Christopher C. Rowe MD
Disclosures

Grants for Investigator Initiated Studies
- Bayer Pharma AG
- Avid Radiopharmaceuticals
- GE Healthcare
- Astra Zeneca

Advisory Board Member
- Bayer Pharma AG
- GE Healthcare
- Astra Zeneca
Amyloid PET in Clinical Practice

- Potential applications.
- Is a binary yes or no result enough?
- Should interpretation account for age?
- Are amyloid tracers comparable for clinical use?
Clinical applications of Aβ imaging

• Early onset dementia (<65 yrs of age) – AD clinical features and MRI often atypical and FTD relatively common.

• MCI – 60% AD, 10% other dementias, 30% not neurodegenerative.

• Dementia with atypical or focal features – primary progressive aphasia (50% AD), cortico-basal syndrome (40% AD), behavioural, visual, apraxia.

• Complex Assessment – severe depression, stroke, language barrier, etc.
Is a binary yes or no result enough?
PiB neocortical SUVR in AIBL+

<table>
<thead>
<tr>
<th>Group</th>
<th>SUVR Mean ± SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>1.40 ± 0.4</td>
<td>195</td>
</tr>
<tr>
<td>MCI</td>
<td>1.91 ± 0.6</td>
<td>92</td>
</tr>
<tr>
<td>AD</td>
<td>2.30 ± 0.4</td>
<td>79</td>
</tr>
</tbody>
</table>

(n = 366)
Aβ Imaging

$^{11}$C-PiB

<table>
<thead>
<tr>
<th>Neocortical SUVR</th>
<th>HC (n = 194)</th>
<th>MCI (n = 92)</th>
<th>AD (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td></td>
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<tr>
<td>1.50</td>
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<tr>
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<tr>
<td>0.50</td>
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<td></td>
</tr>
<tr>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Discrimination of AD from HC

(79 AD vs 194 HC)

<table>
<thead>
<tr>
<th>PiB threshold</th>
<th>1.4</th>
<th>1.5</th>
<th>1.7</th>
<th>1.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>% HC+</td>
<td>33%</td>
<td>31%</td>
<td>25%</td>
<td>14%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.99</td>
<td>0.99</td>
<td>0.95</td>
<td>0.85</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.67</td>
<td>0.69</td>
<td>0.75</td>
<td>0.80</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.77</td>
<td>0.78</td>
<td>0.79</td>
<td>0.78</td>
</tr>
<tr>
<td>PPV</td>
<td>0.55</td>
<td>0.57</td>
<td>0.61</td>
<td>0.62</td>
</tr>
<tr>
<td>NPV</td>
<td>0.99</td>
<td>0.99</td>
<td>0.97</td>
<td>0.93</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>158</td>
<td>174</td>
<td>56</td>
<td>33</td>
</tr>
</tbody>
</table>

RASAD 2012
PiB SUVR cut-point 1.5
3 year clinical progression

<table>
<thead>
<tr>
<th>Group</th>
<th>Negative Aβ (n)</th>
<th>Positive Aβ (n)</th>
<th>Progression to MCI/AD</th>
<th>Progression to AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>134</td>
<td>60</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>MCI</td>
<td>28</td>
<td>64</td>
<td>19%*</td>
<td>66%*</td>
</tr>
</tbody>
</table>

Risk or Hazard Ratio 3.2
*(p= 0.016)*
Corrected for age, gender, education

Risk Ratio 11.1
*(p< 0.0001)*
## Predictive accuracy

HC to MCI/AD over 3 years

<table>
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<tr>
<th>PiB threshold</th>
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<tbody>
<tr>
<td>% HC+</td>
<td>33%</td>
<td>31%</td>
<td>25%</td>
<td>14%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.58</td>
<td>0.57</td>
<td>0.53</td>
<td>0.37</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.70</td>
<td>0.72</td>
<td>0.78</td>
<td>0.88</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.56</td>
<td>0.56</td>
<td>0.57</td>
<td>0.59</td>
</tr>
<tr>
<td>PPV</td>
<td>0.18</td>
<td>0.18</td>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>NPV</td>
<td>0.94</td>
<td>0.94</td>
<td>0.94</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Risk Ratio**

- 2.9
- 3.2
- 3.4
- 3.6

**Odds Ratio**

- 3.2
- 3.6
- 3.8
- 4.3
<table>
<thead>
<tr>
<th>PiB threshold</th>
<th>1.4</th>
<th>1.5</th>
<th>1.7</th>
<th>1.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>% MCI+</td>
<td>71%</td>
<td>69%</td>
<td>63%</td>
<td>55%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.96</td>
<td>0.95</td>
<td>0.89</td>
<td>0.82</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.52</td>
<td>0.54</td>
<td>0.60</td>
<td>0.69</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.79</td>
<td>0.80</td>
<td>0.76</td>
<td>0.76</td>
</tr>
<tr>
<td>PPV</td>
<td>0.65</td>
<td>0.66</td>
<td>0.67</td>
<td>0.71</td>
</tr>
<tr>
<td>NPV</td>
<td>0.93</td>
<td>0.93</td>
<td>0.85</td>
<td>0.81</td>
</tr>
<tr>
<td>Risk Ratio</td>
<td>10.7</td>
<td>11.4</td>
<td>5.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>23</td>
<td>25</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>
But what about negative vs low vs high results?

