Imaging Biomarkers in Predicting MCI and Dementia

Ronald C. Petersen, Ph.D., M.D.

Alzheimer’s Disease Research Center

Mayo Clinic College of Medicine

Rochester, MN

Mild Cognitive Impairment Symposium

Miami

January 18, 2014
Disclosures

- Pfizer, Inc. and Janssen Alzheimer Immunotherapy: Chair DMC

- Roche: Consultant

- Merck: Consultant

- Funding
  - National Institute on Aging:
    - U01 AG006786
    - P50 AG016574
    - U01 AG011378
Introduction to the Recommendations from the National Institute on Aging-Alzheimer’s Association Workgroups on Diagnostic Guidelines for Alzheimer’s Disease

Clifford R. Jack, Jr, Marilyn S. Albert, David S. Knopman, Guy M. McKhann, Reisa A. Sperling, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

Alz and Dementia, 2011
Hypothetical Model of Dynamic Biomarkers of the Alzheimer’s Pathological Cascade

- Aβ: Abnormal
- Tau-mediated neuronal injury and dysfunction: Abnormal
- Brain structure: Abnormal
- Memory: Abnormal
- Clinical function: Abnormal

Normal: Cognitively normal
MCI
Dementia

Clinical disease stage

Jack et al: Lancet Neurol 2010
Criteria Approach

• Clinical criteria

• Biomarkers

• Molecular neuropathology
  CSF AB42
  Amyloid imaging

• Measures of neuronal injury
  Structural, e.g., MRI
  Functional, e.g., FDG PET
  CSF tau
Alzheimer’s Disease Spectrum

Preclinical AD

MCI Due to AD

Dementia Due to AD
The Diagnosis of Dementia Due to Alzheimer’s Disease: Recommendations from the National Institute on Aging-Alzheimer’s Association Workgroups on Diagnostic Guidelines for Alzheimer’s Disease


Alz and Dementia, 2011
## Dementia Due to AD

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>$\text{A}\beta$ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD dementia</td>
<td>Uninformative/available</td>
<td>Conflicting/indeterminant or unavailable</td>
<td></td>
</tr>
<tr>
<td>Probable AD with evidence of path AD</td>
<td>Intermediate High</td>
<td>? Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Possible AD dementia atypical with path</td>
<td>High consider secondary</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Dementia unlikely AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

McKhann et al: 2011
The Diagnosis of Mild Cognitive Impairment Due to Alzheimer’s Disease: Recommendations from the National Institute on Aging-Alzheimer’s Association Workgroups on Diagnostic Guidelines for Alzheimer’s Disease

Marilyn S. Albert, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gamst, David M. Holtzman, William J. Jagust, Ronald C. Petersen, Peter J. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps
## MCI Due to AD

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>Uninformative</td>
<td></td>
<td>Conflicting/indeterminant or unavailable</td>
</tr>
<tr>
<td>MCI due to AD – intermediate likelihood</td>
<td>Intermediate Intermediate Untested</td>
<td>Positive Untested Positive</td>
<td></td>
</tr>
<tr>
<td>MCI due to AD – high likelihood</td>
<td>Highest Positive</td>
<td>Positive Positive</td>
<td></td>
</tr>
<tr>
<td>MCI – unlikely due to AD</td>
<td>Lowest Negative</td>
<td>Negative Negative</td>
<td></td>
</tr>
</tbody>
</table>

Albert et al: 2011
Alzheimer’s Disease Spectrum

Preclinical AD

MCI Due to AD

Dementia Due to AD
Toward Defining the Preclinical Stages of Alzheimer’s Disease: Recommendations from the National Institute on Aging-Alzheimer’s Association Workgroups on Diagnostic Guidelines for Alzheimer’s Disease


*Corresponding author. Tel.: +1-617-732-8085; Fax: +1-617-264-5212.
E-mail address: reisa@rics.bwh.harvard.edu

