NACC for Data Mining:

Clinical-pathological correlations in dementia with Lewy bodies (DLB)
UK ADC:
Long-term longitudinal autopsy series with emphases on data quality, continuity, nondemented controls, and Alzheimer’s Disease.

Dr. William Markesbery

UK ADC Database
• Independent/outside validation
• Remove some “local biases”
• More varied demographics
• More statistical power
Clinical-pathological correlations are extremely relevant as we enter an age of tailored neurotherapeutics.

Goals:
Help Researchers
Help Clinicians
Clinical-pathological correlations in DLB
Clinical-pathological correlations in DLB

Challenges:

What is the gold standard? (clinical? pathological? biomarkers?)

What to do with AD + DLB cases?

What about Parkinson’s disease dementia?
Clinical-pathological correlations in DLB

Challenges:

What is the gold standard?

NEUROPATHOLOGY IS THE GOLD STANDARD

What to do with AD + DLB cases?

TREAT AD, DLB, AND AD+DLB AS DIFFERENT CATEGORIES

What about Parkinson’s disease dementia?

FOR THE TIME BEING, EXCLUDE/IGNORE IT
NACC data:

For DLB clinical-pathological correlations, N~3000
Questions:

1. How do clinical (antemortem) diagnoses of AD, DLB, and AD+DLB match up with pathological results?

2. How is DLB pathology associated with global cognitive decline or severity?

3. Are there risk factors for DLB pathology among NACC Registry cases?
Question #1:

How do antemortem clinical diagnoses of AD, DLB, and AD+DLB match up with pathological results?
Dementia with Lewy bodies

Ian McKeith, Jacobo Mintzer, Dag Aarsland, David Burn, Helen Chiu, Jiska Cohen-Mansfield, Dennis Dickson, Bruno Dubois, John E Duda, Howard Feldman, Serge Gauthier, Glenda Halliday, Brian Lawlor, Carol Lippa, Oscar L Lopez, João Carlos Machado, John O'Brien, Jeremy Playfer, and Wayne Reid on behalf of the International Psychogeriatric Association Expert Meeting on DLB

## Validity and reliability of consensus criteria for DLB

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of cases</th>
<th>Diagnostic criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>( \kappa )</th>
<th>Comments and recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mega et al.</td>
<td>4</td>
<td>24 AD</td>
<td>Probable</td>
<td>75</td>
<td>79</td>
<td>100</td>
<td>98</td>
<td>F=0.25, H=0.59, P=0.46</td>
</tr>
<tr>
<td>Litvan et al.</td>
<td>14</td>
<td>105 PD, PSP, MSA, CBD, AD</td>
<td>None applied; retrospective clinical diagnosis</td>
<td>18</td>
<td>99</td>
<td>75</td>
<td>89</td>
<td>0-19-0-38</td>
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<td>Holmes et al.</td>
<td>9</td>
<td>80 AD, VaD</td>
<td>Probable</td>
<td>22</td>
<td>100</td>
<td>100</td>
<td>91</td>
<td>NA</td>
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<tr>
<td>Luis et al.</td>
<td>35</td>
<td>56 AD</td>
<td>Probable</td>
<td>57</td>
<td>90</td>
<td>91</td>
<td>56</td>
<td>F=0.30, H=0.91, P=0.61</td>
</tr>
<tr>
<td>Verghese et al.</td>
<td>18</td>
<td>94 AD</td>
<td>Probable</td>
<td>61</td>
<td>84</td>
<td>48</td>
<td>90</td>
<td>F=0.57, H=0.67</td>
</tr>
<tr>
<td>Lopez et al.</td>
<td>8</td>
<td>40</td>
<td>Probable</td>
<td>89</td>
<td>28</td>
<td>23</td>
<td>91</td>
<td>P=0.90</td>
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<td>Höh et al.</td>
<td>5</td>
<td>10 AD</td>
<td>Probable</td>
<td>100</td>
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<td>McKeith et al.</td>
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<td>50 AD, VaD</td>
<td>Probable</td>
<td>83</td>
<td>95</td>
<td>96</td>
<td>80</td>
<td>NA</td>
</tr>
<tr>
<td>Lopez et al.</td>
<td>13</td>
<td>26 AD</td>
<td>Probable</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>43</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Sensitivity** 58%  **Specificity** 84%  **PPV** 77%

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**Dementia with Lewy bodies**

Ian McKeith, Jacobo Mintzer, Dag Aarsland, David Burn, Helen Chiu, Jiska Cohen-Mansfield, Dennis Dickson, Bruno Dubois, John E Duda, Howard Feldman, Serge Gauthier, Glenda Halliday, Brian Lawlor, Carol Lippa, Oscar L Lopez, João Carlos Machado, John O'Brien, Jeremy Playfer, and Wayne Reid on behalf of the International Psychogeriatric Association Expert Meeting on DLB

