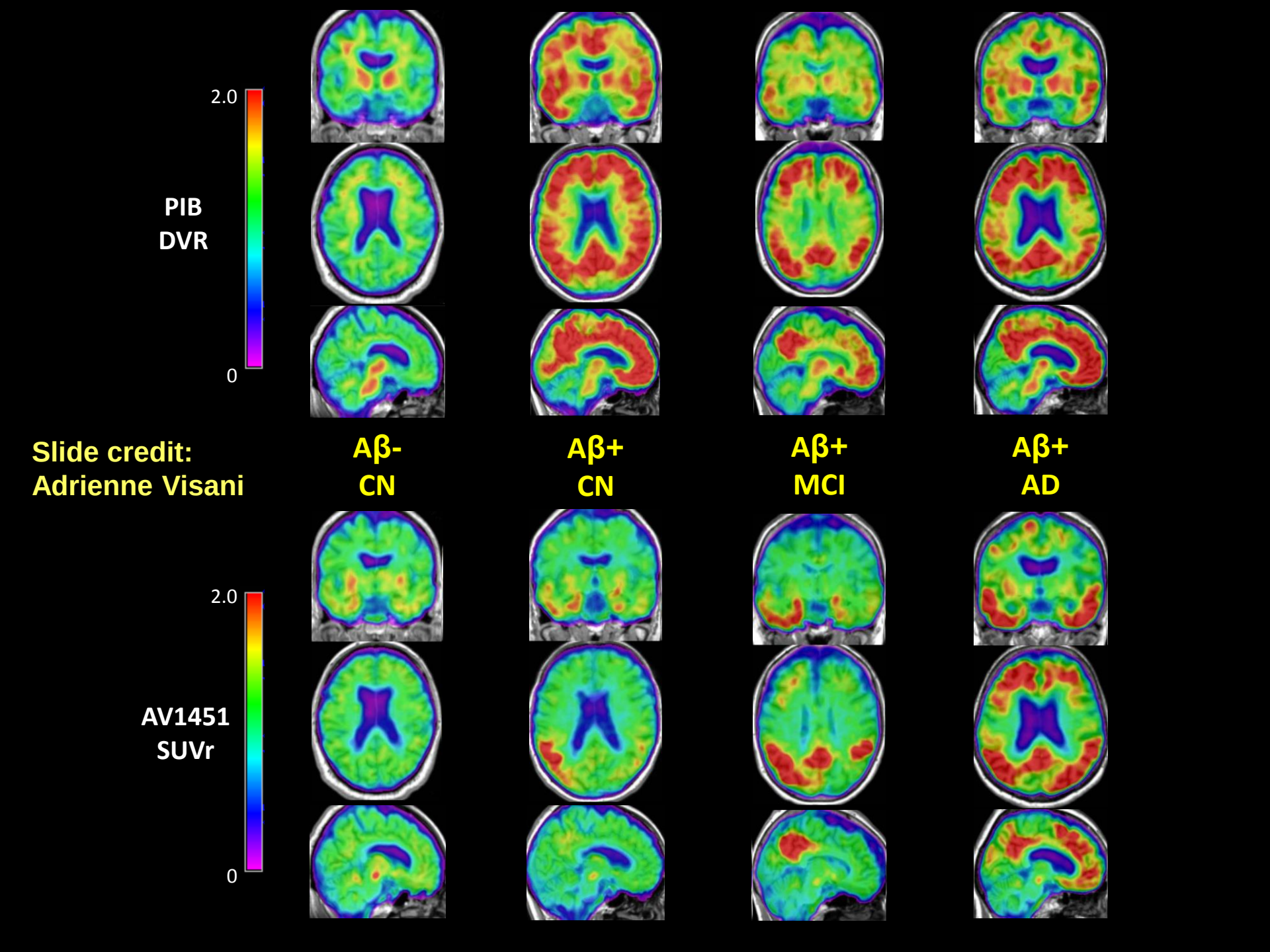
# Aβ and Tau: Distinct Spatial Patterns

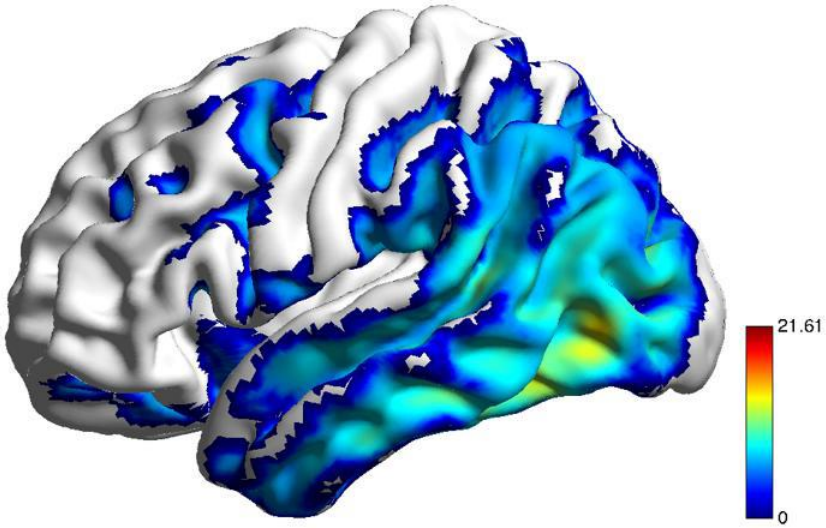
**Thal Aβ staging**



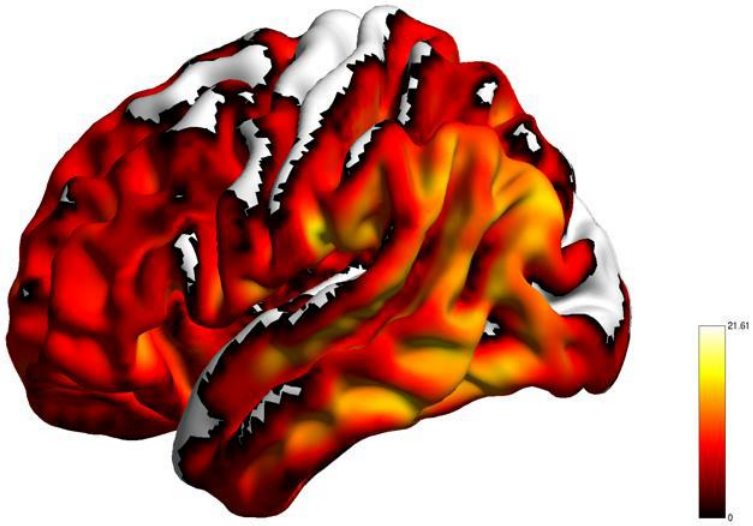

**Braak NFT staging**


2.0
PIB
DVR
0
Slide credit:
Adrienne Visani
