Multiparametric QI Biomarker Measures: Examples from Alzheimer’s Disease

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Pathology in Alzheimer’s Disease

Amyloid plaque

Neurofibrillary tangles (of abnormal tau)

Images: National Institutes of Health
Adapted from: Jack C et al:

Subject inclusion in trials, or clinical diagnosis

- Does this patient have Alzheimer’s pathology
- Are they at risk for AD pathology spread
- Identify patient confounds

Prognosis

- Match progression rates between study arms
- Clinical planning and treatment

Treatment effect detection

- Measure effects on pathology (removal, slowing)
- Measure effects on neurodegeneration
- Detect symptomatic effects
### QI Biomarker Applications in Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Modality</th>
<th>Type</th>
<th>Metric</th>
<th>Application</th>
<th>Status</th>
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<tr>
<td>MRI</td>
<td>Volumetric</td>
<td>Hippocampal volume</td>
<td>Stratification</td>
<td>Large trials</td>
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<td>Ventricular vol, shift</td>
<td>Treatment effect - met</td>
<td>Observational Emerging</td>
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<td>Cortical thickness</td>
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<td>Multivariate patterns</td>
<td>Inclusion, prognosis</td>
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<td>FLAIR</td>
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<td>White lesion volume</td>
<td>Exclusion, AEs</td>
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<td>DTI</td>
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<td>WM directionality</td>
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<td>Blood flow</td>
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<td>fMRI</td>
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<td>Function</td>
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<td>PET</td>
<td>Amyloid</td>
<td>SUVR</td>
<td>Subject inclusion</td>
<td>Large trials and clinical (pending reimbursement)</td>
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<td>Multivariate patterns</td>
<td>Treatment effect: remove or slow</td>
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<td>FDG</td>
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<td>SUVR</td>
<td>Effect detection</td>
<td>Smaller trials</td>
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<td>Multivariate patterns</td>
<td>Inclusion, stratification, treatment effect</td>
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<td>Tau</td>
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<td>SUVR</td>
<td>Inclusion, stratification, treatment effect</td>
<td>Research Small-large trials</td>
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</table>
Stratification for clinical progression rate using baseline FDG

Longitudinal MMSE scores in late MCI patients

Amyloid negative

Amyloid positive

MMSE of LMCI with AD Progression Score < -1.3

MMSE of LMCI with AD Progression Score > 1.8
Considerations

Methods Matter

- 1271 subjects (Landau, 2009) vs. 110 MCI subjects (Chen, 2010) per arm required to detect 33% slowing in MCI using FDG
- 8,076 (cerebellum ref region) vs. 2,718 (pons ref) vs. 325 subjects (white ref) required to detect 25% slowing in rate of amyloid accumulation over 12 months (Chen, 2015)

Logistical

- Subject burden
- Clinical trial cost
- Diagnostic reimbursement
- Vendor differences and internal standards

Longitudinal change in PIB SUVR in MCI (ADNI)

Schmidt et al, 2012