Neuroimaging in Alzheimer’s Disease
Why we need standardization!

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Clinical Trial Site Investigator:
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   American Federation of Aging Research
   American Health Assistance Foundation
Why do we need to standardize neuroimaging in AD?

- Clinical practice - diagnosis and management
- Moving towards earlier diagnosis (prodromal and preclinical stages of AD)
- Participant selection for clinical trials
- Safety monitoring in clinical trials
- Outcome measures in clinical trials
Evolving “Gold Standards”

• Neuropathology – gold standard
• Clinical – gold standard
• Will biomarkers supplant these standards?
• Biomarkers shouldn’t be held to higher standard than neuropathology – same conundrums still apply
So many new criteria!
“Well, if it doesn’t matter who’s right and who’s wrong, why don’t I be right and you be wrong?”
The Continuum of Alzheimer’s Disease

Cognitive Function

Disease Progression

Preclinical

(Asymptomatic Pre-symptomatic)

MCI due to AD

(Prodromal AD)

AD Dementia
Neuropathology of AD
Abnormal

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/fMRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Clinical Disease Stage

Figure adapted from Jack et al. 2010
Sperling et al Alzheimer & Dementia 2011
### Biomarker Harmonization

#### AD Dementia

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>$\alpha$ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD dementia</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>Intermediate</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>With three levels of evidence of AD pathophysiological process</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Unavailable or indeterminate</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation)</td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
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<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 evidence of AD pathophysiological process</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Dementia-unlikely due to AD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AD, Alzheimer’s disease; MRI, magnetic resonance imaging.

#### MCI due to AD

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>$\alpha$ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI—core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminant/untested</td>
<td>Conflicting/indeterminant/untested</td>
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<td>MCI due to AD—intermediate likelihood</td>
<td>Intermediate</td>
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<td>Untested</td>
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<td>MCI due to AD—high likelihood</td>
<td>Highest</td>
<td>Positive</td>
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<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
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</tbody>
</table>

**Abbreviations:** CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

#### Preclinical AD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>$\alpha$ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
<th>Evidence of subtle cognitive change</th>
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</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Asymptomatic cerebral amyloidosis</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
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<tr>
<td>Stage 2</td>
<td>Asymptomatic amyloidosis + “downstream” neurodegeneration</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
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<tr>
<td>Stage 3</td>
<td>Amyloidosis + neuronal injury + subtle cognitive/behavioral decline</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
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</tbody>
</table>

**Abbreviations:** AD, Alzheimer’s disease; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose (18F); sMRI, structural magnetic resonance imaging.
Incorporation of Biomarkers in NIA-AA Criteria

• Used to enhance certainty of diagnosis
• Two categories – need both for high likelihood
• Markers of amyloid-β accumulation
  – CSF
  – PET amyloid imaging
• Markers of neuronal injury
  – CSF tau and phospho-tau
  – Synaptic dysfunction: FDG-PET (fMRI)
  – Atrophy: MRI cortical thinning, hippocampal atrophy
### Lessons from the cardiovascular field

<table>
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<tr>
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<th>LDL (bad) CHOLESTEROL</th>
<th>HDL (good) CHOLESTEROL</th>
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<td>120</td>
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<td>290</td>
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<td><strong>Very High</strong></td>
<td><strong>Very High</strong></td>
<td><strong>Protective</strong></td>
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<tr>
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Lessons from the cardiovascular field

Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

The risk assessment tool below uses information from the Framingham Heart Study to predict a person’s chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 and older who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.

Age: [ ] years
Gender: [ ] Female  [ ] Male
Total Cholesterol: [ ] mg/dL
HDL Cholesterol: [ ] mg/dL
Smoker: [ ] No  [ ] Yes
Systolic Blood Pressure: [ ] mm/Hg
Are you currently on any medication to treat high blood pressure. [ ] No  [ ] Yes

Calculate Your 10-Year Risk
The Continuum of Alzheimer’s Disease

Cognitive function

“Normal” Aging

Preclinical

MCI (Prodromal AD)

Dementia

Years
Why do we want to detect AD earlier?