Aβ-
CN
Aβ+
CN
Aβ+
MCI
Aβ+
AD
2.0
AV1451
SUVr
0




**AV1451**

**P<0.05 FWE**




**PIB**

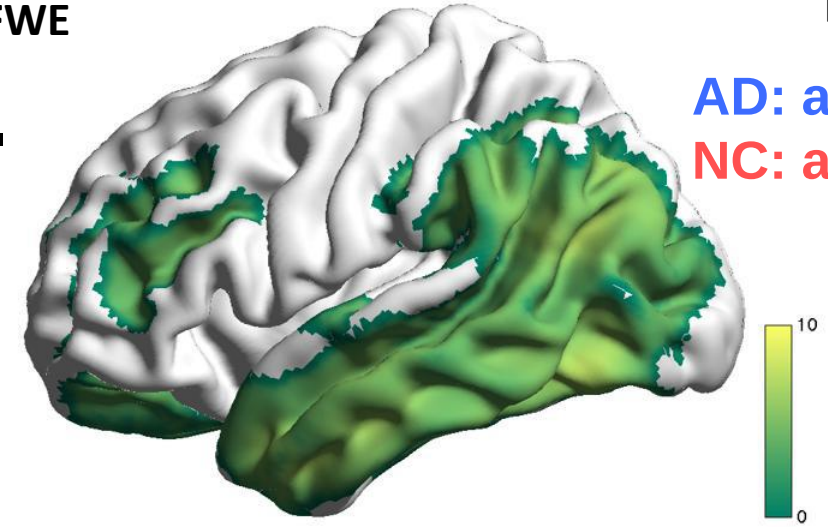
**P<0.05 FWE**

**30 Aβ+ AD vs.**

**12 Aβ-neg NC**

**AD: age 62.4, MMSE 21.3**

**NC: age 77.3**




**GM loss (VBM)**

**P<0.001**

**Iaccarino et al., under revision**

VIEWS & REVIEWS

# A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers

OPEN

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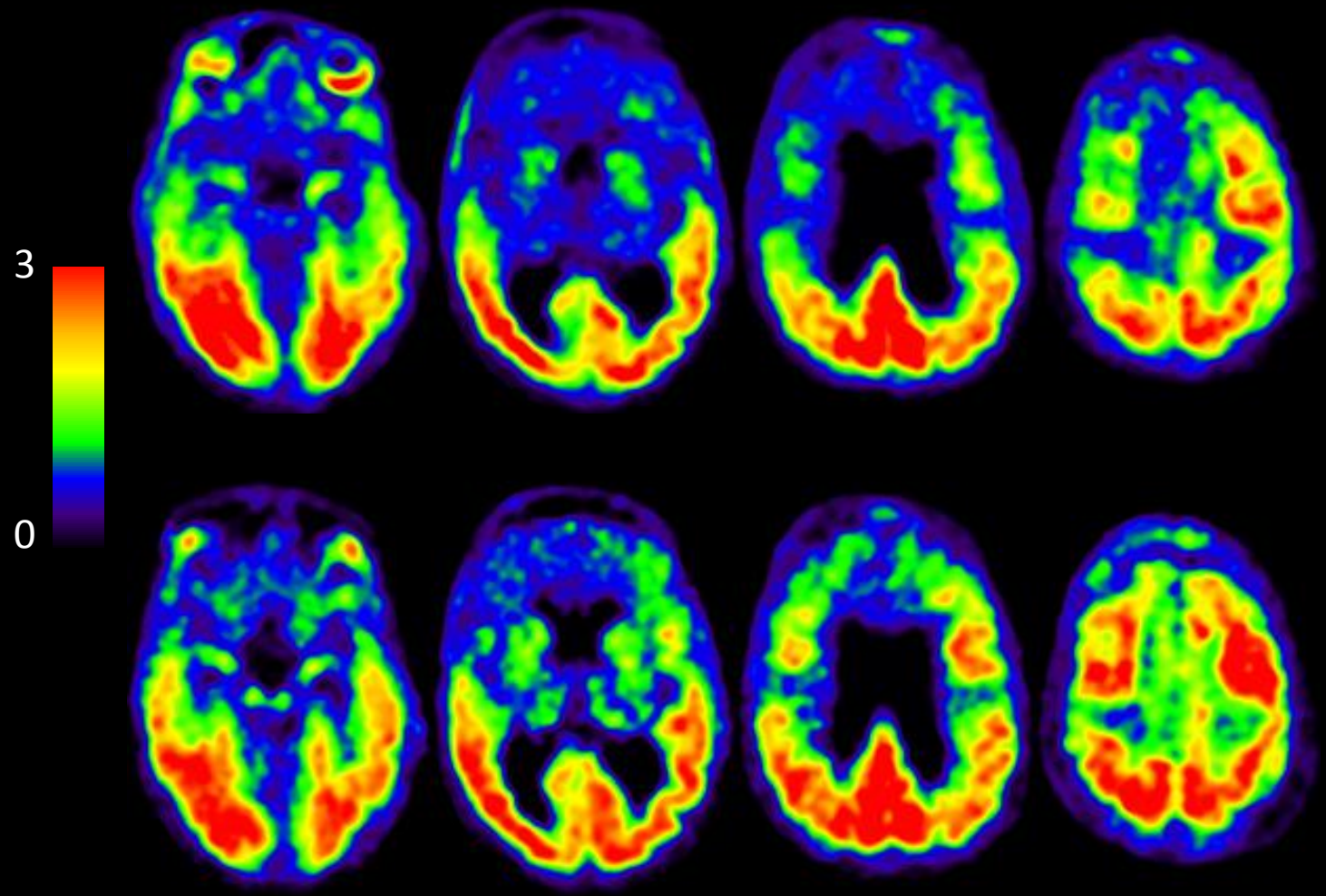
## ABSTRACT

