PET Imaging and Dementia in 2015 and Beyond

Peter Herscovitch, M.D., FRCPC, FACP

Director, PET Department, NIH Clinical Center
President, SNMMI
Outline

- Past achievements
  - Aβ imaging with PET - \(^{11}\text{C}-\text{PIB}\) and \(^{18}\text{F}\) radiotracers
  - Biomarkers for AD pathogenesis and diagnostic criteria
  - Appropriate Use Criteria for amyloid imaging

- 2015 and beyond
  - Tau imaging
  - Amyloid imaging in therapeutic drug trials
  - U.S. Medicare coverage and IDEAS study
Alzheimer’s Disease

1907 paper: “A Unique Illness Involving the Cerebral Cortex”

- 51 y.o. pt with progressive presenile dementia

Described 2 pathological hallmarks:

Alois Alzheimer (1864–1915)
> 10,000 $^{11}$C PiB PET scans in ~ 60 research centers

- Stimulated development of $^{18}$F labeled Aβ radiotracers, preferable because of 2 hr T½ in comparison to 20 min for $^{11}$C PiB
$^{18}$F Amyloid Radiotracers

$^{11}$C-PiB

$^{18}$F-florbetaben

$^{18}$F-florbetapir

$^{18}$F-flutemetamol

Rowe and Villemagne 2011
Amyloid Radiotracers in Neurodegeneration: Sensitive to the Clinical Diagnosis

F-18 Florbetaben, Villemagne JNM 2011
Amyloid Imaging in Healthy Elderly Subjects

- ~15 – 30% of healthy elderly are PIB +ve
- Positivity increases with age, with presence of ApoE4

Morris Ann Neurol 2010
Amyloid Imaging in Healthy Elderly Subjects

11C PIB positivity in HCs

» Associated with a greater risk of cognitive decline, faster rate of brain atrophy, and progression to AD

» Probably indicates preclinical AD

Table 2. Cox Proportional Hazards Model Testing MCBP for PiB as a Predictor of Time to DAT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>MCBP</td>
<td>4.82 (1.22-19.01)</td>
<td>.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.14 (1.02-1.28)</td>
<td>.03</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.91 (0.69-1.19)</td>
<td>.49</td>
</tr>
<tr>
<td>APOE e4 carrier</td>
<td>0.98 (0.20-4.90)</td>
<td>.98</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.54 (0.10-2.90)</td>
<td>.48</td>
</tr>
</tbody>
</table>

r=0.38, p<0.034

Morris et al., Arch Neurol 2009
Pike et al, Brain 2007
Amyloid Deposition over Time

- Jack et al., Neurology 2013
- Modeled the temporal trajectory of amyloid deposition from serial $^{11}$C-PiB PET scans
- $N=260$, age $>70$
- U-shaped curve of amyloid deposition rate as a function of baseline SUVr
- Integral shows a sigmoid shape, approaching a plateau
- Note length of time during which there is ongoing accumulation
**Amyloid in Healthy Elderly Subjects**

- $^{11}$C PiB positivity in HCs similar to postmortem data
- Suggests that amyloid deposition precedes clinical AD by ~ 15 yr

Rowe at al., Neurobiol Aging 2010

![Graph showing prevalence of plaques and AD](image)
Mild Cognitive Impairment

- Clinical criteria (Petersen 1999)
  - Cognitive concern reflecting a change in cognition reported by patient or informant
  - Objective evidence of impairment in one or more cognitive domains, typically including memory
  - Preservation of the abilities of daily living
  - Patient not demented

- Often the symptomatic pre-dementia phase of AD
  - ~12% of MCI patients convert to AD per year
Amyloid Imaging: Prediction of Conversion of MCI to AD

PIB positivity in MCI ~ 50-70 %

Nordberg, Eur J N M Mol Imaging 2012

64 MCI subjects followed for 28 +/- 15 mo

»29/43 (67%) PIB +ve converted to AD;
»0/21 PIB -ve converted

Data suggest that amyloid imaging has the potential for preclinical dx of AD and for indicating prognosis in MCI
[\textsuperscript{18}F]Florbetapir Validation

Clark, JAMA 2011
N=29
N=14 Amyloid –ve autopsy
14/14 PET –ve
100% specific for amyloid

Clark, Lancet Neurol 2012
N=59
96% sensitivity
100% specificity
April 2012 U.S. FDA approval of $^{18}$F-florbetapir

- “… for PET imaging of the brain to estimate Aβ in patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.”