1552-5260/5 - see front matter © 2011 The Alzheimer’s Association. All rights reserved.
doi:10.1016/j.jalz.2011.03.003

Alz and Dementia, 2011
### Preclinical AD

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Sperling et al: 2011
NIA-AA Preclinical AD Staging in Relation to Our Hypothetical Model of Biomarkers

- Normal Biomarker magnitude
- Abnormal

Cut points

Preclinical Stage
0 1 2 3

Aβ, Neuronal injury

Clinical disease stage

Cognitively normal MCI Dementia

Clinical disease stage
Do the Criteria Work?

Mayo Clinic Study of Aging (MCSA)
Mayo Olmsted County Study of Aging (U01 AG006786)
Mayo Clinic
Study of Aging

Population-based study of 3000-4000 nondemented persons age 50-89 years in Olmsted County, MN
Mayo Clinic Study of Aging

2004

Oct.

Enrollment

F-U Cycle 2

F-U Cycle 3

F-U Cycle 4

F-U Cycle 5
Data analysis

F-U Cycle 6
Data analysis

F-U Cycle 7
Data analysis

Replen cohort

Replen cohort

Replen cohort

Replen cohort

Replen cohort

F-U = follow-up
Mayo Clinic Study of Aging

≥70 year olds

2004  ‘06  ‘08  ‘10  ‘12  ‘14
Oct
Enrollment
F-U Cycle 2
F-U Cycle 3
F-U Cycle 4
F-U Cycle 5
F-U Cycle 6
F-U Cycle 7

n=2000

≥50 year olds

2011  ‘12  ‘13  ‘14
Enrollment
F-U Cycle 2
F-U Cycle 3

n=2000

F-U = follow-up
Evaluation

Consent form

Blood draw

Clinical evaluation

Nurse/SC interview

Neurological evaluation

Cognitive assessment

Consensus conference

Participant
- Family history
- Current medications
- Demographic information
- Memory & orientation
- Medical history & risk assessment
- Neuropsychiatric inventory
- Study partner
- Clinical dementia rating
- Functional assessment (FAQ)

Neurological history
- Short test of mental status
- Modified Hachinski scale
- Prime MD (physician form)
- Neurological examination and modified UPDRS

Memory
- Logical memory (delayed)
- Visual reprod (delayed)
- AVLT

Executive function
- Trails A & B
- Digit symbol substitution

Visuospatial
- Picture completion
- Block design

Language
- Boston naming test
- Category fluency

Cognitive assessment
Resources Acquired

- 4000 non-demented subjects
  - 3000 cognitively normal
  - 800 MCI
- 2500 quantitative MRI scans
- ~ 4000 DNA samples
- ~ 4000 frozen plasma/serum samples plus annual samples
- Clinical and performance measures
Extension of MCSA

- Add new subjects older cohort
- Add 1000+ subjects younger cohort
- Continue annual clinical follow-ups
- Continue serial MRI scans
- Collect annual plasma/serum
- Perform 800 CSF’s
- Perform 1200 FDG-PET scans
- Perform 1200 PiB PET scans
So, How Do the Criteria Fare in the General Population?
MCI Due to AD
Assessing Biomarkers in the Community

- **Biomarker negative**
  - Amyloid neg
  - FDG PET/MRI neg

- **Amyloid positive Neurodegen neg**
  - Amyloid pos
  - FDG PET/MRI neg

- **Amyloid pos Neurodegen pos**
  - Amyloid pos
  - FDG PET/MRI pos

- **Neurodegen only**
  - Amyloid neg
  - FDG PET/MRI pos
All MCI MCSA
Population Frequencies