Biomarkers have become an essential component of Alzheimer disease (AD) research and because of the pervasiveness of AD pathology in the elderly, the same biomarkers are used in cognitive aging research. A number of current issues suggest that an unbiased descriptive classification scheme for these biomarkers would be useful. We propose the "A/T/N" system in which 7 major AD biomarkers are divided into 3 binary categories based on the nature of the pathophysiology that each measures. "A" refers to the value of a β-amyloid biomarker (amyloid PET or CSF $A\beta_{42}$); "T," the value of a tau biomarker (CSF phospho tau, or tau PET); and "N," biomarkers of neurodegeneration or neuronal injury ($[^{18}F]$-fluorodeoxyglucose–PET, structural MRI, or CSF total tau). Each biomarker category is rated as positive or negative. An individual score might appear as A+/T+/N−, or A+/T−/N−, etc. The A/T/N system includes the new modality tau PET. It is agnostic to the temporal ordering of mechanisms underlying AD pathogenesis. It includes all individuals in any population regardless of the mix of biomarker findings and therefore is suited to population studies of cognitive aging. It does not specify disease labels and thus is not a diagnostic classification system. It is a descriptive system for categorizing multidomain biomarker findings at the individual person level in a format that is easy to understand and use. Given the present lack of consensus among AD specialists on terminology across the clinically normal to dementia spectrum, a biomarker classification scheme will have broadest acceptance if it is independent from any one clinically defined diagnostic scheme. *Neurology*® 2016;87:539–547

**Jack et al., Neurology 2016**

# Longitudinal Change in AV1451

60 yo woman with AD




Baseline (Sept 2014)
MMSE 28/30

Dec 2016
2.2 years later
MMSE 18/30

# Chronic Traumatic Encephalopathy in a National Football League Player

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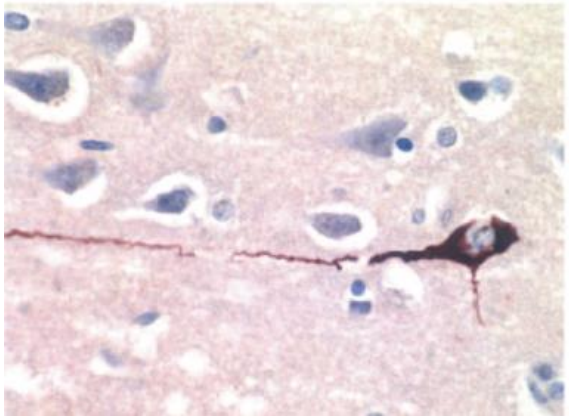
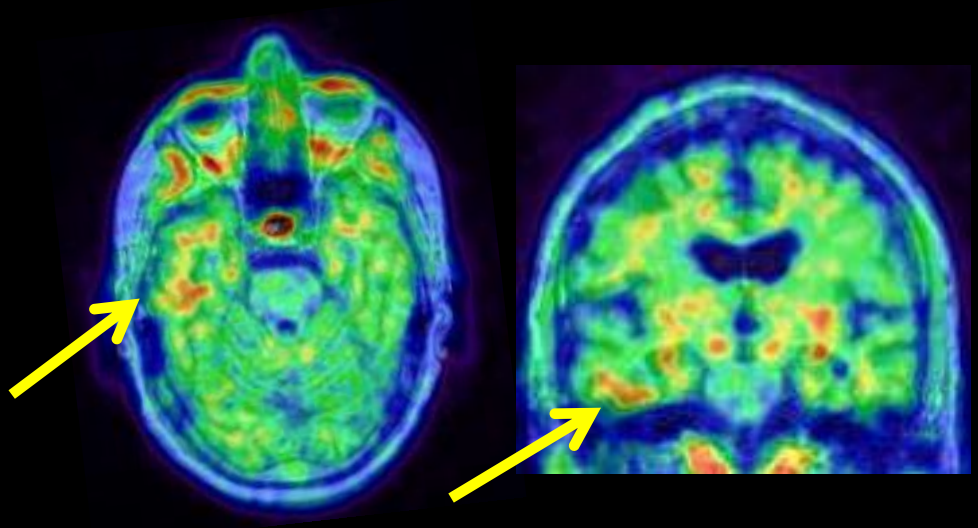
**Bennet Omalu, MD MPH**