- “A -ve scan indicates sparse to no Aβ and is inconsistent with a neuropathological diagnosis of AD; it reduces the likelihood that a patient’s cognitive impairment is due to AD.”

- “A +ve scan indicates moderate to frequent Aβ plaques; this amount of Aβ is present in patients with AD, but may also be present in patients with other neurologic conditions as well as in older people with normal cognition.”

- 2 other radiotracers subsequently approved
Outline

Where we are now
  » Aβ imaging with PET - $^{11}$C-PIB and $^{18}$F radiotracers
  » Biomarkers for AD pathogenesis and diagnostic criteria
  » Appropriate Use Criteria for Amyloid Imaging

2015 and beyond
  » Tau imaging
  » Amyloid imaging in therapeutic drug trials
  » U.S. Medicare coverage and IDEAS study
AD Pathogenesis: Amyloid Hypothesis

Mathis et al. NMB 2007
AD Pathophysiology: Amyloid Hypothesis and Biomarkers

Early biomarkers
- Aβ

Later biomarkers of downstream effects
- neurodegeneration or neuronal injury

PET Aβ ↑

PET FDG ↓ neuronal hypometabolism

CSF Aβ ↓

Structural MRI ↓ brain volume, atrophy

CSF tau protein ↑
Biomarker Continuum of AD

Jack et al., Radiology 2012
New NIA/AA Diagnostic Criteria for AD - 2011

- Replaced the 1984 NINCDS/ADRDA Criteria
- Incorporated PET imaging and CSF biomarkers
- “In persons who meet the core clinical criteria for probable AD, biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process.”

McKhann et al., Alzheimer’s & Dementia 2011
# New NIA/AA Diagnostic Criteria for AD - 2011

McKhann et al., Alzheimer’s & Dementia 2011

<table>
<thead>
<tr>
<th>AD dementia criteria incorporating biomarkers</th>
<th>Biomarker probability of AD etiology</th>
<th>Aß (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probable AD dementia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With three levels of evidence of AD pathophysiological process</td>
<td>Intermediate</td>
<td>Unavailable or indeterminate</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>Positive</td>
<td>Unavailable or indeterminate</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Possible AD dementia (atypical clinical presentation)</strong></td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With evidence of AD pathophysiological process</td>
<td>High but does not rule out second etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Dementia-unlikely due to AD</strong></td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
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  - Aβ imaging with PET - \(^{11}\)C-PIB and \(^{18}\)F radiotracers
  - Biomarkers for AD pathogenesis and diagnostic criteria
  - Appropriate Use Criteria (AUC) for Amyloid Imaging
- 2015 and beyond
  - Tau imaging
  - Amyloid imaging in therapeutic drug trials
  - U.S. Medicare coverage and IDEAS study
Preamble:
Amyloid imaging is appropriate for 3 indications, provided that:

i. a cognitive complaint is objectively confirmed

ii. AD is a possible dx, but the dx is uncertain after a comprehensive evaluation by a dementia expert

iii. knowledge of Aβ pathology is expected to increase diagnostic certainty and alter management
Appropriate Indications

1. Patients with persistent or progressive unexplained MCI

- A +ve scan raises the level of certainty that the patient’s impairment is based on AD pathology and represents early AD
- Prognosis. Reports suggest that the majority of patients with amnestic MCI and a +ve scan will progress to AD
2. Patients satisfying core clinical criteria for possible AD, but with unclear clinical presentation

There is doubt about the diagnosis:

(i) an atypical course (e.g., sudden onset) or inadequate history

(ii) a comorbid condition that confounds the interpretation of the clinical data, e.g., cerebrovascular disease
Appropriate Indications

3. Patients with progressive dementia and atypically early age of onset (usually defined < 65 y.o.)

- Patients often harder to diagnose, FTLD more common
- Purpose is to manage symptomatic treatment; make appropriate lifestyle decisions; possibly refer the patient to a clinical trial
Non – Indications for Aβ Imaging

1. Patients with core clinical criteria for probable AD with typical age of onset
2. To determine dementia severity
3. Based solely on a positive family history of dementia or presence of APOE e4
4. Patients with a cognitive complaint that is unconfirmed on clinical examination
5. In lieu of genotyping for suspected autosomal mutation carriers
6. In asymptomatic individuals
7. Nonmedical use is inappropriate
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Proteinopathies in Neurodegenerative Diseases

