Biomarkers in Neurological Disease: Current and Future

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Objectives

• Define terminology of biomarkers
• Discuss the role of prognostic and predictive biomarkers in Parkinson’s Disease
• Review the current regulatory landscape and the FDA’s perspective on biomarkers and the future of personalized medicine

Some definitions

• BIOMARKER:
  – “a laboratory measurement that reflects the activity of a disease process”

• SURROGATE MARKER:
  – “a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy”

  Katz R. NeuroRx 2004 April; 1(2): 189–195

Parkinson Disease

• Clinical triad of asymmetric tremor, rigidity, bradykinesia, plus gait, balance disturbance, postural instability
• Loss of dopaminergic neurons in substantia nigra; Lewy body pathologic hallmark

When and where does PD begin?

PPMI Study Details: Synopsis

Study population
- 400 de novo PD subjects (‘possible PD’ with positive DaT and unmedicated)
- 200 age- and gender-matched healthy controls
- Subjects will be followed for a minimum of 3 years and a maximum of 5 years

Assessments/Clinical data collection
- Motor assessments
- Neuropsychiatric/cognitive testing
- Olfaction
- DaTSCAN imaging, MRI

Biologic collection
- DNA collected at screening
- Serum and plasma collected at each visit; urine collected annually
- CSF collected at time and then annually
- Samples aliquotted and stored in central biorepository

Initial Verification studies
- Lead biologic candidates to be tested:
  - Alpha-synuclein (CSF)
  - DJ-1 (CSF and blood)
  - Urate (blood)
  - Abeta 1-42 (CSF)
  - Total tau, Phospho-tau (p-181) (CSF)

PD treatment
- Can participate in other clinical trials (including interventional trials) after 12 months
DaTSCAN

- Ioflupane ($^{123}$I) which binds to presynaptic dopamine transporter
- Recently FDA approved for use with Single Photon Emission Computerized Tomography (SPECT)
- Detects striatal dopamine transporter density in Parkinsonian syndromes

PARS Study Objectives

- To estimate the frequency of DAT deficit in olfactory asymptomatic relatives of PD patients and healthy non-relatives with olfactory loss.
- To compare imaging, biological, genetics biomarkers of a defined ‘at risk’ cohort.
- To determine if olfaction can enrich a population at risk for DAT deficit.
- To determine if decreased DAT density at baseline predicts the onset of clinical PD at 2-year follow-up.

Bowel Movement Frequency in Hyposmics and Normosmics

<table>
<thead>
<tr>
<th>Bowel Movement Frequency</th>
<th>Normosmics N = 4330</th>
<th>Hyposmics N = 669</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 per day</td>
<td>696 (16%)</td>
<td>136 (21%)</td>
<td>0.0085</td>
</tr>
<tr>
<td>1 per day</td>
<td>2222 (52%)</td>
<td>335 (51%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 per day</td>
<td>1372 (32%)</td>
<td>189 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

REM Sleep Disorder Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Normosmics N = 3148</th>
<th>Hyposmics N = 465</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Act Out Dreams</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 times per month</td>
<td>185 (6%)</td>
<td>40 (9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1 per week</td>
<td>783 (3%)</td>
<td>17 (4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 per week</td>
<td>883 (2%)</td>
<td>28 (6%)</td>
<td></td>
</tr>
<tr>
<td>Limb/Body Movements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 times per month</td>
<td>325 (12%)</td>
<td>63 (12%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>1 per week</td>
<td>105 (4%)</td>
<td>17 (4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 per week</td>
<td>201 (7%)</td>
<td>51 (12%)</td>
<td></td>
</tr>
<tr>
<td>Violent Movements</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-3 times per month</td>
<td>56 (2%)</td>
<td>25 (6%)</td>
<td></td>
</tr>
<tr>
<td>1 per week</td>
<td>30 (1%)</td>
<td>6 (1%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 per week</td>
<td>33 (1%)</td>
<td>13 (3%)</td>
<td></td>
</tr>
<tr>
<td>Diagnosed by Doctor</td>
<td>63 (2%)</td>
<td>18 (4%)</td>
<td>0.0114</td>
</tr>
</tbody>
</table>

DAT Scan Status for Hyposmics and Normosmics

<table>
<thead>
<tr>
<th>DAT deficit</th>
<th>Normosmics N = 100</th>
<th>Hyposmics N = 203</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= 80%</td>
<td>92 (92%)</td>
<td>146 (72%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>65 – 80%</td>
<td>7 (7%)</td>
<td>34 (17%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 65%</td>
<td>1 (1%)</td>
<td>23 (11%)</td>
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Drugs in development in Parkinson disease

- Almost all drugs under development are targeting motor control, including motor fluctuations and dyskinesia
- Limited compounds under study targeting neuroprotection or non-motor symptoms
- Cause-directed therapy (e.g., drugs targeting α-synuclein) likely a long way from clinic
Examples from other neurodegenerative diseases

- Huntington disease
- Alzheimer disease

Huntington disease

- Autosomal dominant inheritance
- Trinucleotide repeat disorder
- Adult onset in most cases
  - Movement disorder
  - Dementia
  - Psychiatric, behavioral features
- A “simple” genetic disorder
- A model for other trinucleotide repeat disorders, and for some other dominant disorders

“Trait” versus “State” markers in Huntington disease

- DNA test is ~ perfect “trait” marker
- Diagnosis of manifest disease currently based on motor phenotype
- Markers of “preclinical” disease a topic of active enquiry

Striatal volume as a measure of pre-clinical disease in HD

Can be objectively measured
- High inter-/intra-rater reliability
- Reflects pathogenic process
  - Striatal volume decreased in pre-symptomatic subjects
  - Striatal volume decreases as subject approaches onset
  - Longitudinal change can be detected over relatively short time
- Predicts clinical events
  - Rate of change significant 10-12 years prior to sx onset

Alzheimer disease

- Most common form of dementia
- Memory, language, visuospatial skills, reasoning, behavior
- Huge societal and family burden

- Diagnostic criteria recently updated after 25 years
- Established three stages to disease (preclinical, MCI, AD) and incorporated biomarkers into framework
  - http://www.alz.org/research/diagnostic_criteria/overview.asp

CSF markers of Alzheimer disease

- Ratio of total tau (T-tau), phosphorylated tau (P-tau), and β-amyloid 1-42 (Aβ42) can be used to predict conversion of MCI to AD

Imaging markers of Alzheimer disease

- Volumetric MRI – hippocampal atrophy
- FDG-PET
- Pittsburgh B compound
- 18F flutemetamol (flute)
- Florbetaben (BAY 94-9172)
- Florbetapir F 18 (18F-AV-45)
  – Clark et al. JAMA 2011; 305(3):275-83

Conclusions

- Pre-clinical detection of disease increasingly relevant to practice of medicine
- Ability to detect pre-clinical disease generally out of synch with development of therapeutic strategies
- Goals of clinical and research community may be out of synch with desires of patients
- Formulation of consensus recommendations for use of pre-clinical detection tools advised