Clinical ink

Digital Biomarkers as Endpoints in Parkinson's Disease:

Development, Progress, and Outlook for a New Era

Author: David Anderson, PhD

POWER PATIENT OUTCOMES

POWER PATIENT OUTCOMES

Table of Contents

Digital biomarkers are emerging as a promising area of development for complementing existing PD assessments.

Introduction

Parkinson's Disease (PD) is a neuromuscular disorder and the second-most common neurodegenerative disease,[1] affecting more than 10 million people worldwide.[2] PD can impair both motor and non-motor functions and, by consequence, multiple activities of daily living. Medical costs associated with PD are approximately $52 billion per year in the U.S. alone. Due to PD's broad sequela, a diagnosis of the disease can be non-trivial — particularly in the early stages — and progression rates are variable across patients.

The Unified Parkinson's Disease Rating Scale (UPDRS) is the gold standard for diagnosing and staging PD and is a standard primary endpoint in clinical trials to evaluate therapeutic efficacy of novel drugs and interventions. However, the UPDRS is an imperfect stand-alone tool as its scoring can be time consuming, subjective, and episodic. There is, therefore, a critical need for developing and validating biomarkers in conjunction with the UPDRS to generate objective, quantitative metrics of disease probability, severity, and risk for progression. These biomarkers hold potential for screening patients and assessing therapeutic efficiency during clinical trials.

With advances in wearable and sensor technologies, digital biomarkers are emerging as a promising area of development for complementing existing PD assessments across the clinical landscape. Here, we discuss work being done to develop and validate digital biomarkers in PD.

About Parkinson's Disease

PD is a progressive neurodegenerative brain disorder, causing neuromuscular dysfunction that manifests as rigidity, tremor, bradykinesia, impaired balance, and instability.[3] The functional abnormalities that lead to PD include the degeneration of dopaminergic neurons in the brain,[4] resulting in reduced dopamine production and downstream effects on motion, balance, and coordination.[5] Levodopa, a precursor in dopamine synthesis, has been the long-standing, first-line treatment for PD.[6,7,8] Deep brain stimulation, a surgical therapy that uses electrical signals to normalize brain function, is also approved in the U.S. to treat PD tremors.[9] Research efforts continue to focus on developing disease-modifying therapeutics (DMTs) intended to halt or delay disease progression. To this end, the U.S. National Institutes of Health (NIH) awarded approximately $130 million to fund PD research in 2020.[10] Despite these efforts, novel drug discovery for PD is hindered, in part, by the lack of quantitative biomarkers to reliably assess disease severity and progression.[11]