Clinical-pathological correlation in DLB: NO “perfect” way to perform this study!
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<tr>
<td>Mega et al²⁰</td>
<td>4/24 AD</td>
<td>Probable</td>
<td>75</td>
<td>79</td>
<td>100</td>
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<td></td>
<td>Retrospective; suggests 4/6 of H, C, R, B, N, F</td>
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<td>Litvan et al²⁰</td>
<td>105 PD, PSP, MSA, CBD, AD</td>
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<td>18</td>
<td>99</td>
<td>75</td>
<td>89</td>
<td>0-19-0-38</td>
<td>Retrospective; no formal criteria for DBL used; comparison mainly with movement disorder</td>
</tr>
<tr>
<td>Holmes et al²¹</td>
<td>9/80 AD, VaD</td>
<td>Probable</td>
<td>22</td>
<td>100</td>
<td>100</td>
<td>91</td>
<td>NA</td>
<td>Retrospective; no specific recommendations; cases with mixed pathology were hardest to diagnose</td>
</tr>
<tr>
<td>Luis et al²²</td>
<td>35/56 AD</td>
<td>Probable</td>
<td>57</td>
<td>90</td>
<td>91</td>
<td>56</td>
<td></td>
<td>Retrospective; suggests H, P, F, and rapid progression</td>
</tr>
<tr>
<td>Verghese et al²³</td>
<td>94 AD</td>
<td>Probable</td>
<td>61</td>
<td>84</td>
<td>48</td>
<td>90</td>
<td></td>
<td>Retrospective; suggests 3/6 of P, F, H, N, D, and F</td>
</tr>
<tr>
<td>Lopez et al²³</td>
<td>8/40</td>
<td>Possible</td>
<td>89</td>
<td>28</td>
<td>23</td>
<td>91</td>
<td>P=0.90</td>
<td>Retrospective; probable DLB not diagnosed once by a team of four raters; no specific recommendations</td>
</tr>
<tr>
<td>Hofh et al²⁴</td>
<td>5/10 AD</td>
<td>Probable</td>
<td>100</td>
<td>8</td>
<td>83</td>
<td>100</td>
<td>NA</td>
<td>Consensus criteria applied retrospectively; clinician diagnosis without consensus criteria had PPV of 50</td>
</tr>
<tr>
<td>McKeith et al²⁵</td>
<td>50 AD, VaD</td>
<td>Probable</td>
<td>100</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Prospective; false-negative cases associated with comorbid pathology</td>
</tr>
<tr>
<td>Lopez et al²⁶</td>
<td>13/26 AD</td>
<td>Probable</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>43</td>
<td></td>
<td>Prospective; met NINCDS–ADRDA criteria for AD, only four met DBL criteria</td>
</tr>
</tbody>
</table>

PPV=positive predictive value; NPV=negative predictive value; AD=Alzheimer's disease; F=falls; H=hallucinations; C=cogwheeling; P=parkinsonism; R=rigidity; B=bradykinesia; N=neuropsychiatric symptoms; F=fluctuation; NA=not available; PD=Parkinson's disease; PSP=progressive supranuclear palsy; MSA=multiple system atrophy; CBD=corticobasal degeneration; VaD=vascular dementia. Movement Disorders © copyright 2003 Movement Disorders Society.
Tests of Agreement Between Clinical Diagnoses and Pathological Diagnoses
(NACC Registry MDS data, yr 2000- )

ADCs -- state-of-the-art diagnostics

(N = 162 cases of Pure DLB)

(J. NEUROLOGY, In Press)
Tests of Agreement Between Clinical Diagnoses and Pathological Diagnoses
(NACC Registry MDS data, yr 2000-)

<table>
<thead>
<tr>
<th>Event</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>kappa (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD versus others (control or AD+DLB or DLB)</td>
<td>85.0</td>
<td>51.1</td>
<td>64</td>
<td>0.36 (0.33, 0.39)</td>
</tr>
<tr>
<td>AD+DLB versus others (pure AD, pure DLB, control)</td>
<td>12.1</td>
<td>96.0</td>
<td>22</td>
<td>0.10 (0.05, 0.15)</td>
</tr>
<tr>
<td>DLB versus others (control, AD+DLB, pure AD)</td>
<td>32.1</td>
<td>98.3</td>
<td>53</td>
<td>0.37 (0.29, 0.45)</td>
</tr>
</tbody>
</table>

(N=162 cases of Pure DLB)

(J. NEUROLOGY, In Press)
POINT 1:

We may have a ways to go before clinical cues and biomarkers predict DLB pathology accurately
Question #2:

How does DLB pathology, by itself or in combination with other brain disease(s), correlate with cognitive impairment severity?
POINT 2:

“Pure” DLB pathology correlates with a relatively modest loss in final MMSE score whether or not one corrects for obvious confounders.

