Using Consumer Sensor Technologies to Measure Parkinson’s Disease: Lessons Learned from the mPower Study

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What is Parkinson’s disease?

- **Five to seven million people worldwide** live with Parkinson’s disease.
- **Parkinson’s is the second most common brain disease** after Alzheimer’s, and is the fastest growing neurological condition in prevalence, disability, deaths.
- **One in 100 people over age 60 have PD**, though some are diagnosed at 40 or younger. About 8-10 % of total PD is genetic/familial

Parkinson’s is a neurodegenerative disease: loss of dopamine neurons and Lewy body pathology

<table>
<thead>
<tr>
<th>Motor symptoms of PD include:</th>
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<tbody>
<tr>
<td>- resting tremor</td>
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<tr>
<td>- slowness of movement</td>
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<tr>
<td>- rigidity</td>
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<tr>
<td>- issues with balance and gait</td>
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<table>
<thead>
<tr>
<th>Non-motor symptoms include:</th>
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<tbody>
<tr>
<td>- cognitive dysfunction</td>
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<tr>
<td>- pain, depression and anxiety</td>
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<tr>
<td>- constipation and digestion issues</td>
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<tr>
<td>- sleep and smell dysfunction</td>
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The PD therapeutic pipeline is rich … yet clinical trialists face many challenges

Obstacles in PD Drug Development:

- Disease pathogenesis is unknown
- PD is characterized by phenotypic and genotypic heterogeneity
- Biomarkers that reflect disease presence, progression and severity are lacking
- Unpredictable placebo responses
- Concurrent symptomatic therapy may mask efficacy
- **Outcome measures lack precision**

**Source:** Citeline’s Trialtrove, data accessed February 2020

**Lang A. et al. Mov Disord. 2018 May;33(5):660-677**
# Bending the curve on Parkinson’s

<table>
<thead>
<tr>
<th>Current Measures</th>
<th>Smartphone-based measures</th>
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<tbody>
<tr>
<td>Insensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Subjective</td>
<td>Objective</td>
</tr>
<tr>
<td>Episodic (in-clinic)</td>
<td>Continuous</td>
</tr>
<tr>
<td>Provider-centered</td>
<td>Individual-centered</td>
</tr>
<tr>
<td>Unidimensional</td>
<td>Multidimensional</td>
</tr>
<tr>
<td>Limited Feedback</td>
<td>Can be frequent and real-time</td>
</tr>
</tbody>
</table>
The Promise of Digital Health Technologies in PD

- Objective measurement of clinical signs
- Sensors allow highly sensitive measurements of multiple symptoms that impair quality of life
- Remote monitoring enables frequent assessments and continuous monitoring
- Unique way of gathering data on symptom fluctuations, which may be an important part of disease burden
- Passive monitoring measures what people do in day-to-day lives in an ecologically valid manner
- More naturalistic assessment environment removes the bias introduced by testing in the clinic

Context of Use

The current drug development landscape encompasses the following:

• Parkinson’s Disease Motor Symptoms® Clinical Exam by Qualified Rater (e.g. part III MDS-UPDRS score)

• Parkinson’s Disease Progression® Serial and Longitudinal Clinical Exams (e.g. MDS-UPDRS for Proof-of-Concept primary endpoint)

• Non-motor Symptoms of Parkinson’s Disease® (e.g. cognitive impairment, psychiatric symptoms, autonomic dysfunction, sleep disruption)
Proposed Context of Use

The proposed context of use we will focus on based on the data to date is:

- A monitoring biomarker that is used in new drug trials for patients with Parkinson’s Disease who are levodopa responsive with levodopa-induced peak-dose dyskinesias followed by re-emergence of tremor, rigidity, and bradykinesia
- In more plain language PD patients on levodopa who experience “ON” and “OFF” symptoms

Intended uses:

- Proof of concept; and
- Phase II & III clinical trial decision making

mPOWER is focused on 4 symptom domains (voice, gait/balance, dexterity/speed and memory) with corresponding UPDRS and PDQ8 data
Challenges in Parkinson’s Disease Drug Development

- There is a lack of biomarkers to enable decision making in clinical trials (subject selection, prognostics, monitoring, pharmacodynamic)
- Currently accepted outcome measures lack precision, are subjective in nature, and show inter-rater variability
- There is growing recognition that nonmotor symptoms negatively impact quality of life
- Outcomes that truly reflect what is important to patients are lacking
Technology Verification & Validation

Technology = sensor + algorithm

- What is the sensor type (wearable, implantable, other)
  - Smartphone app – sensors and questionnaires

- How does the algorithm produce the measurement?
  - Open source

- Novel or Existing measure?
  - Novel measures
    - Measures of tremor | activity | movement | voice | memory

- Regulatory Pathway (Commercial, FDA cleared, etc)
  - Commercial app
mPower

A feasibility study to evaluate use of smartphones for the remote, digital monitoring of disease severity in Parkinson’s Disease

16,000+ unique participants | 700,000+ activities | 50+ Months
Why mPower was selected as a case example

1. Real-world data collection in Parkinson’s disease
2. Fully remote | large-scale | subjective & objective measures
3. Patient consent to share data from onset
4. Data and results were published in peer review journal
5. Data analyzed by research community via DREAM challenge
6. Learnings can help inform future DHT studies (e.g. retention)
Sense individualized lived experience at population scale

Assess in the moment

Assess in the clinic
(episodic)

Traditional Clinical Research Protocol
What the future of Parkinson’s assessment could look like

Multimodal assessments to help track individualized lived-experience of disease in the real-world
Digital tracking of Parkinson’s disease symptoms

