Disclosures

• Research support
  • NIH-NIA, NIH-NINDS, American College of Radiology, Alzheimer’s Association, Rainwater Charitable Foundation
  • Avid Radiopharmaceuticals, GE Healthcare, Genentech, Life Molecular Imaging

• 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

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

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

18F-florbetaben (Neuraceq™)
FDA approved March 2014
Amyloid PET Visual Reads
PET vs. Autopsy Studies

<table>
<thead>
<tr>
<th>Tracer</th>
<th>N</th>
<th>Report</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florbetapir (Amyvid)(^1)</td>
<td>59</td>
<td>Median</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td>Flutemetamol (Vizamly)(^2)</td>
<td>68</td>
<td>Median</td>
<td>88%</td>
<td>88%</td>
</tr>
<tr>
<td>Florbetaben (Neuraceq)(^3)</td>
<td>82</td>
<td>Median</td>
<td>98%</td>
<td>80%</td>
</tr>
</tbody>
</table>

**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

**Healthy Controls Aβ-**
- Female, 69 y, MMSE 29

**Late Onset AD Aβ+**
- Female, 76 y, MMSE 23

---

Schöll et al. Mol Cell Neurosci 2019
**18F-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

---

**Amyloid plaques [11C]PIB**
- Cognitively normal
- MCI due to AD
- Alzheimer’s dementia
- 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

**Tau tangles [18F]FTP**

Rabinovici Continuum 2019
Baseline Tau Predicts Future Brain Atrophy

32 patients with MCI/AD dementia

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%

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 on 12-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
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

Underrepresented Community Recruitment

- 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

pTau217 blood test 96% accurate compared to tau PET scan

Schindler et al. Neurology 2019
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)

Haeberlein et al. JPAD 2022
Donanemab: “Next Generation” AD Clinical Trial

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

Funding
NIH: NIA, NINDS
Alzheimer’s Association
American College of Radiology
Rainwater Charitable Foundation
Shenandoah Foundation
Gift from Edward and Pearl Fein
Avid/Eli Lilly, GE Healthcare,
Genentech, Life Molecular Imaging

UC Berkeley/LBNL
Bill Jagust
Suzanne Baker
Tessa Harrison
Mustafa Janabi
Susan Landau
Kris Norton

Collaborators
Paul Aisen
Michael Alosco
Liana Apostolova
Maria Carnillo
Hanna Cho
Brad Dickerson
Peggye Dilworth-Anderson
Constantine Gatsonis
Oskar Hansson
Bruce Hillier
Ophir Keret
Bob Koepppe
Chul Lyoo
Maura Malpetti
Niclas Mattsson
Sid O’Bryant
Rik Ossenekoppele
Robert Rissman
Barry Siegel
Rachel Whitmer
Consuelo Wilkins
Prashanthi Venkat