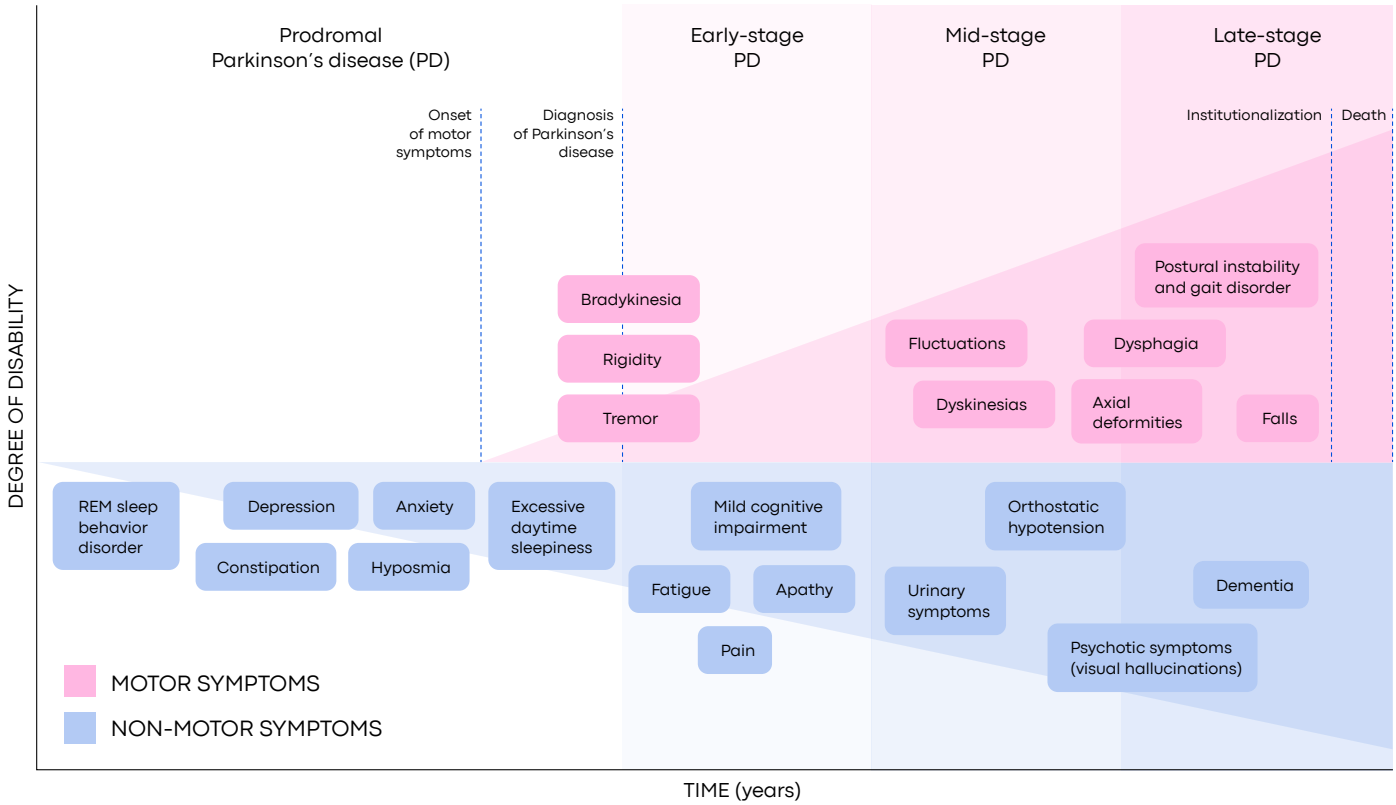
Diagnosing Parkinson's Disease

As seen in Figure 1, many non-motor PD symptoms appear well before the more observable motor symptoms. Motor symptoms used to diagnose the disease — bradykinesia and at least one of the following: resting tremor, muscle rigidity and postural reflex impairment[12] — are typically present only years after the neurodegenerative process has started. By consequence, early diagnosis is difficult, and the rate of misdiagnosis is between 16-20%.[13] Further, rates of PD disease progression are highly variable between patients, leading to the development of personalized treatments that require "more fine-grained insights in progression of PD, ideally at the level of individual patients, or at least tailored to a set of recognizable clinical profiles."[14]

As there are no specific tests that diagnose PD, clinicians base their diagnoses on:[15]

- Medical history and a neurological examination
- Blood and laboratory tests, to rule out other disorders that may be causing the symptoms
- Brain scans to rule out other disorders (Note: computed tomography (CT) and magnetic resonance imaging (MRI) brain scans of people with PD usually appear normal)
- Genetic testing for those rare cases in which patients have an inherited form of PD
- The UPDRS

Figure 1: The Course of Parkinson's Disease



Source: Poewe et al, 2017 Nature Reviews Disease Primers

UPDRS: The Current Gold Standard Assessment

The UPDRS is the clinic gold standard assessment of motor (e.g., tremor, speech, eating, mobility) and non-motor (e.g., cognition, mood, sleep, pain, fatigue) aspects of PD. The UPDRS has four parts covering 1) intellectual function, mood, and behavior, 2) activities of daily living, 3) motor examination, and 4) complications of therapy. Clinicians use the UPDRS to monitor patients' disease progression every six months.