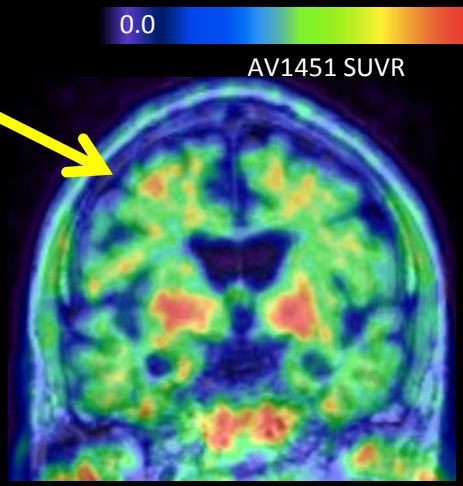
**“Iron Mike” Webster 1952-2002**



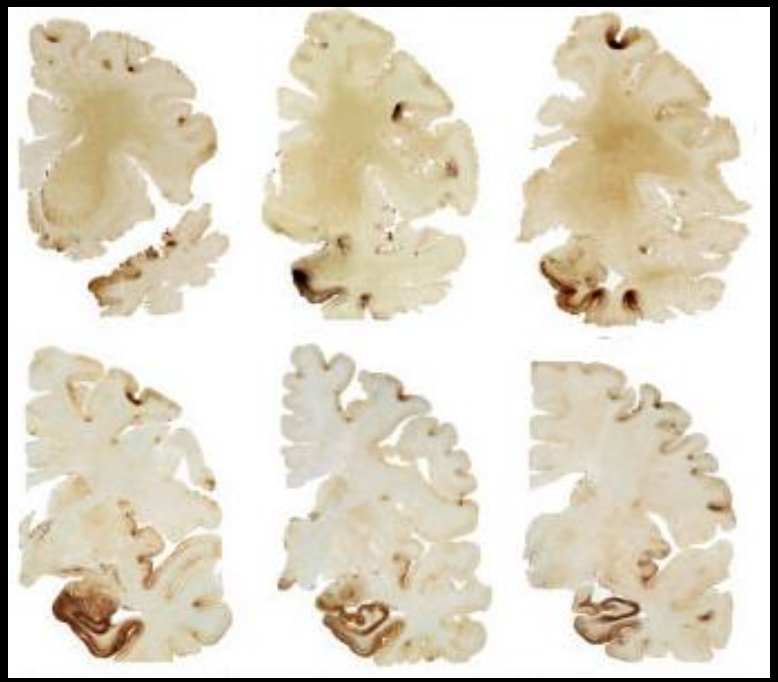
**Omalu et al., Neurosurgery 2005**

# 68 yo retired NFL player with neurobehavioral decline, Aβ-neg






McKee CTE Stage III



**Rabinovici et al., HAI 2015**

# Take Home Points

- Amyloid PET is already in the clinic
  - Support clinical diagnosis with molecular biomarker
  - Strong effect on patient diagnosis and care plan
  - Impact on patient outcomes under evaluation
  - Major role in trials and drug development
- Tau PET a powerful tool in aging-AD spectrum
  - Study relationships between Aβ, tau, neurodegeneration and cognition
  - Unlike Aβ, tau PET correlates with cognition and disease progression
  - Potential to capture non-AD tauopathies

