Predictive Testing of Alzheimer’s Disease

David A. Wolk, M.D.
Assistant Professor
Dept of Neurology
Perelman School of Medicine
Assistant Director
Penn Memory Center
University of Pennsylvania
Overview

• Epidemiology and current diagnosis of AD
• Early Symptomatic Detection
  – Prodromal AD (Mild Cognitive Impairment)
• Pre-symptomatic Detection
  – Preclinical AD
• Neuroethical considerations
  – Biomarker testing at different stages of disease
  – Preclinical AD
Core Contextual Points

• Highly prevalent disease
• Major public health issue
• Tremendous fear of diagnosis
• Incredible development of diagnostic tools
• Treatment is very limited
• Scarce resources
ALTHEIMER
POP. 5 Million
Clinical and Pathological Course of AD

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Normal</th>
<th>Pre-Clinical AD</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic State</td>
<td>No Disease</td>
<td>Early Changes</td>
<td>Mild Mod Changes</td>
<td>Mod-Severe Changes</td>
</tr>
</tbody>
</table>

**Plaques**:
- Normal: No plaques
- Pre-Clinical AD: Early changes
- MCI: Mild changes
- AD: Severe changes

**Tangles**:
- Normal: No tangles
- Pre-Clinical AD: Early changes
- MCI: Mild changes
- AD: Severe changes
Scope of Problem

Prevalence of Dementia essentially doubles every 5 years after the age of 65.

Source, Alzheimer’s Association 2010
Prevalence by Age and Race/Ethnicity

**Figure 1:** Proportion of People Age 65 and Older with Alzheimer’s Disease and Other Dementsias, by Race/Ethnicity, Washington Heights-Inwood Columbia Aging Project, 2006

<table>
<thead>
<tr>
<th>Age</th>
<th>White</th>
<th>African-American</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 to 74</td>
<td>2.9</td>
<td>9.1</td>
<td>7.5</td>
</tr>
<tr>
<td>75 to 84</td>
<td>10.9</td>
<td>19.9</td>
<td>27.9</td>
</tr>
<tr>
<td>85+</td>
<td>58.6</td>
<td>62.9</td>
<td></td>
</tr>
</tbody>
</table>

Alzheimer’s Association, 2012
Number of People with Alzheimer’s Disease

Projecting Numbers of People Age 65 and Over in the U.S. Population with Alzheimer’s Disease Using the U.S. Census Bureau Estimates of Population Growth*

Numbers (in millions)

Numbers: 4.5, 5.1, 5.7, 7.7, 11.0, 13.2

Alzheimer’s Association, 2012
Cost of Care Prediction

Alzheimer’s Association, 2010
5-year Delay in Onset

Alzheimer’s Association, 2010
Aging Versus AD

I may have alzheimer's, but at least I don't have alzheimer's.
Age-Associated Cognitive Decline

Hedden and Gabrieli, 2004
What is Dementia?

- Formal Criteria (DSM IV)
- The development of multiple cognitive deficits manifested by both:
  - Memory Impairment
  - At least one of the following cognitive disturbances:
    - Language
    - Skilled motor activities (praxis)
    - Objects and people knowledge (semantic)
    - Judgment, abstractions, planning (executive function)
  - Decline from a previous level and significantly impairs social or occupational functioning.
  - Not transient (delirium)
- However, memory impairment is not prominent in all dementias
Most Common Dementias in Late Life

- Alzheimer’s Disease
- Vascular Dementia & Mixed AD/VaD
- Frontotemporal Dementias
- Other
Figure 3: Auguste D
Photograph dated November, 1902.
• Amyloid Plaques
  – Extracellular accumulation of Aβ (fragment of the amyloid precursor protein)
  – Abnormal processing of APP critical to pathophysiology of Alzheimer’s disease

• Neurofibrillary Tangles
  – Intracellular, paired helical structures composed of hyperphosphorylated tau.
  – Correlate well with disease severity and neuronal death.
Why is memory loss an early feature of AD