CAA
CTE
FTLDs
PSP
CBD

AD
LBVAD
DLB
PD
MSA

Aβ
αSyn
Tau
Intracellular protein

Binds to and stabilizes microtubules in neurons

Post-translational hyperphosphorylation causes tau to form neurofibrillary tangles in neurons

Exists in different isoforms
  » 3R or 4R repeated microtubule binding domains
  » 3R – Pick Disease; 4R – CBD, PSP; 3R and 4R – AD

Tau pathology is closely related to cognitive impairment and neuronal loss in AD, more than amyloid
Challenges for Tau-binding Radiotracers

Generic PET radiotracer development
- $^{18}$F-labelled
- Cross BBB
- High binding potential and selectivity for protein target
- No radioactive metabolites that cross BBB
- Favorable binding kinetics to permit imaging

Tau related
- Intracellular location of target
- In AD, concentrations of tau lower than Aβ
- Low non-specific binding in cerebral WM (tau in WM)
- Bind to different isoforms (or not)
Tau Imaging with $[^{18}\text{F}]$THK-5105 in AD

Okamura, Brain 2014
Tau Imaging with $[^{18}\text{F}]{\text{THK-5105}}$ vs. $[^{11}\text{C}]{\text{PiB}}$ in AD

Radiotracer SUVr vs. Cognitive Status
Radiotracer SUVr vs. Atrophy Measures

Okamura, Brain 2014
• Okamura et al., SNM Image of the Year, June 2014
• THK5117 retention in temporal cortex closely correlated with dementia severity
• Retention in hippocampus was correlated with hippocampal volume
• Less non-specific binding in WM
Figure 2: PIB and AV1451 in 68 yo retired NFL player with neurobehavioral decline

At risk CTE
Aβ PET
[^11C]PIB

At risk CTE
Tau PET
[^18F]AV1451

Rabinovici et al.; Human Amyloid Imaging Conference, Jan 2015
Future: Tau Imaging

- Which radiotracer, better tracers
- More specific tracers (3R, 4R vs. 3R+4R)
- Role of tau protein in the pathophysiology of AD:
  - time course compared to Aβ, FDG, focal atrophy, CSF biomarkers; relation to cognitive decline
  - testing the Aβ hypothesis
- Use in non-AD neurodegenerative diseases, CTE
- Therapeutic drug trials in dementia
- Define a role in the differential diagnosis of dementia and neurodegenerative diseases
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Disease-Modifying Therapeutic Targets for AD

**Anti-Aβ**
- Decrease Aβ production
- Decrease Aβ aggregation into plaques
- Increase Aβ degradation
- Increase Aβ clearance

**Decrease tau and neurofibrillary tangle formation in neurons**
- Prevent tau hyperphosphorylation
- Decrease tau aggregation
- Stabilize microtubules
- Active and passive immunization against tau

**Neuroprotection or neuroregeneration**
- Antioxidant and other agents to preserve metabolic and/or mitochondrial function
- Antiapoptotic agents
- Decrease inflammatory damage
- Nerve growth factor enhancement
- Stem cell–based neuron replacement

Adapted from Sperling Sci Trans Med 2011
Patient Selection for Clinical Trials in AD

- Accuracy of clinical diagnosis of AD
  - ~70% sensitive and specific (Knopman 2001; Beach 2012)

- Salloway, NEJM 2014:
  *Two phase 3 trials of bapineuzumab in mild-to-moderate AD.*
  - Primary outcome -ve, no change in cognitive function
  - In APOE ε4 non-carriers, 36% of baseline amyloid scans –ve
  - “raises questions about the reliability of diagnoses of AD among noncarriers”
  - Did this decrease the ability of the studies to detect a drug response?
  - Should Aβ imaging be used to select patients for clinical trials of anti-AD and anti-Aβ therapeutics?
Amyloid Imaging in Clinical Trials in AD

- Clinical trials of new drugs now and in the future will incorporate Aβ imaging
- Subject selection for therapeutic trials
  - Confirm the diagnosis of AD
  - Identify subjects with amyloid in the preclinical phase
- For trials of anti-amyloid Rx
  - Confirm presence of the molecular target
- As a biomarker, to monitor effect of therapy
Redefining the Clinical Continuum of AD and the Therapeutic Window