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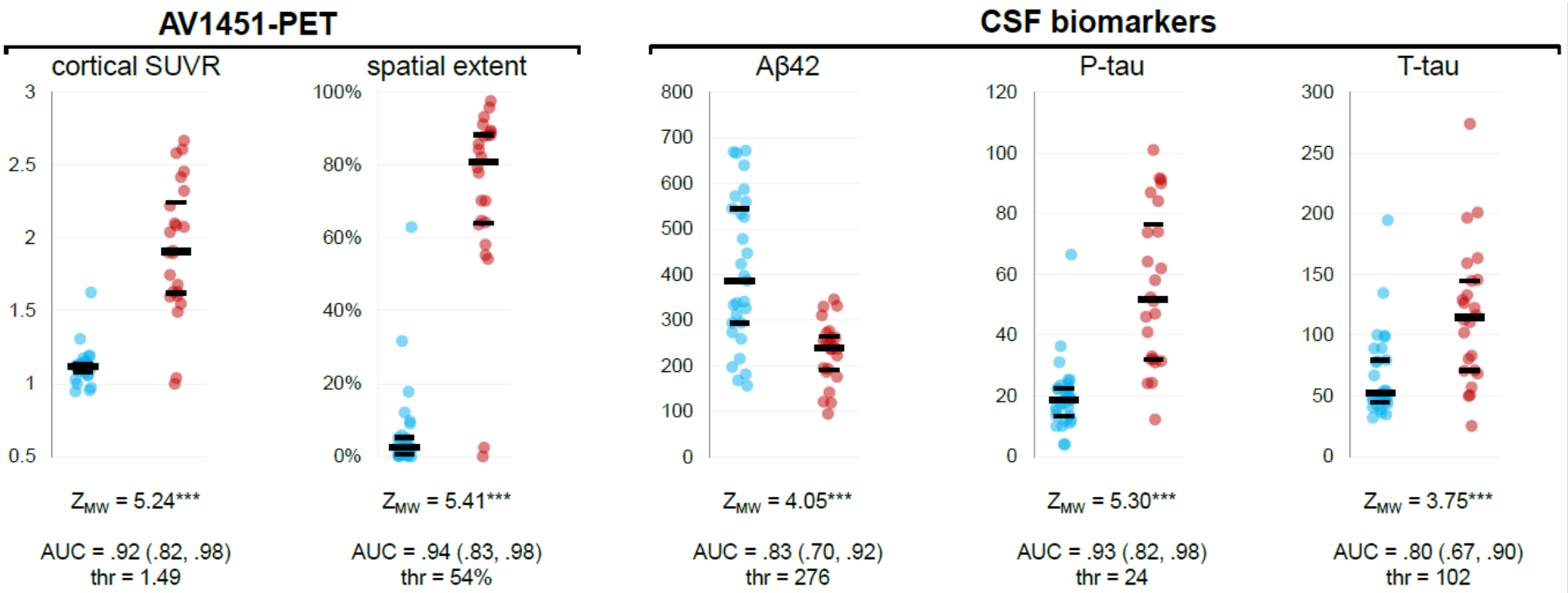
Tau Consortium
Michael J. Fox Foundation
AFTD
Avid Radiopharmaceuticals
Eli Lilly, GE Healthcare, Piramal