Mesulam, 1990; Braak and Braak, 1991
Probable AD

- Presence of dementia
- Insidious onset and progressive worsening of memory and other areas of cognition
- At least two domains of involvement (memory plus...)
  - Language, visuospatial, praxis, executive
- Absence of other disease that could result in dementia syndrome
NINCDS-ADRDA Criteria

• Definite AD
  – Histopathological evidence of AD on autopsy or biopsy in context of clinical probable AD

• Sensitivity: ~ 80% (65-96%)

• Specificity: ~ 70% (23-88%)
  – Dubois et al., Lancet, 2007
Currently Approved Medicines for the Treatment of Alzheimer’s Disease

- Aricept / Donepezil
- Exelon (Rivastigmine)
- Reminyl (Galantamine)
- Namenda (Memantine)
Disease-Modifying Clinical Research Trials Now and on the Horizon for Treatment and Prevention of Alzheimer's Disease

**Oral Pharmacotherapy**
- Anti-Amyloid
  - g- and b- Secretase Inhibitors
- Anti-Tau
  - Methylthioninium
- Others
  - Resveratrol, etc...

**Parenteral, Infusion & Other Immunotherapies**
- Bapineuzumab
- Solenuzumab
- Gammagard
- Epothilones

**Neurosurgical**
- CERE-110 NGF Gene Therapy
- Deep Brain Stimulation
Additional Tests May Enhance Accuracy of Diagnosis – “Biomarkers of AD”

• Markers of Brain Degeneration
  – Look for evidence of brain changes in pattern consistent with AD
  – MRI, Glucose PET scans

• Markers of Brain Pathology
  – Look for molecular evidence of AD
  – Cerebrospinal Fluid (CSF), “Amyloid Imaging”
Qualitative Assessment of Brain Atrophy

Healthy Older Adult  Alzheimer’s Disease
Healthy Older Adult  Alzheimer’s Disease
Semi-Quantitative Visual Rating
Scheltens Visual Rating of Hippocampal Atrophy

Bastos Leite et al.’ 05, based on Scheltens et al.’ 92
Quantitative Measures of Hippocampus

Pluta et al., *JAD*, 2012

7T MRI
FDG (glucose) Positron Emission Tomography (measures brain activity)

Normal  Alzheimer’s  Frontotemporal (bv)
Cerebrospinal Fluid Aβ and tau

• Lumber Puncture to obtain CSF
• Aβ – linked to amyloid plaques
  – Low is abnormal
• Total tau, phospho-tau – linked to neurofibrillar tangles
  – High is abnormal

Shaw et al., *Annals of Neurology*, 2009
Amyloid Imaging

Wolk and Klunk, 2009
[¹⁸F]Florbetapir (Amyvid)

Clark et al., JAMA, 2011
## New AD Criteria Incorporates Biomarkers

**Table 1**

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD dementia</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>Positive</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation)</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>High</td>
<td>Positive</td>
<td>Positive</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>Dementia-unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, $^{18}$fluorodeoxyglucose; MRI, magnetic resonance imaging.

McKhann et al., *Alz & Dementia*, 2011
How much testing should be done?

• Treatments for AD is limited
• When wrong, almost always a non-treatable condition
• The only FDA approved biomarker, amyloid imaging, is relatively expensive
• How much do we value getting the correct diagnosis?
  – Are there circumstances in which it would be more valuable
• Who should order these studies?
<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Normal</th>
<th>Pre-Clinical AD</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive State</td>
<td>No Symptoms</td>
<td>No Symptoms</td>
<td>Mild Symptoms</td>
<td>Mild-Severe Symptoms</td>
</tr>
<tr>
<td>Pathologic State</td>
<td>No Disease</td>
<td>Early Changes</td>
<td>Mild Mod Changes</td>
<td>Mod-Severe Changes</td>
</tr>
</tbody>
</table>

Plaques ➔

Tangles ➔
“Petersen Criteria” for MCI (now referred to as amnestic-MCI)

