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Early Detection of Parkinson’s Disease
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Science Webinar Series
Early Detection of Parkinson’s Disease
The Challenges and Potential of New Biomarkers

April 27, 2011

Brought to you by the Science/AAAS Business Office

Participating Experts:

Andrew Siderowf, M.D., MSCE
University of Pennsylvania School of Medicine
Philadelphia, PA

Michael G. Schlossmacher, M.D., FRCPC
University of Ottawa
Ottawa, Ontario

Norbert Schuff, Ph.D.
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San Francisco, CA

Kenneth Marek, M.D.
Institute for Neurodegenerative Disorders
New Haven, CT

Moderator: Todd Sherer, Ph.D., The Michael J. Fox Foundation\for Parkinson’s Research; New York, NY
Parkinson’s disease: overview and current treatments

- Progressive, neurodegenerative disorder marked predominantly by motor symptoms; non-motor symptoms are also present

- Characterized by selective loss of nigrostriatal dopaminergic neurons and presence of alpha-synuclein positive aggregates (Lewy Bodies)

- Current therapies, based on dopamine replacement, treat some motor symptoms, but lose effectiveness over time and are marked by side effects
Biomarkers are critical for developing disease modifying therapies

- Disease modifying therapeutics that target the underlying disease process remain a major unmet need.

- Current clinical trial design requires large sample size, long duration.

- Trials rely on subjective, clinical outcomes that are influenced by medications.

- PD biomarkers would accelerate PD therapeutic development:
  - Identify patients at earliest stages of disease.
  - Improve patient selection for clinical trials, example DATscan.
  - Assess efficacy of new therapies.
  - Monitor disease progression.
Today’s webinar

- Studying individuals at risk for developing PD – Andrew Siderowf

- Overview of promising biological markers of PD – Michael Schlossmacher

- Overview of new neuroimaging methods as PD biomarkers – Norbert Schuff

- Addressing the challenges in developing PD biomarkers – the PPMI study – Ken Marek
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for Parkinson’s Research; New York, NY
Prevention is the ultimate therapeutic goal in PD

PARS study objectives
• To determine the feasibility of screening for Parkinson’s disease using a combination
  1\textsuperscript{st}: olfactory testing
  2\textsuperscript{nd}: DAT imaging
• To assess clinical and biological features pre-motor PD (defined based on biomarker profile)
• To develop a pre-motor cohort that would be eligible for a preventive interventions
Screening for PD requires large numbers of potential subjects.

A large number of subjects were initially screened with simple, relatively inexpensive tests.
Identifying and targeting highest risk cases improves efficiency

Prodromal PD features cluster in hyposmic individuals, n = 4999

<table>
<thead>
<tr>
<th>feature</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>1.37</td>
<td>1.11, 1.68</td>
</tr>
<tr>
<td>Depression</td>
<td>1.93</td>
<td>1.55, 2.41</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.38</td>
<td>1.14, 1.67</td>
</tr>
<tr>
<td>Motor complaint</td>
<td>1.66</td>
<td>1.36, 2.02</td>
</tr>
<tr>
<td>REM sleep behavior</td>
<td>1.62</td>
<td>1.21, 2.15</td>
</tr>
</tbody>
</table>
Two-staged process is reasonably accurate and reduces costs

- Hyposmics have increased risk of abnormal DAT imaging
- Normosmics have very low risk of abnormal DAT imaging
- Two-staged process reduces # of imaging studies by 80-90%

<table>
<thead>
<tr>
<th>Age expected uptake in lowest putamen</th>
<th>Normosmics</th>
<th>Hyposmics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 100</td>
<td>N = 203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No DAT deficit ≥80%</td>
<td>92 (92%)</td>
<td>146 (72%)</td>
<td></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>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;80%</td>
<td>8 (8%)</td>
<td>57 (28%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
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for Parkinson’s Research; New York, NY
Example of patient enrollment in past PD trials without biomarkers

>1,600 patients screened with subjective rating scales

Selected phenotype: ‘Typical PD’ patients with AOO >50 yrs. Enrollment number for treatment arm of study, n = 800

Subjects without evidence of dopaminergic degeneration: 10% (n = 80)

+ Multiple system atrophy (type P) and other atypical cases of parkinsonism: 5% (n = 40)

Inclusion-positive and synuclein-associated typical PD patients: >75% (n = 600)

+ Inclusion-negative and NON-synuclein-associated cases of PD: <10% (n = 80)

No stratification. 800 pts in treatment arm. If the drug targets synuclein metabolism: no monitoring of target engagement in vivo

At a response rate of 20% in synuclein-related PD cases (n=120 / 600)

P value not significant between the two groups: only 15% (120 / 800) of patients show response = TRIAL FAILURE

Inclusion-positive and synuclein-associated typical PD patients: >75% (n = 600)

Inclusion-negative and NON-synuclein-associated cases of PD: <10% (n = 80)
Marker candidates awaiting validation and/or definition: genetically linked proteins in biological fluids, e.g., $\alpha$-synuclein (total, oligomeric, modified variants); DJ-1; sequence variants, e.g., $GBA1$, $SNCA$, $LRRK2$; urate in CSF and plasma (? progression); metabolome markers in plasma; transcriptome changes in blood cells (e.g., $ST13$ mRNA levels); and exploration of dementia-associated tau and amyloid $\beta$ protein species as markers of cognitive changes in PD subjects.

e.g., Hong et al., 2010; Tokuda et al., 2010; Mollenhauer et al., 2011
8-20% of typical PD patients carry a mutation in one *GBA1* allele; all these subjects feature α-synuclein-positive Lewy body pathology at autopsy. Mutant GBA proteins appear to elevate neural α-synuclein. Thus, *GBA1* carrier status in PD (and DLB) can be considered a reliable surrogate for the process of synucleinopathy in the brain.