MCSA aMCI
Annual Rates of Change

NL 50%  MCI Biom neg  8%  Dementia
42%

NL 36%  MCI Amyloid positive  0%  Dementia
64%

NL 5%  MCI Amyloid + Neurodegen  17%  Dementia
78%

NL 36%  MCI Neurodegen only (sNAP)  22%  Dementia
42%

Risk of Dementia Following Reversion to Normal

- MCI with reversion vs normal: HR = 6.6; P<0.001
- MCI no reversion vs normal: HR = 28.8; P<0.001
- Normal
aMCI

- MCSA
- ADNI

%

- Biom neg
- Amyloid only
- Amyloid + neurodeg
- Degenerative only

Preclinical AD
## Preclinical AD

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>$\text{A}_{\beta}$ (PET or CSF)</th>
<th>Neuronal injury</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Stage 0</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Sperling et al: 2011
NIA-AA Preclinical AD Staging in Relation to Our Hypothetical Model of Biomarkers

Preclinical Alzheimer’s Disease and Its Outcome
A Longitudinal Cohort Study

Stephanie J. B. Vos; Chengjie Xiong; Pieter Jelle Visser; Mateusz S. Jasielec; Jason Hassenstab; Elizabeth A. Grant; Nigel J. Cairns; John C. Morris; David M. Holtzman; Anne M. Fagan

Preclinical Alzheimer’s Disease and Its Outcome: A Longitudinal Cohort Study
Pre-Clinical AD Stages

Neuroimaging vs CSF

- Stage 0
- Stage 1
- Stage 2
- Stage 3
- SNAP
- Uncl

Vos et al: 2013

Petersen, L Neur 2013
Preclinical Progression to MCI/Dementia
Mayo Clinic Study of Aging

Knopman et al., 2012
Progression to CDR $\geq 0.5$ by Preclinical Alzheimer’s Disease Stage

Amyloid-first and Neurodegeneration-first Profiles Characterize Incident Amyloid PET Positivity

Clifford R. Jack, Jr., Heather J. Wiste, Stephen D. Weigand, David S. Knopman, Val Lowe, Prashanthi Vemuri, Michelle M. Mielke, David T. Jones, Matthew L. Senjem, Jeffrey L. Gunther, Brian E. Gregg, Vernon S. Pankratz, Ronald C. Petersen

Neurology, 2013; 81: 1732-1740
The CN groups in blue are the focus of this paper.
Changes in Imaging and Clinical Measures By Amyloid Status
Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer’s disease

Yen Ying Lim,1,2 Paul Maruff,1,2 Robert H. Pietrzak,3 David Ames,4,5 Kathryn A. Ellis,1,4,5 Karra Harrington,1 Nicola T. Lautenschlager,4,6 Cassandra Szoeke,5,7 Ralph N. Martins,8 Colin L. Masters,1 Victor L. Villemagne1,9,10 and Christopher C. Rowe9,10, for the AIBL Research Group

1 The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia
2 CogState Ltd., Melbourne, Victoria, Australia
3 Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
4 Academic Unit for Psychiatry of Old Age, St. Vincent’s Health, Department of Psychiatry, The University of Melbourne, Kew, Victoria, Australia
5 National Ageing Research Institute, Parkville, Victoria, Australia
6 School of Psychiatry and Clinical Neurosciences and WA Centre for Health and Ageing, The University of Western Australia, Perth, Western Australia, Australia
7 CSIRO Preventative Health Flagship, Parkville, Victoria, Australia
8 Centre of Excellence for Alzheimer’s Disease Research and Care, School of Exercise, Biomedical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia
9 Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Victoria, Australia
10 Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia

Correspondence to: Yen Ying Lim
The Florey Institute of Neuroscience and Mental Health,
155 Oak Street, Parkville,
VIC 3052, Australia,
E-mail: yenlim@florey.edu.au