Placeholder: Jim’s Slides

# Tau PET vs. CSF for Diagnosis

53 patients with PIB, AV1451, CSF biomarkers

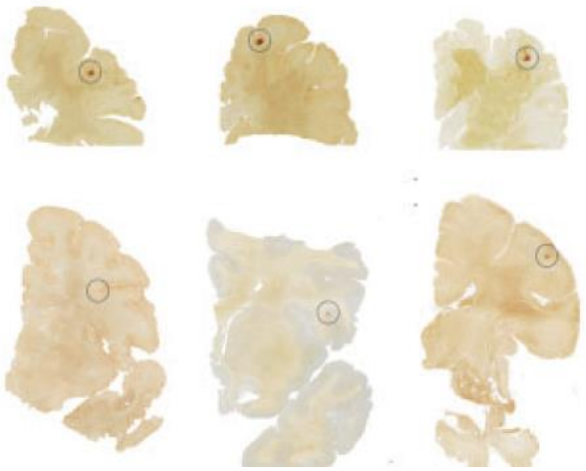
24 PIB+ AD, 29 PIB- non-AD dementias




**La Joie et al., in prep**

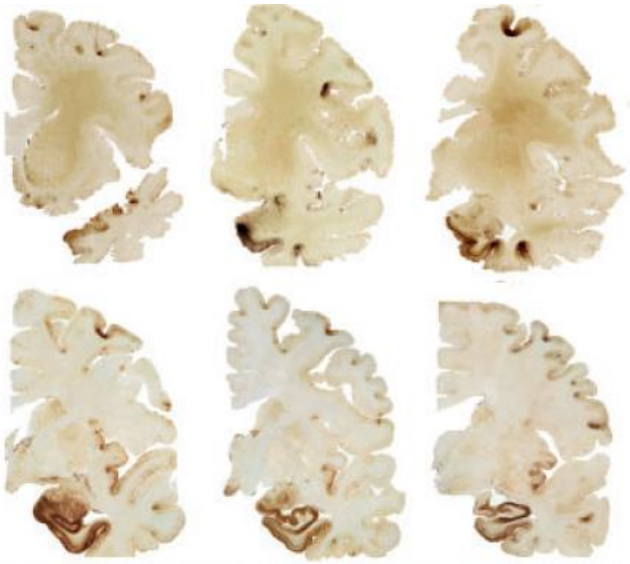
# Tau Pathology in CTE

**Stage I**

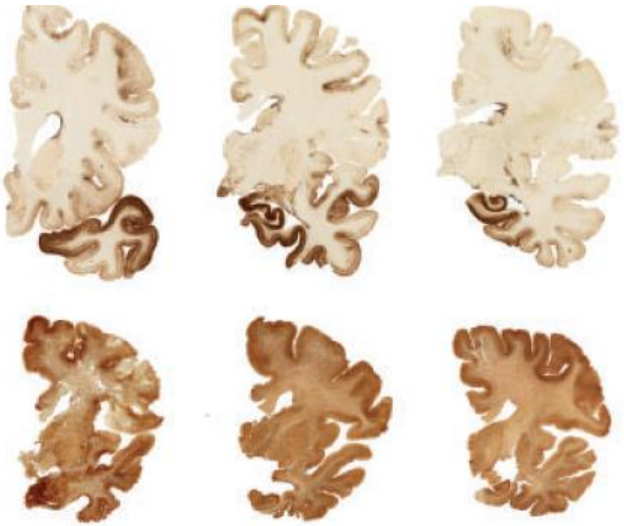


**Stage II**

**Stage III**



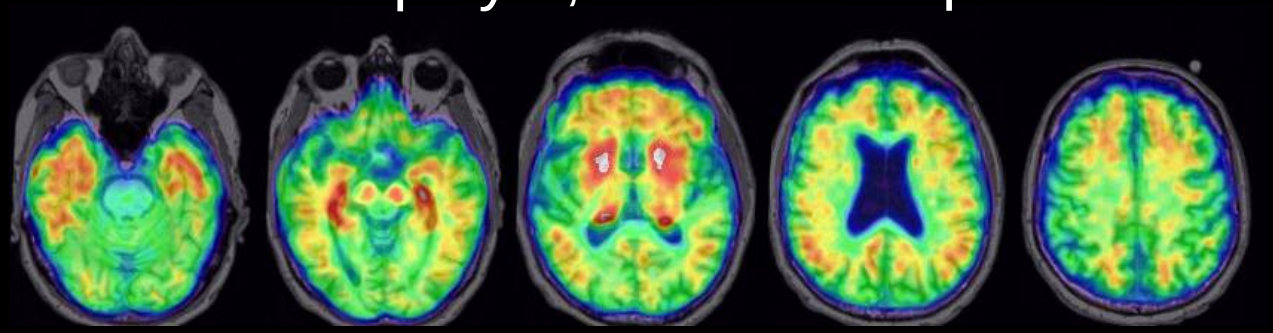