Sperling J Alzheimer’s Dis Dementia 2011
Aβ imaging as a biomarker for efficacy of anti-Aβ drugs

{}^{11}\text{C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer’s disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study}

*Lancet Neurol* 2010; 9: 363–72
3 Clinical trials of anti-Aβ Rx in preclinical AD; use Aβ imaging

Trials will not only test drugs, but also test the “Aβ hypothesis”, potentially accelerating the future development of anti-AD drugs

Alzheimer’s Prevention Initiative (API)
- will test the preventive effect of crenezumab in asymptomatic subjects from a large kindred in Colombia, with a genetic mutation predisposing carriers to early-onset AD

DIAN Consortium Trial
- will test solanezumab in 400 subjects with genetically-determined (familial) early-onset AD

The A4 Study
- will test 1,000 older persons with Aβ on screening PET, to determine if treatment will slow the rate of cognitive decline
A4 Clinical Trial Using Aβ PET

Screening and randomization algorithm

Subjects 65-85 years of age, cognitively intact

Active treatment with solanezumab

Sperling Sci Trans Med 2014
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Radiopharmaceutical Insurance Coverage in the US

- U.S. FDA approval of a radiopharmaceutical permits manufacturers to market it, clinicians to use it
- *Does not* necessarily lead to insurance coverage
- No coverage → no meaningful clinical translation
- Centers for Medicare and Medicaid Services (CMS)
  - “Medicare” for patients 65 years and older
- CMS coverage of a radiopharmaceutical is critical; it covers a large # of patients and sets an example for other insurers
- FDA-approved PET tracers for brain and heart are automatically *not* covered by CMS
  - Not the case for SPECT and oncologic PET tracers
  - A National Coverage Decision is needed from CMS
National Coverage Determination

- CMS mainly uses published data
- Possible outcomes:
  - **Covered** - current evidence shows the procedure is reasonable & necessary
  - **Not Covered** - evidence shows that the procedure is not reasonable & necessary
  - **Coverage with Evidence Development (CED)** - evidence suggests the procedure *might* be reasonable & necessary, but is not compelling enough for coverage
- For CED, Medicare will cover the procedure to obtain additional evidence in an approved trial or registry
CMS Expectations for (PET) Coverage

The Preferred Road to Diagnostic Coverage

✓ Provide adequate evidence that
✓ The incremental information obtained by new diagnostic technology compared to alternatives
✓ Changes physician recommendations
✓ Resulting in changes in therapy
✓ That improve clinically meaningful health outcomes
CMS Expectations for (PET) Coverage in an NCD

Health Outcomes of Interest

More Persuasive*

- Longer life and improved function/participation
- Longer life with arrested decline
- Significant symptom improvement allowing better function/participation
- Reduced need for burdensome tests and treatments
- Quality of life

Less Persuasive

- Longer life with declining function/participation
- Improved disease-specific survival without improved overall survival
- Surrogate test result better
- Image looks better
- Doctor feels confident

• Improved patient health outcomes are difficult to demonstrate for diagnostic imaging
• Especially if the disease has no effective Rx or is slowly progressive over many years (e.g., AD)
CMS Consideration of Amyloid Imaging

• 2012: CMS was asked to cover amyloid PET

• Sept 2013: Evidence is insufficient that amyloid imaging is reasonable and necessary for Dx or Rx of illness or to improve patient health outcomes

• Cover 1 scan per patient through CED, in clinical research studies that
  (1) develop better treatments or prevention strategies for AD, or
  (2) resolve difficult dx’s (e.g., FTD versus AD) where the use of Aβ imaging appears to improve health outcomes.
IDEAS Study

- AA coordinating a registry-type study related to changes in management and outcomes

- IDEAS Study: Imaging Dementia—Evidence for Amyloid Scanning Study

- An open-label, longitudinal cohort study to assess the impact of amyloid PET on patient outcomes under CED in patients meeting AUC for amyloid PET

- Primary hypothesis: in diagnostically uncertain cases, knowledge of PET amyloid status will lead to significant changes in patient management, and this will translate into improved medical outcomes.
Assess the impact of amyloid PET on management of patients meeting AUC

Projected sample size is 11,050

Primary Objective:
Test whether amyloid PET leads to a ≥ 30% change between intended and actual patient management within ~90 days

The hypothesis will be tested separately for MCI and dementia patients
IDEAS Study: Aim 2

- Assess the impact of amyloid PET on hospital admissions and ER visits in patients enrolled in the study cohort compared to matched patients not scanned in the CMS Claims Data Base.