High amyloid has been associated with substantial episodic memory decline over 18 and 36 months in healthy older adults and individuals with mild cognitive impairment. However, the nature and magnitude of amyloid-related memory and non-memory change from the preclinical to the clinical stages of Alzheimer’s disease has not been evaluated over the same time interval. Healthy older adults (n = 320), individuals with mild cognitive impairment (n = 57) and individuals with Alzheimer’s disease (n = 36) enrolled in the Australian Imaging, Biomarkers and Lifestyle study underwent at least one positron emission tomography neuroimaging scan for amyloid. Cognitive assessments were conducted at baseline, and 18- and 36-month follow-up assessments. Compared with amyloid-negative healthy older adults, amyloid-positive healthy older adults, and amyloid-positive individuals with mild cognitive impairment and Alzheimer’s disease showed moderate and equivalent decline in verbal and visual episodic memory over 36 months (d’s = 0.47–0.51). Relative to amyloid-negative healthy older adults, amyloid-positive healthy older adults showed no decline in non-memory functions, but amyloid-positive individuals with mild cognitive impairment showed additional moderate decline in language, attention and visuospatial function (d’s = 0.47–1.12), and amyloid-positive individuals with Alzheimer’s disease showed large decline in all aspects of memory and non-memory function (d’s = 0.73–2.28). Amyloid negative individuals with mild cognitive impairment did not show any cognitive decline over 36 months. When non-demented individuals (i.e. healthy older adults and adults with mild cognitive impairment) were further dichotomized, high amyloid-positive non-demented individuals showed a greater rate of decline in episodic memory and language when compared with low amyloid positive non-demented individuals.
Figure 1.

Linear trend of performance on the verbal memory composite (A) and the visual memory composite (B) for HA-Aβ−, HA-Aβ+, MCI-Aβ−, MCI-Aβ+, and AD-Aβ+ groups, from baseline to 36 months.

Lim YY et al, Brain 2013.
Mayo Clinic Study of Aging

Role of amyloid status in progression from healthy control to MCI in the general population
Role of Amyloid in Predicting Progression in Imaging and Cognitive Biomarkers

- Amyloid positive vs. amyloid negative
  - Imaging biomarkers
    - PiB PET
    - FDG PET
    - MR ventricular volume
  - Cognitive measures
    - Global
    - 4 cognitive domains
## Baseline Characteristics of Subjects with Serial Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Serial Cognitive Data (n = 484)</th>
<th>Serial Imaging Scans (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>78 (75, 82)</td>
<td>78 (75, 82)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>269 (56)</td>
<td>121 (60)</td>
</tr>
<tr>
<td>APOE e4 carrier, no (%)</td>
<td>120 (25)</td>
<td>57 (28)</td>
</tr>
<tr>
<td>Education, years, median (IQR)</td>
<td>14 (12, 16)</td>
<td>14 (12, 16)</td>
</tr>
<tr>
<td>Short Test Score, median (IQR)</td>
<td>35 (34, 37)</td>
<td>35 (33, 37)</td>
</tr>
<tr>
<td>Cognitive domain z-scores, median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>0.75 (0.16, 1.25)</td>
<td>0.71 (0.13, 1.23)</td>
</tr>
<tr>
<td>Memory</td>
<td>0.70 (0.02, 1.38)</td>
<td>0.70 (-0.04, 1.32)</td>
</tr>
<tr>
<td>Language</td>
<td>0.50 (-0.02, 1.02)</td>
<td>0.47 (-0.04, 0.99)</td>
</tr>
<tr>
<td>Attention</td>
<td>0.59 (-0.00, 1.11)</td>
<td>0.59 (0.02, 0.99)</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>0.64 (0.02, 1.22)</td>
<td>0.61 (0.00, 1.20)</td>
</tr>
<tr>
<td>PIB ratio, median (IQR)</td>
<td>1.38 (1.31, 1.63)</td>
<td>1.38 (1.30, 1.61)</td>
</tr>
<tr>
<td>FDG ratio, median (IQR)</td>
<td>1.40 (1.30, 1.50)</td>
<td>1.40 (1.30, 1.50)</td>
</tr>
<tr>
<td>Hippocampal volume, cm³, median (IQR)</td>
<td>7.0 (6.4, 7.5)</td>
<td>7.0 (6.4, 7.5)</td>
</tr>
<tr>
<td>Hippocampal volume/TIV, median (IQR)</td>
<td>0.47 (0.43, 0.52)</td>
<td>0.47 (0.42, 0.52)</td>
</tr>
<tr>
<td>Number of follow-up visits, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>261 (54)</td>
<td>171 (86)</td>
</tr>
<tr>
<td>2</td>
<td>181 (37)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>3</td>
<td>29 (6)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>4</td>
<td>10 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5</td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Change in STMS by PiB Over Time