Critics of the UPDRS have noted issues with its reliability given that it is:[16]

- **Subjective**. It reflects the clinician's interpretation. Two neurologists can assign two different scores to the same patient. Indeed, research has shown that UPDRS results in substantial error variance. One study determined that the within-subject reliability of one-year change scores ranged from 0.13 to 0.62.[17], where reliability >0.6 is generally viewed as the threshold for acceptability.
- **Episodic**. Measures are taken at six-month intervals and provide insight into the patient's condition only at a snapshot in time.
- **Variable**. Patient performance can depend on a number of factors such as how recently medication was taken, the time of day, etc.
- **Non-linear**. Increments from one score to the next are not uniform. Therefore, a simple extrapolation may not provide meaningful measure of change.
- **Without context**. The same motor score may be given to two different patients, each suffering from vastly different motor symptoms.

This lack of reliability affects the accuracy of diagnosis and monitoring, which in turn impacts patient treatment plans.

Improving Measurement Accuracy for PD

Given the limitations of the UPDRS, ongoing investigations seek to develop complementary quantitative biomarkers that can accurately detect PD in the early stages and demonstrate treatment efficacy. Digital measures derived from wearable sensors have demonstrated the potential to assess physiologic, motor, speech, and cognitive functions in PD. Indeed, multiple digital measures will need to be validated against, and combined with, the UPDRS to capture the broad sequalae of PD. Digital measures hold several advantages over the UPDRS alone:

- **Objectivity**. The objective nature of the measurements ensures reliability and repeatability of the signal.
- **Sensitivity**. Digital devices have the potential to gather more specific, sensitive data on the same activities and tasks that are also evaluated in the clinic. Indeed, the best examples of digital biomarkers have been modeled after in-clinic assessments.
- **Continuous, real-time data collection**. The data collection can be continuous, or as frequent as needed, overcoming the episodic nature of other, in-clinic evaluations. The U.S. Food and Drug Administration (FDA), in its guidance on using digital health technologies (DHTs) in clinical trials has stated that such continuous monitoring "may provide a broader picture of how participants feel or function in their daily lives."
- **Improved compliance**. Relatedly, patients/participants are using technology more widely today, so the devices are more easily integrated into their everyday lives, which bolsters compliance. iPhones and Apple Watches have built-in sensors that allow for the collection of multi-modal data without patients having to access or manipulate multiple pieces of software or external sensor systems.
- **Patient convenience**. Wearable devices and digital sensors can be used by patients at home, in the clinic, or both. To the extent that measures are taken remotely at home, PD patients, many of whom have difficulties with mobility, can be spared the need to travel to sites.

Today, both the iPhone and Apple Watch are equipped with hardware and sensors capable of tracking a patient's life space, mobility, activity levels, physiology, speech, and cognition. In PD, this translates to the ability to measure steps, gait, tremor, vocal atrophy, and cognitive deficit. Data can be collected from these tools either passively (automatically detected by sensors) or actively (requiring the patient's intentional engagement).

Developing Digital Biomarkers for PD

Designing reliable instruments and a secure and intuitive platform for capturing and transferring digital measures, like Clinical ink's BrainBaseline™ platform, requires collaboration across multiple disciplines. Success is ultimately dependent upon having advanced engineering and analytic capabilities to accommodate and mine the voluminous, rich data generated by digital technologies. Consider that digital sensors can passively record continuous signals 10 to 1,000 times per second, allowing scientists to remotely capture millisecond-by-millisecond fluctuations.