• No effective disease-modifying treatment
• Nine Ten negative Phase III trials at the stage of mild/mod dementia
• Evidence that dementia is relatively late stage of AD pathophysiological process
• Think about what happens when we wait to treat these diseases after symptoms have been present for several years:
  • Cancer, Cerebrovascular disease/Stroke, Cardiovascular disease/Myocardial Infarction, HIV/AIDS, Osteoporosis, Diabetes…
PiB-PET Amyloid Imaging

Harvard Aging Brain Study

Sperling R, Johnson K *Neuromolecular Med* 2010
PiB-PET Amyloid Imaging in Older Normal Cohorts

AIBL Study

Mayo Clinic

Wash U

Kantarci Jack

Villemagne and Rowe

Mintun and Morris
Preclinical Alzheimer’s Disease?

**Prevalence of PiB+ve PET in HC**

**Prevalence of plaques in HC**

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

~15 yrs

**Prevalence of AD**

(Tobias, 2008)

Rowe C et al *Neurobiology of Aging* 2010
Staging Framework for Preclinical AD

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ_{1-42}

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI → AD dementia

NIA-AA Preclinical Workgroup
Sperling et al Alzheimer’s & Dementia 2011
One threshold for all?

- **Age**
  - Prior probability assumptions for 55 vs. 85 year old
- **APOE genotype**
  - Differential conversion from PiB to CSF (Weigand 2010)
- **Cognitive reserve**
  - May influence the relationship between biomarker and cognition (Rentz 2010, Roe 2010)
- **Gender**
- **Co-morbidities**
Exploit the advantages of neuroimaging – the anatomy!

• Lack of clear regional brain-behavior relationships with amyloid imaging but topology of selective vulnerability to Aβ deposition
• Functional imaging strongly suggests specific network vulnerability
• Atrophy patterns may evolve over the course of the disease – unclear whether medial temporal lobe is really the earliest…
• How will we standardize measurement of anatomic progression?
Topography of Progression and Selective Vulnerability

PiB-PET  fMRI  FDG-PET  vMRI

Molecular  Electrophysiological  Microscopic
Standardization for early intervention trials

• Critical to standardize acquisition parameters
  – Tension between state-of-the-art and widely available standard for multi-center studies (lowest common denominator)
  – Improvements likely over 5 year longitudinal studies
  – Multiple MR platforms (ADNI) and PET tracers (very few comparison studies – no longitudinal comparisons)

• Standardization of analytic techniques and “thresholds” likely to continue to evolve
Spectrum of Amyloid Related Imaging Abnormalities

- Multi-focal gray and white matter Involvement (ARIA-E)
- Sulcal Effusion (ARIA-E)
- Subtle leptomeningeal Involvement (ARIA-E)
- Micro-hemorrhage (ARIA-H)

Sperling et al. Alz & Dementia 2011
Amyloid Related Imaging Abnormalities (ARIA) in non-immunotherapy trials

BMS gamma-secretase Phase II trial–Sperling R et al AAICAD 2011 (under review)
MR Sequence Dependent Detection of ARIA-H Microhemorrhage

Sperling R et al. *Alz & Dementia* 2011 (Figure courtesy of Goos and Scheltens)
Multi-modality Imaging in Anti-Amyloid Therapy

Evidence of immunotherapy related decreases in fibrillar Aβ burden on PiB-PET imaging

Rinne *Lancet Neurology* 2010  
Ostrowitzki *Arch Neurol* 2011
High amyloid burden in normal elderly associated with default network dysfunction at rest.

Hedden et al. *J Neurosci* 2009
(Also see Shelline *Bio Psych* 2010; Mormino *Cerebral Cortex* 2011; Drzezga *Brain* 2011)
DIAN – Familial AD Resting Connectivity

**A**

Brain images with color-coded areas indicating DMN Component Loading with F-Value values.

**B**

Graph showing DMN Component Loading for different groups (CDR0 M-, CDR0 M+, CDR0.5 M+, CDR1+ M+). The graph includes error bars and significance levels (p<0.05, p<0.001, ns).