- Memory complaint (preferably corroborated by informant)
- Episodic Memory impairment for age and education
- Largely intact general cognitive function
- Essentially preserved activities of daily living
- Do not meet criteria for dementia
Amnestic MCI

- Enriched in patients with AD pathology
  - Specialty Clinics
    - 10 to 15% “Conversion” to clinical AD per year
      - 1-3% in cognitively normal adults
    - 50-80% over 5 years
  - Community Studies (PAQUID, MoVIES)
    - Lower conversion rate (4 to 8%/year)
    - Reversion to normal (10 to 40% over 2 years)
Mild Cognitive Impairment

• Heterogeneous Population
  – AD
  – Other neurodegenerative disorders
  – Age-Associated memory loss
    • At border of diagnosis of MCI
  – CVD
  – Hippocampal sclerosis
  – Depression
  – Medications
Can we predict who will develop clinical AD?

- AD biomarkers enhance prediction
- Lots of biomarker data on the imaging, CSF, psychometric characteristics of AD
- The more you look like AD, the more likely you will convert to AD!
Hippocampal Volume

Jack et al., 1999
Amyloid Imaging

Wolk et al., *Annals of Neurology*, 2009
PiB+ a-MCI vs. Controls
  - Atrophy includes bilateral medial temporal lobes
  - PiB- a-MCI vs. Controls
    - No difference
  - PiB+ vs. PiB- a-MCI
    - Greater atrophy in PiB+ patients in masked regions
Amyloid Imaging

- 23/26 patients have had follow-up ADRC evaluations and consensus discussion
  - Mean f/u: 24.0 months (6-57 months)
  - 13 PiB positive (Mean: 23.6 months)
  - 10 PiB negative (Mean: 24.5 months)

Wolk et al., *Annals of Neurology*, 2009
Combination of CSF Total-tau (↑) and Aβ42 (↓):

- Sensitivity of 95% and a specificity of 83% for detection of incipient AD in patients with MCI
- Relative risk of progression to AD = 17.7 (p<0.0001)

Hansson et al., *Lancet Neurol*, 2006
# NIA-AA MCI Criteria

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Biomarker Driven Probability of AD Etiology</th>
<th>Presence of Cerebral Amyloidosis (PET, CSF)</th>
<th>Evidence of Neuronal Injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI-core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminate/untested</td>
<td>Conflicting/indeterminate/untested</td>
</tr>
<tr>
<td>MCI due to AD – Intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Untested</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Untested</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI due to AD – High likelihood</td>
<td>Highest</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI – unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Albert et al., *Alzheimer’s & Dementia*, 2011
How should we use biomarkers in MCI?

- Prognostic value (although numbers are still very fuzzy)
- Possibly, but unlikely to alter management
- Many patients want to know what is causing their memory issues – value in knowing
- Issues of disclosure
- Potential for discrimination
Clinical and Pathological Course of AD

Clinical State

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Normal</th>
<th>Pre-Clinical AD</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive State</td>
<td>No Symptoms</td>
<td>No Symptoms</td>
<td>Mild Symptoms</td>
<td>Mild-Severe Symptoms</td>
</tr>
<tr>
<td>Pathologic State</td>
<td>No Disease</td>
<td>Early Changes</td>
<td>Mild Mod Changes</td>
<td>Mod-Severe Changes</td>
</tr>
</tbody>
</table>

Plaques ➔

Tangles ➔
Preclinical Alzheimer’s Disease

• 25-30% of CN adults with AD molecular biomarker profile
• Consistent with autopsy data

Morris et al., *Annals of Neurology*, 2010
Amyloid Imaging and Cognitive Decline in CN Adults

Roe et al., *Neurology*, 2013

**Figure 3** Bubble plot of progression to CDR (Clinical Dementia Rating) >0 as a function of mean cortical binding potential, age, and time.
Abnormal