Once the data is captured, conducting feature engineering allows high-dimensional information to be extracted from these digital measurements. Feature engineering demands a highly trained and specific knowledge set, including:

- **Therapeutic expertise**. This is essential to interpreting the significance and quality of the signal, identifying which features that can be associated with physiological and behavioral states, and accurately mapping those features onto the disease, in this case PD.
- **Signal processing expertise**. This is required to know which tools are appropriate for teasing out relevant information, processing it, and summarizing it in a meaningful way.
- **Software development expertise**. This is required to develop methods to deploy signal processing tools and integrate them into a data management platform.

After the work of feature engineering is complete, the next phase is to deploy machine learning to build a model capable of identifying the data features that are selective for the disease. Selecting the appropriate model is critical and should be predicated on the properties of the data, the outcome measures of interest being predicted, and the model's performance. A model's performance is evaluated based on its accuracy, sensitivity, and specificity for predicting an existing clinical gold standard (e.g., UPDRS scores). Sensitivity is the probability of the model predicting a positive test (e.g., PD) given the data features that reflect a true PD diagnosis, whereas specificity is the probability of the model predicting a negative test given the data features that reflect a true non-PD diagnosis. Once developed, the model should be applicable to all projects generating the same data features.

The Validation Process

Digital biomarkers are considered exploratory until they have undergone regulatory approval. In the case of PD, regulatory approval of digital endpoints depends on mapping these new measures onto existing clinical standard measures, or proving that an extracted feature model (such as discussed above) accurately and reliably predicts UPDRS scores with high sensitivity and specificity.

Digital biomarkers must also be scalable and translatable across different studies, levels of severity, and demographic factors within the same disease. They may also be translatable from one indication to another – for example from PD to other movement disorders such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP).

Fortunately, there is an organization dedicated to advancing new development tools in PD: The Critical Path for Parkinson's Consortium (CPP). This international organization of scientists, academics, governments, and patient advocates aims to attain regulatory endorsement of novel translational biomarkers and drug disease trial models for use in clinical drug development.[18]

The WATCH-PD Study

The Clinical ink team managed a collaborative research study with partners in academia and the pharmaceutical industry to validate remote, digital assessments for use in capturing clinical endpoints in PD. The goal was to demonstrate the suitability of the technology coupled with the BrainBaseline™ platform for screening patients and evaluating treatment efficacy. Ultimately, such evidence should lead to regulatory acceptance and widespread adoption of the assessments in clinical development and medical practice.

The multi-site observational study used consumer-grade mobile devices (the iPhone and Apple Watch) to standardize digital measurements for PD and was designed to replicate the type of assessments performed by clinicians. We sought answers to two questions:

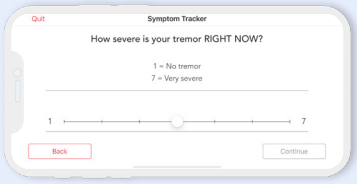
Q1 Can "at-home" kinematic measures acquired via wearable sensors provide greater insight into disease progression than clinic visits alone;

Q2 Can a customized wearable/mobile platform used outside of the clinic meaningfully supplement in-clinic measures of PD motor and non-motor symptom progression.

The study recruited 50 healthy volunteers and 82 patients diagnosed with PD who were asked to make six visits to a clinic and complete mobile assessments, which Clinical ink conceptualized and developed, twice a month for 12 months. Passive data was collected from their iPhone and Apple Watch seven days after their clinic visits to continuously measure tremors, gait, and balance. At home, patients completed tasks on their phone to assess their mood, fatigue, cognition, mobility, tremor, and bradykinesia. They also completed psychomotor and speech tasks on their phone to assess measured finger tapping, fine motor coordination, verbal phonation, and reading. Instrumented motor tasks measured their gait, balance, and tremors (see Figure 2).