Short Test of Mental Status

Time (years)

Age=75, PIB-
Age=75, PIB+
Age=82, PIB-
Age=82, PIB+

PIB, P=0.002
Change in Global Cognition by PiB Over Time

- Age=75, PiB-
- Age=75, PiB+
- Age=82, PiB-
- Age=82, PiB+

PIB, P=0.02

Global z-score vs Time (years)
Change in Attention by PiB Over Time

- Age=75, PIB-
- Age=82, PIB-
- Age=75, PIB+
- Age=82, PIB+

PIB, P=0.005

Attention z-score vs. Time (years)
ApoE and PiB Cognitive Measures

- **Global z-score**
  - APOE4+, PIB+
  - APOE4+, PIB-
  - APOE4-, PIB+
  - APOE4-, PIB-

- **Attention z-score**
  - APOE4+, PIB+
  - APOE4+, PIB-
  - APOE4-, PIB+
  - APOE4-, PIB-

- **Short Test Mental Status**
  - APOE4+, PIB+
  - APOE4+, PIB-
  - APOE4-, PIB+
  - APOE4-, PIB-

Annual change
-0.1 0.0 0.1

©2014 MFMER | 3320473-52
Change in PiB Levels by PiB Over Time

PIB, P≤0.001

Time (years)

PiB ratio

Age=75, PIB-
Age=75, PIB+
Age=82, PIB-
Age=82, PIB+
Change in Ventricular Volume by PiB Over Time

Ventricular volume (cm$^3$)

- Age=75, PiB-
- Age=75, PiB+
- Age=82, PiB-
- Age=82, PiB+

PiB, P=0.001
ApoE and PiB Imaging Biomarkers

![Graph showing annual change in PIB and ventricular volume for different ApoE and PiB categories.]

- APOE4+, PIB+
- APOE4+, PIB-
- APOE4-, PIB+
- APOE4-, PIB-
Education, PBI by ApoE Interaction and Hippocampal Volume

- Education (12 vs 16 yr)
- Among ApoE4- / PIB +
- Among ApoE4+ / PIB +
- PIB + ApoE4+ vs PiB – ApoE4-
- Among PiB + APOE4 +
- Among PiB - APOE4+
- HV/TIV (P25 vs P75)
Evolving Field on Biomarkers

• **Pre-clinical**
  - Amyloid alone slow progression
  - Amyloid plus neurodegeneration
  - Amyloid plus ApoE4 additive

• **MCI**
  - Amyloid alone slow progression
  - Amyloid plus neurodegeneration
Mayo Clinic AD Research

Rochester
Brad Boeve
Dave Knopman
Cliff Jack
Val Lowe
Bob Ivnik
Mary Machulda
Michelle Mielke
Rosebud Roberts
Walter Rocca
Shane Pankratz
Jenny Whitwell
Kejal Kantarci
Joe Parisi
Eric Tangalos

Jacksonville
Neill Graff-Radford
Steve Younkin
Dennis Dickson
John Lucas
Tanis Ferman
Rosa Rademakers
Nilufer Taner-Erketin
Len Petruccelli
Guojin Bu
Otto Pedraza

Scottsdale
Rick Caselli
Bryan Woodruff
Yonas Geda
Thank You