Alzheimer’s Disease Biomarkers: Transforming Care and Drug Development

Gil Rabinovici, MD
Edward Fein and Pearl Landrith Endowed Professor
UCSF Department of Neurology

James Hendrix, PhD
Director, Global Science Initiatives
Alzheimer’s Association

Health Research Alliance Members Meeting
Alzheimer’s Association, Chicago
September 18, 2017
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

Cog normal: low PIB
Cog normal: intermediate PIB
Cog normal: high PIB
Alzheimer’s disease

Mintun 2006; Pike 2007; Mormino 2009 & 2011; Sperling 2011; Chételat 2012; Petersen 2015
Aβ PET+ Predicts Cognitive Decline in Aging

Donohue et al., et al., JAMA 2017
Amyloid PET in Drug Development: Subject Selection and Early Intervention

What is the A4 study?
**18F-florbetapir (Amyvid™)**
FDA approved April 2012

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

**18F-florbetaben (Neuraceq™)**
FDA approved March 2014
Pathology Validation: Florbetapir PET

A. Participant age at death, 82 y
   Mean cortical SUVR = 0.87, PET score = 0
   β-Amyloid burden = 0.15%
   Low likelihood of Alzheimer disease
   92% positive when amyloid was present at autopsy

B. Participant age at death, 78 y
   Mean cortical SUVR = 1.17, PET score = 2
   β-Amyloid burden = 1.63%
   High likelihood of Alzheimer disease
   95% negative when amyloid was absent at autopsy

C. Participant age at death, 79 y
   Mean cortical SUVR = 1.68, PET score = 4
   β-Amyloid burden = 7.92%
   High likelihood of Alzheimer disease

Clark et al. JAMA 2011, Lancet Neurol 2012
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 (Vizamyl)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>

**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
• 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-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.

Rabinovici et al., AAIC 2017
Aim 1 Study Flow

**Pre-PET visit:**
Care plan assuming no access to amyloid PET

**Scan completed with FDA-approved ligand:**
Communicate results to patients
Recommend changes to care plan as appropriate

**90 day post-PET visit:**
Document *implemented* care plan following PET

% change comparing pre-PET to post-PET?
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

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

MMSE – Mini-Mental State Exam; MoCA – Montreal Cognitive Assessment
High Rate of Management Changes After PET

<table>
<thead>
<tr>
<th>Condition</th>
<th>Change in Management Composite (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>67.6%</td>
</tr>
<tr>
<td>MCI</td>
<td>67.8%</td>
</tr>
<tr>
<td>Dementia</td>
<td>65.9%</td>
</tr>
</tbody>
</table>

Rabinovici et al., AAIC 2017
## Change by Management Domain

<table>
<thead>
<tr>
<th>Domain</th>
<th>MCI</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD drugs</td>
<td>47.8%</td>
<td>47.7%</td>
</tr>
<tr>
<td>Non-AD drugs</td>
<td>36.0%</td>
<td>32.2%</td>
</tr>
<tr>
<td>Counseling</td>
<td>23.9%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Overall</td>
<td>67.8%</td>
<td>65.9%</td>
</tr>
</tbody>
</table>

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
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

Slide courtesy of Victor Villemagne
[\textsuperscript{18}F]AV1451/T807/FTC: PHF-Tau Tracer

PHF tau IHC (AT8)  [\textsuperscript{18}F] T807 autoradiography  Amyloid β IHC

![Graphs showing correlation between PHF-tau loading and [\textsuperscript{18}F] T807 autoradiography, and between Aβ loading and [\textsuperscript{18}F] T807 autoradiography.]

Xia et al., Alz and Dem 2013
Aβ and Tau: Distinct Spatial Patterns

Thal Aβ staging

Braak NFT staging
Slide credit: Adrienne Visani
AV1451
P<0.05 FWE

PIB
P<0.05 FWE

30 Aβ+ AD vs.
12 Aβ-neg NC

GM loss (VBM)
P<0.001

AD: age 62.4, MMSE 21.3
NC: age 77.3

Iaccarino et al., under revision
A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers

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 Aβ42); “T,” the value of a tau biomarker (CSF phospho tau, or tau PET); and “N,” biomarkers of neurodegeneration or neuronal injury ([18F]-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
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

Bennet I. Omalu, M.D., M.P.H.
Departments of Pathology and Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania

Steven T. DeKosky, M.D.
Departments of Human Genetics and Neurology, University of Pittsburgh, Pittsburgh, Pennsylvania

Ryan L. Minster, M.S.I.S.
Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania

M. Ilyas Kamboh, Ph.D.
Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania

Ronald L. Hamilton, M.D.
Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania

Cyril H. Wecht, M.D., J.D.
Departments of Pathology and Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania

Omalu et al., Neurosurgery 2005

Bennet Omalu, MD MPH

“Iron Mike” Webster
1952-2002
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
Acknowledgments

UCSF-MAC
Bruce Miller
Jalayne Arias
Nagehan Ayakta
Alexandre Bejanin
Viktoriya Bourakova
Jungho Cha
Kiran Chaudhary
Leonardo Iaccarino
Manja Lehmann
Orit Lesman-Segev
Rik Ossenkoppele
Julie Pham
Daniel Schonhaut
Salvatore Spina
Richard Tsai
Adrienne Visani
Adam Boxer
Lea Grinberg
Marilu Gorno-Tempini
Anna Karydas
Joel Kramer
Zach Miller
Howie Rosen
Bill Seeley

UC Berkeley/LBNL
Bill Jagust
Suzanne Baker
Mustafa Janabi
Sam Lockhart
Anne Maass
Kris Norton
Jim O’Neill
Michael Scholl

IDEAS Study Team
Charlie Apgar
Maria Carrillo
C Gatsonis
Ilana Gareen
Lucy Hanna
Bruce Hillner
Cynthia Olson
Barry Siegel
Rachel Whitmer

Funding
NIA R01-AG045611, P01-AG1972403, P50-AG023501
NINDS U54NS092089
Alzheimer’s Association
American College of Radiology 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