HC (n = 194)

MCI (n = 92)

AD (n = 79)
MCI progression to AD
3 class interpretation

• Low positive (n=11) vs negative scan (n=28)
  (SUVR 1.4-1.9 vs <1.4)
  PPV 36%  Odds Ratio 7.7

• High positive (n=53) vs negative scan (n=28)
  (SUVR > 1.9 vs <1.4)
  PPV 72%  Odds Ratio 33
Should interpretation account for age?
% PiB+ HC vs Age (by decade)

(PiB+ when SUVR >1.5)

Prevalence of plaques in HC

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

Prevalence of AD
(Tobias, 2008)
Aβ burden
effect on clinical progression
(by decade of age)

<table>
<thead>
<tr>
<th>Decade</th>
<th>HC+ (n=60)</th>
<th>MCI+ (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>56-69</td>
<td>14% to MCI/AD (n=14)</td>
<td>79% to AD (n=14)</td>
</tr>
<tr>
<td>70-69</td>
<td>15% to MCI/AD (n=26)</td>
<td>57% to AD (n=33)</td>
</tr>
<tr>
<td>80-89</td>
<td>25% to MCI/AD (n=20)</td>
<td>71% to AD (n=17)</td>
</tr>
</tbody>
</table>
Are amyloid tracers comparable for clinical use?
Aβ Imaging with PET

- $^{18}$F-Florbetapir (Avid $AV-45$)
- $^{18}$F-Florbetaben (Bayer $AV-1$)
- $^{11}$C-PiB
- $^{18}$F-Flutemetamol (GE $F-PiB$)
- $^{18}$F-AZD4694 (Astra Zeneca)
$^{18}$F-Florbetapir and $^{11}$C-PIB PET Scans are Strongly Correlated in ADNI Dataset

**Negative Subject**

PIB

Florbetapir

**Positive Subject**

PIB

Florbetapir

**PiB vs. Florbetapir**

$r = 0.97$
Florbetapir vs $^{11}$C-PiB

Neocortical SUVR $^{18}$F-tracers vs Neocortical SUVR $^{11}$C-PiB

FLORBETAPIR ($r=0.97$, slope 0.60)
$^{18}$F-Florbetaben vs $^{11}$C-PiB head to head comparison in 20 subjects

Villemagne. EJNMMI 2012 In Press
$^{18}$F-amyloid ligands vs $^{11}$C-PiB

Neocortical SUVR $^{18}$F-tracers vs Neocortical SUVR $^{11}$C-PiB

- FLORBETABEN ($r=0.97$, slope 0.71)
- FLORBETAPIR ($r=0.97$, slope 0.60)
ACRIN-PA 4004 Study: Comparison of [F-18] Flutemetamol and [C-11] PiB in Normal Control and Alzheimer’s Subjects

Mountz JM¹, Zhang Z², Laymon C¹, Price J¹, Boudhar S³, Newberg AB⁴, Mathis, CA¹
4. Thomas Jefferson U, Philadelphia, PA
For [F-18] flutemetamol the accuracy of the visual score to correctly classify NL from AD produced an AUC of 0.92 (95% CI 0.81 to 1.00).
Comparison of $^{18}$F-amyloid ligands vs $^{11}$C-PiB

FLUTEMETAMOL ($r=0.92$, slope 0.80)
FLORBETABEN ($r=0.97$, slope 0.71)
FLORBETAPIR ($r=0.97$, slope 0.60)

Neocortical SUVR $^{18}$F-tracers vs Neocortical SUVR $^{11}$C-PiB

RASAD 2012
Amyloid PET in Clinical Practice

• Is a binary yes or no result enough?
  • YES but 3 categories is better.

• Should interpretation account for age?
  • NO.

• Are amyloid tracers comparable for clinical use?
  • YES for binary read.
Recommendation

• Binary read for clinical purposes is appropriate but need to examine F-18 tracer data for 2 vs 3 categories of scan interpretation to see if this improves prognostic value.
Florbetapir

$^{11}$C-PiB

aibl RASAD 2012