25th Annual Southern California Alzheimer’s Disease Research Conference

New Guidelines and Importance of Brain Donation

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National Alzheimer’s Project Act (NAPA)

• Signed into law by President Obama
  – January 2011

• National Plan to Address Alzheimer’s Disease
  – “Preventing and effectively treating Alzheimer’s disease, including Alzheimer’s disease–related dementias, by 2025”
Scientific and Medical Input to NAPA

• *Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention*

• *Alzheimer’s Disease–Related Dementias: Research Challenges and Opportunities*
  – *Neurology, 2014*
Cognitive Impairment and Dementia

• Syndrome

• In older adults ...
  – An idiosyncratic convergent trait
    • AD, VBI, LBD, HS
  – Caused by chronic diseases
    • Dementia
    • Prodrome
    • Latency

• In middle-aged adults
  – Less co-morbidity
  – AD, FTD, LBD
Molecular Complexity

- 22 IGAP loci

GWAS: Cases & Controls
- VBI – none
- CAA - APOE $10^{-23}$
- LBD - APOE $10^{-12}$
- HS - KCNMB2 $10^{-8}$

Future
- Molecular phenotype
  - Brain
  - CSF
AD Research Summit 2012 (NIA)

• **AD dementia**
  – G. McKhann
  – Alzheimer's & Dementia 2011;7:263-269

• **Mild Cognitive Impairment due to AD**
  – M. Albert
  – Alzheimer's & Dementia 2011;7:270-279

• **Toward defining preclinical stages of AD**
  – R. Sperling
  – Alzheimer's & Dementia 2011;7:280-292

• **Guidelines for neuropath assessment of AD**
  – B. Hyman and T. Montine
  – Alzheimer's & Dementia 2012;8:1-13. 165 citations
AD-Related Dementias 2013 (NINDS & NIA)

• Fronto-temporal dementia
• Lewy Body Disease
• Vascular Brain Injury
• Multi-etiologic dementia
• Health Disparities
  – T. Montine
  – Neurology, August 2014
Parkinson’s Disease 2014 (NINDS)

• Motor and non-Motor symptoms (including dementia)
  – T. Montine
  – *Annals of Neurology, September 2014*
2012 Guidelines for neuropath assessment

- Thomas G. Beach
- Eileen H. Bigio
- Nigel J. Cairns
- Dennis W. Dickson
- Charles Duyckaerts
- Matthew P. Frosch
- Bradley T. Hyman
- Eliezer Masliah
- Suzanne S. Mirra
- Thomas J. Montine
- Peter T. Nelson
- Creighton H. Phelps
- Julie A. Schneider
- Dietmar Rudolf Thal
- John Q. Trojanowski
- Harry V. Vinters
## Major Changes to NP Assessment

<table>
<thead>
<tr>
<th>Issue</th>
<th>1997</th>
<th>2012</th>
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<tr>
<td>Dx of dementia required for NP AD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NP assessment</td>
<td>Braak stage and CERAD score</td>
<td>These plus Thal phase</td>
</tr>
<tr>
<td>Common co-morbid diseases</td>
<td>Little guidance</td>
<td>Explicit</td>
</tr>
<tr>
<td>Minimum regions</td>
<td>Silent</td>
<td>Explicit</td>
</tr>
<tr>
<td>Reporting and CPC</td>
<td>Silent</td>
<td>Guidelines</td>
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# AD Neuropathologic Change

<table>
<thead>
<tr>
<th>&quot;A&quot; Thal Phase for Aβ plaques [57]</th>
<th>&quot;B&quot; Braak and Braak NFT Stage [14,15]</th>
<th>&quot;C&quot; CERAD neuritic plaque score [41]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 or 2</td>
<td>1 or II</td>
<td>Sparse</td>
</tr>
<tr>
<td>3</td>
<td>III or IV</td>
<td>Moderate</td>
</tr>
<tr>
<td>4 or 5</td>
<td>V or VI</td>
<td>Frequent</td>
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<thead>
<tr>
<th>AD Neuropathologic Change</th>
<th>B&lt;sup&gt;1&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>A&lt;sup&gt;2&lt;/sup&gt; C&lt;sup&gt;3&lt;/sup&gt; 0 or 1</td>
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<tr>
<td>0</td>
<td>Not&lt;sup&gt;4&lt;/sup&gt;</td>
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<tr>
<td>1</td>
<td>Low</td>
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<tr>
<td>2 or 3&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>Any C</td>
</tr>
<tr>
<td>3</td>
<td>0 or 1</td>
</tr>
<tr>
<td>2 or 3</td>
<td>Low&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Braak and Braak NFT stages
<sup>2</sup> Thal phase for Aβ plaques
<sup>3</sup> CERAD neuritic plaque score
<sup>4</sup> Not present
<sup>5</sup> Present
<sup>6</sup> Mild
<sup>7</sup> Moderate
B (Braak) Score in primary visual cortex

PHF-1 antibody was generously provided by Dr. Peter Davies
## Lewy Body Disease

| Type                        | Description                                                                 |
|-----------------------------|=============================================================================|
| None                        | No LBs or related changes in IHC for α-synuclein                           |
| Brainstem-predominant       | LBs in medulla, pons, or midbrain                                          |
| Limbic (Transitional)       | LBs in cingulate or entorhinal cortices, usually with brainstem involvement|
| Neocortical (Diffuse)       | LBs in frontal, temporal, or parietal cortices usually with involvement of brainstem and limbic sites, which may include amygdala |
| Amygdala-predominant        | LBs in amygdala with paucity of LBs in the above regions                   |
Lewy Body Disease

Anti-alpha-synuclein antibody KM51 (Novocastra, Newcastle, United Kingdom)
Cerebrovascular Disease and Vascular Brain Injury

• **CVD**
  - Report using standardized approach

• **VBI**
  - Record size and location of gross infarcts
  - Enumerate microinfarcts in standard screening sections
    - > 2 sufficient to explain cognitive impairment
Cerebrovascular Disease and Vascular Brain Injury

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Major Challenges Remain

- Almost all of our knowledge about dementia in the US comes from people of European decent
- Incomplete knowledge about disease mechanisms
  - Knowledge about potential interactions is very limited
  - AD VBI meeting held by NINDS and AA in 2014
- Representative experimental models are needed to fuel therapeutic discovery
Next Steps ...

- Fall 2014
  - Updated milestones
- 9-11 February 2015
  - AD Research Summit II
- Winter 2016
  - ADRD II
- 2025
  - “Preventing and effectively treating Alzheimer’s disease, including Alzheimer’s disease–related dementias”, NAPA
Thank you