- Projected sample size is 18,488 (includes Aim 1 patients).

- Primary Objective:
  Determine if use of amyloid PET is associated with a ≥ 10% relative reduction in:
  a) hospital admissions over 12 mo
  b) ER visits over 12 mo
IDEAS Study

- **Dementia specialist:**
  Certified in neurology, psychiatry, or geriatrics; devotes ≥25% of time to evaluation and care of adults with acquired cognitive impairment or dementia (from AUC)

- **PET facility (>100):**
  Experience in administering and interpreting amyloid PET (including vendor-specific training). Free-standing PET facility accredited ACR or IAC or hospital-based accredited by JC.

- **Cost:**
  Scans (CMS): 18,488 scans x ~$4,000 = ~ $74 M
  Study database, administration, CRF’s, etc.: ~ $20 M

- **Radiopharmaceuticals:** any of the 3 approved

- **Timelines:** Start in 9 mo after CMS approval; scanning over 2 yrs
Merci!
SCHEMA: Longitudinal Cohort & Matching Controls

**Site Procedures**
- Treating Physician: Screen and Consent Participants (T0)
- Refer for Amyloid PET Scan
- Amyloid PET Scan within 30 Days after T0 (T1)
- Care by Treating Physician per Standard Practice (Aims 1 & 2)
- Follow Up on CMS Claims Data for 1 Year (Aim 2)

**Data Collection**
- Submit Pre-PET Clinical CRF (Aims 1 & 2)
- Submit PET Report and PET CRF within 75-105 Days after Amyloid PET Scan (Aims 1 & 2)
- Submit Post-PET CRF within 75-105 Days after Amyloid PET Scan (Aim 1)
- STUDY COHORT: CMS Claims Data for 12 Months (Aim 2)
- MATCHED CONTROLS: CMS Claims Data for 12 Months (Aim 2)
# How to Demonstrate Value of Imaging

Classic paper: Fryback & Thornbury, 1991, *The Efficacy of Diagnostic Imaging*

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<tbody>
<tr>
<td><strong>1. Analytic validity</strong></td>
<td>Interpretable scan resolution, accuracy and reliability of tests of CSF proteins to measure CSF protein levels, inter-reader and inter-laboratory reliability of test results</td>
<td>Sensitivity/specificity vs. gold standard test or vs. some other standard</td>
<td>Change in presumptive diagnosis following introduction of new test results</td>
<td>Initiation or cessation of treatment; impact on use of additional diagnostic studies</td>
<td>Cognitive/functional decline, time to institutionalization, side effects of treatment driven by test results, mortality</td>
<td>Cost-effectiveness of testing</td>
</tr>
</tbody>
</table>
Areas for Future Work

For molecular imaging community

- Quality of image interpretation and reporting, effect of training programs for readers
- Use of quantitative methods to assess radiotracer uptake; SUVr, automated reading programs
- Development of procedure guidelines to standardize imaging (SNMMI, EANM)
- Comparison of the performance of different F-18 labeled Aβ radiotracers in the same patients
- Define relative roles for Aβ tracers, FDG, I-123 ioflupane
- Development of radiotracers for tau (AD, FTD, CTE)
Areas for Future Work

For dementia and MI community

- Definition of dementia expert / referring physician (AIT)
- Use in pt. populations outside of the clinical research/academic environment
- Prognosis of a +ve scan in MCI, healthy subjects
- Relationship to other biomarkers – CSF, MRI
- Impact on patient management and health outcomes (medication use, use of other tests – CED study)
- Role in anti-AD drug trials, eventual drug prescribing
Can Aβ imaging be used to determine when to start drug Rx in anti-AD clinical trials?

Primary Prevention
- Delay onset of AD pathology
- Decrease Aβ42 production
- Prevent tangle formation

Secondary Prevention
- Delay onset of cognitive impairment in individuals with evidence of pathology
- Decrease accumulated Aβ burden
- Decrease neurodegeneration with anti-tau or neuroprotective agents

Tertiary Prevention and Treatment
- Delay onset or progression of dementia
- Neuroprotection-prevent neuronal loss
- Enhance function of remaining neurons
- Neurotransmitter repletion

Sperling, Sci Trans Med 2012