**Stage IV**



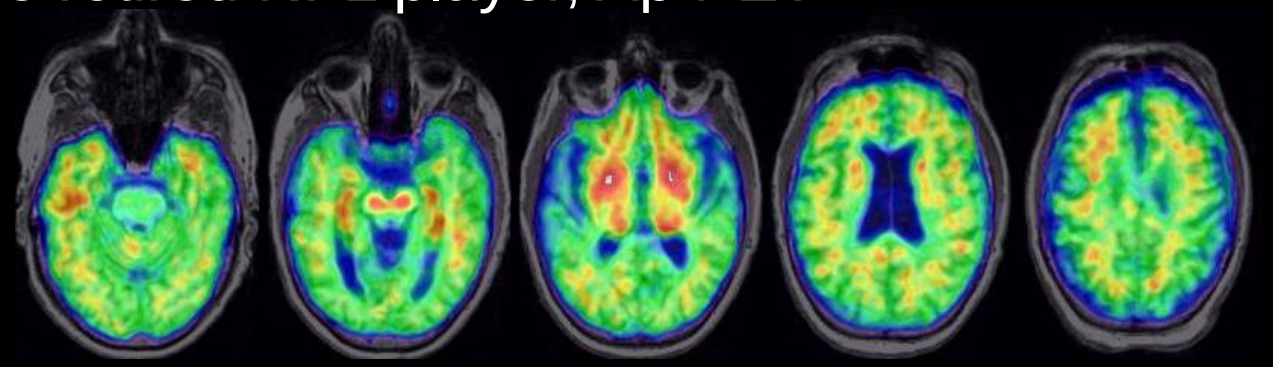
**McKee et al., Brain 2013**

# Range of AV1451 Binding in Suspected CTE

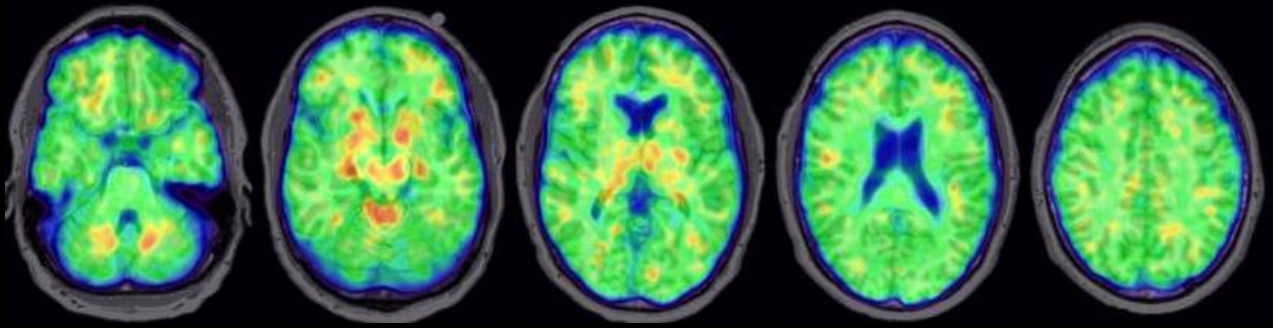
77 yo retired NFL player, borderline Aβ PET+



68 yo retired NFL player, Aβ PET-



47 yo rugby and high school football, Aβ PET-




**Lesman-Segev et al., in prep**