Biomarker Magnitude

Normal

Normalized

Clinical disease stage

Presymptomatic

MCI

Dementia

Modified from Jack et al., 2010
Abnormal

Amyloid (PiB)

Biomarker Magnitude

Normal

Clinical disease stage

Presymptomatic

MCI

Dementia

Modified from Jack et al., 2010
Modified from Jack et al., 2010
Abnormal

- Amyloid (PiB)
- Function
- Psychometrics

Normal

Biomarker Magnitude

Normal

Presymptomatic

MCI

Dementia

Clinical disease stage

Modified from Jack et al., 2010
Abnormal

<table>
<thead>
<tr>
<th>Clinical disease stage</th>
<th>Normal</th>
<th>Presymptomatic</th>
<th>MCI</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker Magnitude</td>
<td>Normal</td>
<td>Abnormal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloid (PiB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychometrics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain Structure (MRI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Jack et al., 2010
Abnormal

Normal

Biomarker Magnitude

Clinical disease stage

Presymptomatic

MCI

Dementia

Modified from Jack et al., 2010
NIA-AA Preclinical AD Criteria

• Research criteria!!
• Stage 1 – presence of amyloid (CSF or PET)
• Stage 2 – amyloid + evidence of neurodegeneration
• Stage 3 – amyloid + neurodegeneration + subtle cognitive change
Implications of Preclinical AD

• Shift in boundary between normal aging and Alzheimer’s Disease
  – Some “age-related” changes likely due to AD pathophysiology

• AD is uncoupled from clinical symptoms
  – Change in concept of disease?
  – Disease defined by risk and predictors
    • Or perhaps the critical issue is the risk that “the disease” will produce symptoms
Who should be tested?

• General consensus is that preclinical diagnosis should not be brought into clinical practice
  – However, many want it
• Will be disclosed in several “preclinical AD” treatment trials (secondary prevention)
  – Anti-Amyloid Treatment in Asymptomatic AD
  – Autosomal dominant trials
    • Columbian PSEN1 trial
How to Communicate Diagnosis

• Risk associated with dx
  – Anxiety/depression

• What are the benefits
  – Some want to know and others don’t
  – What actions can be taken if evidence of high risk?

• What is appropriate counseling?
ApoE as a Model of Disclosure of Risk

Disclosure of APOE Genotype for Risk of Alzheimer’s Disease

Robert C. Green, M.D., M.P.H., J. Scott Roberts, Ph.D.,
L. Adrienne Cupples, Ph.D., Norman R. Relkin, M.D., Ph.D.,
Peter J. Whitehouse, M.D., Ph.D., Tamsen Brown, M.S.,
Susan LaRusse Eckert, M.S., Melissa Butson, Sc.M., A. Dessa Sadovnick, Ph.D.,
Kimberly A. Quaid, Ph.D., Clara Chen, M.H.S., Robert Cook-Deegan, M.D.,
and Lindsay A. Farrer, Ph.D., for the REVEAL Study Group*
ApoE as a Model of Disclosure of Risk

- Exclusions based on anxiety and depression scales
- Information provided in written and oral format with genetic counselor
- Monitored mood and anxiety after
- Emergency contact
- Assess to mental health
- Similarities and differences to ApoE testing
  - Both assess risk, but is there something different about knowing the pathology is really there
Gaps in Knowledge of What Biomarkers Tell Us

• Specifics are still unknown
  – Absolute risk in any individual
    • Studies are small and populations not always representative
    • Temporal prediction poor
    • Standardization poor
  – Should we be using measures when much of the data just isn’t in yet
Legal Ramifications

• Given uncoupling of cognitive capacity and diagnosis, need for privacy and confidentiality laws
  – Insurance risks
  – Discrimination in workplace and elsewhere

• Policy for assessment of capacity in financial and other matters
  – Certain professions that require more rigorous testing?
Development of Health Policy

• What kind of evidence is needed for determining who will receive preclinical testing
• Political impact of a disease of millions
• Who should develop guidelines