Neocortical DLB pathology by itself is NOT generally a pathological substrate associated with “end-stage” global dementia although it may be otherwise a debilitating disease.
These results can provide practical guidance to clinicians and help to decrease antemortem diagnostic mistakes:

• “Undercall” (false-negative) clinical diagnosis of DLB

• “Overcall” (false-positive) clinical diagnosis of DLB
"Overcalls" and "Undercalls" of neocortical LBs by Final MMSE Score

Global cognitive impairment severity

(J. NEUROLOGY, In Press)
We may have a ways to go before clinical cues and biomarkers predict DLB pathology accurately

However:

• Clinical ‘false positives’ are relatively frequently seen in very impaired patients

• Clinical ‘false negatives’ are relatively frequently seen in the context of moderate global cognitive impairment
Question #3: Are there risk factors for DLB pathology?
### Pathology

**Persons dying with “Pure” DLB pathology are much more likely to be male than female**

*Arch. Neurol., Submitted*

<table>
<thead>
<tr>
<th></th>
<th>AD only</th>
<th>DLB Only</th>
<th>AD+DLB</th>
<th>Total</th>
<th>Neither AD nor DLB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NACC</strong> Male</td>
<td>734</td>
<td>109</td>
<td>240</td>
<td>451</td>
<td>1534</td>
</tr>
<tr>
<td><strong>NACC</strong> Female</td>
<td>883</td>
<td>42</td>
<td>230</td>
<td>483</td>
<td>1638</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1617</td>
<td>151</td>
<td>470</td>
<td>934</td>
<td>3172</td>
</tr>
<tr>
<td>Relative risk (M:F)</td>
<td>0.89</td>
<td><strong>2.77</strong></td>
<td>1.11</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.83-0.95</td>
<td>1.95-3.93</td>
<td>0.94-1.32</td>
<td>0.90-1.11</td>
<td></td>
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<th>Total</th>
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</thead>
<tbody>
<tr>
<td><strong>UK ADC Male</strong></td>
<td>77</td>
<td>22</td>
<td>35</td>
<td>141</td>
<td>275</td>
</tr>
<tr>
<td><strong>UK ADC Female</strong></td>
<td>147</td>
<td>11</td>
<td>61</td>
<td>164</td>
<td>383</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>224</td>
<td>33</td>
<td>96</td>
<td>305</td>
<td>658</td>
</tr>
<tr>
<td>Relative risk (M:F)</td>
<td>0.73</td>
<td><strong>2.79</strong></td>
<td>0.80</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.58-0.92</td>
<td>1.37-5.65</td>
<td>0.52-1.17</td>
<td>1.02-1.40</td>
<td></td>
</tr>
</tbody>
</table>
Higher risk for males dying with DLB pathology holds true across different age-at-death cohorts.

Highest M:F risk ratio is seen in persons dying with “diffuse” (neocortical) DLB path subtype.
Clinical diagnostic mistakes in DLB: Males versus Females (NACC Registry, N=2862)

- Rate of Undercalls ("False negatives")
  - Males
  - Females

- Rate of Overcalls ("False positives")
  - Males
  - Females
**POINT 3:**

The likelihood of dying with neocortical DLB pathology is much higher in males than females.

Females tend to be “overcalled” for DLB.

Males tend to be “undercalled” for DLB.

Relationship between female gender and risk of dying with AD pathology is more dependent on age of death.
NACC data: personal experience–

Fantastic for retrospective case:control clinical-pathological correlation

--VERY rich clinical and pathological repertoire

--Can help harmonize clinical and pathological parameters

--Can help evaluate clinical and environmental risk factors

(How many other such datasets in the world?)

Administration has been professional, helpful, and efficient
Thanks
Dr. William Markesbery

NIH/NIA    Pilot Grant
NIH/NINDS  K08 Grant
NIH/NINDS  R01 Grant
Alz Association  NIRG Grant

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Erin Abner, MPH
Dick Kryscio, PhD
Greg Jicha
MD, PhD
Fred Schmitt, PhD
Areas where NACC Registry data is currently of limited utility:

- Longitudinal ("disease course") questions
- Sensitive cognitive testing questions
- True population epidemiology questions
- Quantitative neuropathology
- Areas such as cerebrovascular disease where the basic rubrics for clinical-pathological correlation are lacking
NACC data: Started with ~11,000 cases

Initial exclusions: Yr<1998
(~4000 excluded)

FTD, CBD, PSP, Pick’s, prion disease
triplet repeat disorders
(~3,000 excluded)

Additional exclusions due to missing
clinical and/or pathological data: ~1000