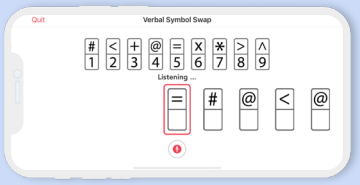
Figure 2: At-Home, Patient-Administered Activities

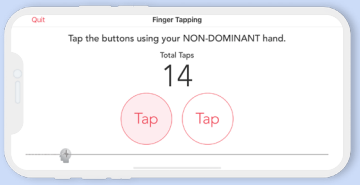
ePRO



- Mood
- Fatigue
- Cognition
- Tremor
- Bradykinesia

Cognitive and Psychomotor Tasks





- Trailmaking
- DSST
- Visual WM
- Finger Tapping
- Fine Motor
- Speech, Reading

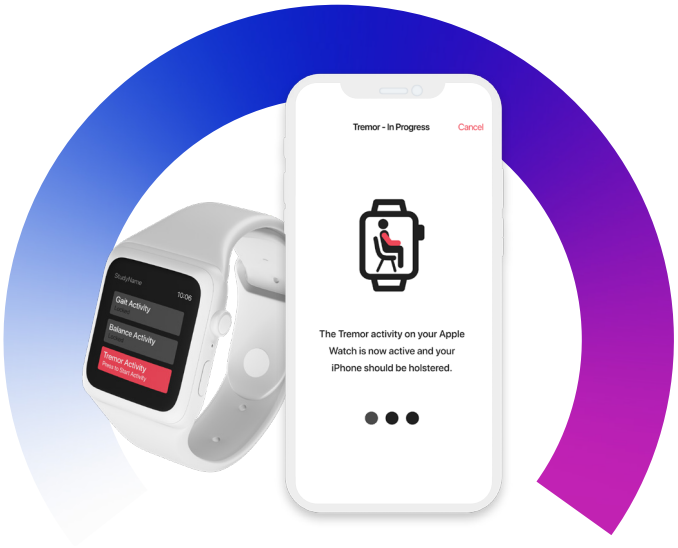
Instrumented Motor Task; Continuous Passive Collection

- Gait
- Balance
- Tremor
- Continuous Data (tremor, accel, gyro)

Our model distinguished healthy volunteers from patients with early-stage PD, providing preliminary support for the use of our platform in generating digital biomarkers associated with PD status.

A total of 3,622 data features were extracted from nine different assessments, 39.5 percent of which were selective for PD status. By incorporating the 100 most selective features into a logistic regression model, we were able to attain disease classification accuracy of 92% with 100% sensitivity and 89% specificity. Data features of primary interest were generated from gait, tremor, and finger tapping tasks. Thus, our model was able to distinguish the healthy volunteers from patients with early-stage PD, providing preliminary support for the use of our platform in generating digital biomarkers associated with PD status. Critically, our platform has demonstrated that more frequent and extensive remotely monitored measures hold potential to yield greater insights into disease progression.

Working with the CPP, we will determine next steps to engage regulatory bodies with the goal of outlining a path for the inclusion of these novel digital endpoints in trials of early PD. This will lead to a tool of choice and industry-wide standard for diagnosing movement disorders, screening patients for trials, and evaluating patients' progress and the efficacy of treatments in development.



Outlook for the Future

Advances in technology combined with a desire to increase patient centricity in trial designs will continue to drive a shift toward more decentralized or hybrid trials that take advantage of remote data collection. Thus, we believe consumer-grade wearables and personal devices will become standard in augmenting traditional clinical trial data as they continue to add more applications for patients' daily lives. Certainly, the volume of instrumented data will continue to expand — a factor that will determine which platform is best for data collection, management, and analysis.

In PD specifically, we foresee that clinicians will want to continue using the UPDRS because it evaluates every facet of the disease. It is a multi-system scale that remains industry gold standard. However, the best approach will likely be to use proven, tested, point-in-time clinician assessments coupled with at-home digital assessments serving as decision support tools.

Novel signal processing and algorithmic routines will continue to push the development of new, digital biomarkers, and eventually there could be a library of standard tools for assessment/data collection that could be used in a variety of clinical settings. In fact, this is a goal of the Digital Medicine Society (DiME).