*Eblan N et al., NEJM 2005*
*Goker-Alpan O et al., Neurology 2006*
*Neumann J et al., Brain 2009*

![Image](image-url)
Scenario for a biomarker-supported clinical trial of PD in the future

**STEP 1:**
Selected phenotype of ‘Typical PD’ patients with AOO >50 yrs. Subjects selected for treatment arm at **STEP 1:** n = 800

**STEP 2: Stratification using objective biomarker values**

- Subjects without evidence of dopaminergic degeneration (10%). **EXCLUDED** by imaging, n = 80
- Atypical parkinsonism cases (MSA-P, PSP etc.; 5%). **EXCLUDED** by imaging and smell test, n = 40
- Inclusion- and synuclein-positive PD patients (75%): 300 / 600 pts **CONFIRMED** by biological markers
- Inclusion-negative PD cases (10%). **EXCLUDED** by neg smell test and neg GBA1 testing, n = 80

**STEP 3:** Monitoring of target engagement by biochemical monitoring reveals success in cases of synuclein-assoc. PD

- Only 300 patients chosen for treatment arm of trial
- At a response rate of 20% in target group, 60 of 300 patients will show a positive effect for drug
- If significant difference detected in treatment group at a lower cost: = **TRIAL SUCCESS**

Klein C et al., Arch Neurol 2011
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Approaches In Neuroimaging

- **Functional Changes**
  - Receptor availability for neurotransmitters (SPECT, PET)
  - Cerebral metabolism and blood flow (PET, SPECT, MRI)
  - Brain networks (functional MRI)

- **Morphological Changes**
  - Regional brain volumes (MRI)
  - Brain iron content (MRI, Transcranial sonography)
  - Tissue microstructure (DTI)
  - Brain connectivity (DTI-tractography)
  - β-amyloid deposition (PET)
Some Existing Imaging Methods

**Dopamine Transporter SPECT**

A: Healthy subject  
B: Unilateral PD (left putamen)  
C: Bilateral PD (left and right putamen)

**MRI**

A: Patient with multiple system atrophy  
B: Patient with Parkinson's disease

SWI = susceptibility weighted imaging; sensitive to brain iron content

With permission: BMJ Publishing Group Ltd  
Kägi G et al. J Neurol Neurosurg Psychiatry 2010;81:5-12
Some Emerging Imaging Methods

MRI

DTI*

PET: Dopaminergic and glutaminergic pathways

*maps of fractional anisotropy (FA), an index of microstructural integrity. Smaller FA of the substantia nigra completely separated PD patients from controls (Vaillancourt et al. Neurology, 2009, 21;72(16):1378-84)

Averaged FDOPA (first row) and MP4A k3 images (second row) of the study subgroups. Note the severe global k3 reduction in Parkinson disease dementia, whereas only a slight parieto-occipital k3 decrease is obvious in Parkinson disease. Hilker, R; et al, Neurology. 65(11):1716-1722, December 13, 2005.

With permission: AAN Enterprises, Inc. Published by Lippincott Williams & Wilkins, Inc.
Key Points: Neuroimaging Markers For PD

- **Existing methods**
  - DAT SPECT and PET are reasonably effective in identifying dopamine deficits but not reliable for a differentiation of idiopathic PD from atypical PD.
  - MRI mapping of structural changes in PD are valuable but a large overlap with normal values remains.

- **Emerging methods**
  - New PET ligands will be useful to study the effect of PD on other neurotransmitters.
  - β-amyloid PET will be useful to study the role of amyloid in PD.
  - DTI has potential as an early marker for PD and to study the impact of PD on white matter.
  - Resting state functional MRI will be useful to study the consequences of dopamine depletion on brain functional connectivity.
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Utility of biomarkers in clinical trials

- Disease mechanism
- Drug mechanism
- Dosage determination
- Study eligibility-early/accurate diagnosis
- Pre-motor diagnosis
- Monitoring disease progression
- Stratification into PD sub-types
- Correlation with clinical signals

• Disease modifying PD therapeutics remain a major unmet need
• Biomarkers will potentially shorten study duration, reduce study sample size, limit study costs.
Biomarkers likely have a temporal pattern. Biomarkers can be used to define and inform at different disease stages.
Developing the Parkinson’s Progression Markers Initiative


Requirements for Biomarker Infrastructure

Specific Data Set
- 400 early stage PD and 200 controls
- Clinical (motor/non-motor) and imaging data
- Corresponding biologic samples (DNA, blood, CSF)

Standardization
- Uniform acquisition of data and samples
- Uniform storage of data and samples
- Strict quality control/quality assurance

Access/Sharing
www.ppmi-info.org
- Data available to research community → data mining, hypothesis generation & testing
- Samples available for studies
### PPMI Study Details: Synopsis

| Study population | 400 *de novo* PD subjects (newly diagnosed 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 baseline, 6mo 12 mo 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 | *De novo* for ~6 months  
|              | Can participate in other clinical trials (including interventional trials) after 12 months |
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