Objective sensor-based assessments

<table>
<thead>
<tr>
<th></th>
<th>Motor Initiation</th>
<th>Gait/Balance</th>
<th>Hypophonia</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveys</strong></td>
<td>MDS-UPDRS PDQ8</td>
<td>MDS-UPDRS PDQ8</td>
<td>MDS-UPDRS PDQ8</td>
<td>MDS-UPDRS PDQ8</td>
</tr>
<tr>
<td><strong>Passive</strong></td>
<td>GPS - Displacement Vectors</td>
<td>GPS - Displacement Vectors</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td>All structured activities also include timing with relation to Rx administration and/or patient reported modulators</td>
<td></td>
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</table>
These measures are summarized

E.g. - number of steps; average acceleration; variation in acceleration; step frequency

E.g. - number of taps; tapping fatigue; tapping variation
Response is highly personalized
In the wild measurements:

What is happening in real life?
Signal in the noise: Variation is a sign of disease in PD
Treatment effects observed over a month

Objective measure tapping

Days

before L-Dopa
after L-Dopa
Variation is a sign of disease in PD

Short term effects of L-Dopa on Performance

If you are not careful ML can overestimate your signal

(performance due to the confounding signal alone)

\( \alpha \hat{\pi}^* \)

(performance due to disease and confounding signals)

\( m_o \)

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mPower accuracy relative to clinical measures of disease

First participant enrolled in Phase III Clinical Trial March 2017

Evaluation in clinical cohort studies to assess accuracy in measuring disease progression and treatment effects

Objective Measure
Finger Tapping
Providing mobile sensor data for use across the research community
Parkinson’s Disease Digital Biomarker DREAM Challenge

Community-based competition to identify sensor-based features that most accurately reflect treatment effect and disease state

mPower data  Fox Insight data

17,000 analysts
ML in Health + Wisdom of the Crowd

Teams

AUROC

BEAT-PD DREAM Challenge
Biomarker & Endpoint Assessment to Track Parkinson's Disease
**mPower 2.0 – mPower progression**

**Motivation:** Is it possible to detect long term trends in disease progression more precisely and at a lower burden?
- Are the perturbations to PD?
- Is there more utility to participants?
- What motivates someone to track themselves?
- etc…
mPower 2.0 – mPower progression

Welcome to mPower!

Seems you are new to the mPower study! Thanks for being interested in joining the mPower study. Before jumping into the study, let’s learn more about the study to ensure it is appropriate for you.

Back  Next
Need for objectively assessing participant enrollment and retention in remote research

- socioeconomic status
- race/ethnicity
- age
- gender
- incentives offered
If you can’t measure it, you can’t fix it
Bias in real-world data collection

Participant diversity & digital divide

Balance the needs of researchers & end-users

Bias - “I’m feeling unsteady. Am I going to stop and log in the app and indicate—the answer of course is no”

Value Proposition - "might be interesting information but it’s also kind of meaningless"
Risk/Benefit considerations

- Digital tools to capture clinical endpoints for clinical trial participants
- Digital companions and solutions to assist patients in managing disease (e.g. symptom tracking, medication monitoring)
State of evidence

Current evidence available:
- Focus on the evidence relevant to the decision being made.
- Single or multi-component measure?
- Existing analytical and clinical validation?

Additional evidence needed to meet the minimum evidentiary standards given the benefit/risk assessment:
- Additional analytical and clinical validation needed?
- Highlight gaps in the data that would need to be filled in order to make a confident decision
- Keep in mind that the decision maker is either the FDA reviewer or the industry/trial sponsor
Recommendations to accelerate progress in the future

• Assure what is being measured is important to patients

• Adopt open science strategy:
  o Sharing of all data (raw + algorithms) collected to date (multiple independent studies)
  o Methodology / open source platforms for future studies
  o Assess device performance in normal subjects
  o Test/retest reliability
  o Identify and define sources of variability
  o Quantify ability of device to monitor progression and drug effects in multiple independent studies
Neuroscience drug development challenges

- Difficult to examine in vivo; in vitro and animal models frequently lack translation to humans
- Lack of target identification and validation, lack of biomarkers
- Long observation time, large heterogeneity with lack of clinical phenotyping, dependence on subjective endpoints for registration

CNS Drugs have 31% Longer Regulatory Approval Times

CNS Drugs Face 18% Longer Clinical Development Times
People with PD experience evolving symptoms with complex responses to therapy

There remains a significant opportunity to utilize digital health technologies in PD to achieve better outcome measures for PD registration trials

Characteristics of Types of Evidence

As identified in Evidentiary Criteria Workshop – July 2018

- **Universality**
  - PD is a movement disorder with hallmark motor symptoms directly measurable in the form of tremor, bradykinesia and dyskinesia
  - These motor symptoms + fluctuations can be objectively measured using digital tools

- **Plausibility**
  - In many ways because of the fluctuating nature of PD, more frequent monitoring (using wearable sensors) likely will be more reflective of what a patient experiences than the episodic assessment with UPDRS
  - Clinical trial history is full of promising phase II trials that never met phase III endpoints using these subjective clinical rating scales
  - Technology that assesses patients with more granularity (wearable sensors/environmental monitors) can generate NEW clinically relevant information rather than trying to measure concepts assessed by traditional outcome measures (UPDRS)
“Looking around the auditorium at an ocean of stooped, shuffling, struggling people who carry on with clipped wings, ...wearable monitoring technology development seems necessary, not merely clever, as research and care delivery must get more efficient to keep us all moving.”
Question and answer session
Three Pillar Theorem to Phase 2 Survival

Pillar 1
• Exposure at the target site of action

Pillar 2
• Binding to the target

Pillar 3
• Expression of pharmacology

Morgan P. Drug Discov Today, 2011