It is possible that a combination of biomarkers could predict the motor progression or cognitive impairment of PD.[19] It is even conceivable that digital devices could be used as surveillance tools "in the wild" to detect potential PD patients, suggesting the need for further evaluation, and directing them to clinical trials of interest.

Conclusion

Clinical ink's work with the existing WATCH-PD study will continue with the intention of securing regulatory approval of our digital biomarkers for use in PD clinical trials. Nonetheless, Sponsors working in PD may want to pursue their own research to validate these digital assessments specific to their patient population, in which case our existing model can be updated as needed. It is important to note that this type of approach can also be applied with modifications in other movement disorders.

Before finalizing any protocol for a PD or movement disorder study, Sponsors should fully explore the options available for using digital devices to supplement clinical assessments. Capabilities are changing rapidly, with new measures being developed all the time. Clinical ink's work to date has demonstrated that digital devices can be easy for patients to use, secure, and valuable in detecting disease and tracking patients' ongoing status. The biomarkers that these consumer-grade tools help generate can differentiate between healthy subjects and those with PD. In time, we believe that they will be used in conjunction with other scales to determine an individual's disease probability, severity, and risk for progression, with applications in clinical trials as well as medical practice.

References

1. Tianbai Le, "Biomarkers for Parkinson's Disease: How Good Are They?" Neurosci. Bull, Feb 20201 3692): 183-194.
2. https://parkinson.org/understanding-parkinsons/statistics
3. https://parkinson.org/understanding-parkinsons/statistics
4. Triarhou LC. Dopamine and Parkinson's Disease. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6271/
5. https://www.healthline.com/health/parkinsons/dopamine-parkinson
6. https://www.drugs.com/medical-answers/levodopa-parkinsons-disease-3554930/
7. Salat D, Tolosa E. Levodopa in the treatment of Parkinson's disease: current status and new developments. J Parkinsons Dis. 2013 Jan 1;3(3):255-69. doi: 10.3233/JPD-130186. PMID: 23948989.
8. http://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm326192.htm
9. https://www.parkinson.org/Understanding-Parkinsons/Treatment/Surgical-Treatment-Options/Deep-Brain-Stimulation
10. https://www.ninds.nih.gov/Current-Research/Focus-Disorders/Parkinsons-Disease
11. https://www.ihealthcareanalyst.com/global-parkinsons-disease-therapeutics-market/
12. https://parkinsonsdisease.net/basic/statistics
13. Tianbai Le, "Biomarkers for Parkinson's Disease: How Good Are They?" Neurosci. Bull, Feb 20201 3692): 183-194.
14. Luc J.W. et al, "Measuring Parkinson's Disease Over Time: The Real-World Within-Subject Reliability of the MDS-UPDRS," Movement Disord, Vol 34 No 10, 2019.
15. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Parkinsons-Disease-Hope-Through-Research
16. https://scienceofparkinsons.com/2019/03/06/updrs/
17. Luc J.W. et al, "Measuring Parkinson's Disease Over Time: The Real-World Within-Subject Reliability of the MDS-UPDRS," Movement Disord, Vol 34 No 10, 2019.
18. https://c-path.org/programs/cpp/
19. Tianbai Le, "Biomarkers for Parkinson's Disease: How Good Are They?" Neurosci. Bull, Feb 20201 3692): 183-194.

Clinical ink

POWER PATIENT OUTCOMES

Clinical ink is the global life science company that brings data, technology, and patient science together.

Our deep therapeutic-area expertise, coupled with Direct Data Capture, eCOA, eConsent, telehealth, neurocognitive testing, and digital biomarkers advancements, drive the industry standard for data precision and usher in a new generation of clinical trials.

By harnessing digital data, we power sponsors, CROs, researchers, and patients to recenter decentralized trials and rewrite the clinical development experience.

WORLDWIDE INQUIRIES

+1 336 714 7402

info@clinicalink.com

Clinicalink.com