**C**

Graph showing DMN Component Loading in PPC over Time From Onset (TFO). The graph includes lines for TFO M- and TFO M+ with correlation values (Group Corrected r = +0.01; p=0.95, Group Corrected r = -0.42; p<.001) and significance levels.
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 and neurotoxic forms of Aβ
- 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 replenishment

Sperling, Jack, Aisen Science Translational Medicine (in press)
Figure adapted from Jack et al. 2010; Sperling et al. 2011
Preclinical intervention trials

• Need to test the amyloid hypothesis at a stage when amyloid may still drive the disease process and prior to widespread irreversible neuronal loss

• Secondary prevention trials in preclinical populations already in planning stages:
  – Dominantly Inherited Alzheimer Network
  – Alzheimer Prevention Initiative
  – Studies on Prevention of AD (StoP-AD)
  – Anti-Amyloid Treatment in Asymptomatic AD (A4)
A4 Trial Proposal – ADCS Proposal

- **Anti-Amyloid treatment in Asymptomatic AD**
- Older individuals (>age 70) – Amyloid positive
  - High tracer retention on PET amyloid imaging
- Clinically normal/asymptomatic*
- Treat with biologically active anti-amyloid compound for 3 years – longer clinical follow-up
- Test the hypothesis that altering “upstream” amyloid accumulation will impact “downstream” neurodegeneration and rate of cognitive decline
Definition of Amyloid Positivity

Amyloid Negative HC

Amyloid Positive HC
A4 Screening and Randomization Algorithm

- Telephone Screen: N > 10,000
- In clinic screen: N = 5000
- PET Amyloid imaging: N = 3300
- Obtain MRI on Aβ + N = 1100
- Aβ + MRI OK: N = 1000
- Randomization (with stratification)
  - Active Treatment: N = 500
  - Placebo: N = 500
- Treatment completers: N = 350
- Placebo completers: N = 375
- Natural History Arm of Aβ – (Age and education matched): N = 500
- Natural History Aβ – completers: N = 350
Power Calculations for A4 (Why we need better biomarkers and cognitive measures in the future)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Outcome</th>
<th>Δ (p-value)</th>
<th>% of Δ study is powered to detect with N=1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBL: N=114 Aβ- vs N=50 Aβ+, 1.5 yr follow-up</td>
<td>Composite</td>
<td>-2.01 (0.011)</td>
<td>22%</td>
</tr>
<tr>
<td>ADNI: N=60 Aβ- vs N=37 Aβ+, 2 yr follow-up</td>
<td>Composite</td>
<td>-1.45 (0.075)</td>
<td>34%</td>
</tr>
<tr>
<td>PI: N=310 ε4- vs N=103 ε4+, 3 yr follow-up</td>
<td>Composite</td>
<td>-1.60 (&lt;0.001)</td>
<td>35%</td>
</tr>
<tr>
<td>PI: N=388 CDR-SB stable vs N=19 CDR-SB progressors 3 yr follow-up</td>
<td>Composite</td>
<td>-4.19 (&lt;0.001)</td>
<td>11%</td>
</tr>
<tr>
<td>Wash U ADRC: N=82 PiB- vs N=32 PiB+, 1 to 5.7 yr follow-up</td>
<td>Composite</td>
<td>-0.56 (0.003)</td>
<td>12%</td>
</tr>
</tbody>
</table>
Summary

• Standardization is critically needed for neuroimaging particularly as we move towards earlier intervention trials

• Likely that we need a combination of demographic variables, neuroimaging, fluid biomarkers, and sensitive cognitive measures to best predict and track outcome

• We need standardization of current biomarkers so we can learn what we don’t yet know about AD…
NIA-AA Preclinical Work Group

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Maria Carrillo and Bill Thies  
Alzheimer’s Association

Mollie Wagster ,Marcelle Morrison-Bogorad, Tony Phelps  
National Institute on Aging
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<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
<tr>
<td>Keith Johnson, M.D.</td>
<td></td>
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<tr>
<td>J. Alex Becker, Ph.D.</td>
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<tr>
<td>Gad Marshall, M.D.</td>
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<td>Patrizia Vannini, Ph.D.</td>
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<td>Chris Gidiscin</td>
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<td>Randy Buckner, Ph.D.</td>
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<td>Dorene Rentz, Psy.D.</td>
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<td>Rebecca England, Ph.D.</td>
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**Support:** NIA, Alzheimer’s Association, AFAR, AHAF