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Point of view

Digital phenotyping in Parkinson's disease: Empowering neurologists for measurement-based care

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ABSTRACT

There remains a significant mismatch between the complexity and variability of symptoms and disabilities in Parkinson's disease (PD), and the capabilities of existing validated assessment tools to objectively measure and monitor them. However, with the advances of circuit and sensor technologies, it is now possible to apply the concept of digital phenotyping to PD, providing a moment-by-moment quantification of individual patient phenotypes using personal digital devices, such as smartphones. Such technology holds considerable potential if a patient-centered multidisciplinary team is able to select digital outcomes that are not only clinically relevant, but also provide measurement-based care results that support individual patient clinical decision making. However, it is likely to be a long road, requiring large collaborative efforts to undertake a number of essential steps before full integration and synchronization of these outcomes into patient management platforms that can deliver individualized data to patients, caregivers, and treating neurologists. In the meantime, both neurologists and patients can empower themselves with digital technologies, working as a team to define the ways that new technologies can be most powerfully employed in PD management. Once digital phenotyping becomes feasible and widely adopted in PD communities, it is likely to expand our understanding of individual PD patients' lives and priorities, leading to targeted treatments and better outcomes for PD patients and their families.

Clinical problem

In a busy Parkinson's out-patient clinic in a tertiary referral center, a 45-year-old man with Parkinson's disease (PD) was seen for a 20-min follow-up. He was seen during his 'on' period, performing well on various motor tasks, scoring 15 on Part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS UPDRS-III). Although he could not be precise with timings, he recalled several episodes throughout the day when he shuffled, associated with right arm stiffness and tremor, interspersed with bouts of fidgety movements which was interpreted by his colleagues as restlessness. Also, his wife reported a few episodes each week when he acted out during the night and had difficulty getting out of bed in early mornings. He was also constipated. Although he attempted to complete a paper diary, as instructed by his neurologist, inconsistencies in his responses raised concern about his understanding of the task. Moreover, he noted down several symptoms that he experienced in a separate worksheet (e.g. constipation, fatigue) as he felt that these symptoms were beyond the scope of the diary. The patient was also very anxious asking his neurologist about his future ability to continue working as a mechanic and if he would become physically dependent in a near future.

1. Introduction

This case illustrates an example of a typical mid-stage PD patient whose disabilities are complex. He has fluctuations of both motor and non-motor symptoms and his case represents a common situation in a busy neurology practice where there is a lack of objective, clinically relevant, data about the patient's subjective disability and reported problems. PD patients often present subjective narratives about their symptoms, including misinterpretations and inaccuracies, due to recall bias, misconceptions about their disease, and a lack of medical knowledge [1]. They particularly struggle with accurate understanding of symptom fluctuations, as identified in a recent study that demonstrated

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barriers in communications about 'off' periods between healthcare providers and a majority of PD patients [2]. Physicians experienced patient difficulty in recognizing and understanding their 'off' symptoms and patients expressed that the variability of their symptoms made them unsure if they were part of the spectrum of 'off' period [2]. This confusion probably reflects patients' difficulty in understanding the two 'artificial' states that were created by physicians to dichotomize complex symptomatology in PD into 'off' and 'on' periods. There are also limited tools available to physicians to capture patients' symptoms with clinical interviews being the most commonly used. In tertiary PD referral centers, specialists may undertake more comprehensive assessments, employing validated rating scales (e.g. MDS-UPDRS), but the assessments are provider-centered, limited to brief episodic and subjective evaluations of selected features of interest, and usually not in the patients' own environment (lacking ecological validity). There is often limited availability of certified and qualified clinicians to complete rating scales in clinical practice [3]. Although questionnaires and scale-based evaluations are suitable and efficient methods for screening large numbers of patients or evaluating symptoms of interest in large clinical trials and busy practice settings, they are prone to insensitivity, rater bias and variability, and potentially miss certain disease-specific features due to unidimensional assessment [4]. Moreover, scale-based assessments do not correlate well with the daily activity of PD patients and are unable to provide continuous assessment, which is becoming essential, especially in those patients with fluctuating symptoms [4,5].

2. Evolution of objective assessments in Parkinson's disease: towards digital phenotyping of clinically actionable phenotypes

Many aspects of PD can be measured either by biological assays, performance measures, or objective procedures to provide results in real numbers on an interval scale. Here, 'objective assessment' refers to the technology-based objective measures of physical characteristics of a pathological phenomenon in PD (e.g. sensors to measure the frequency and amplitude of tremor) [4]. Indeed, the idea of objective assessment in PD was conceived even in Charcot's time when dynamometers were used to study the cardinal feature of slowness in PD [6]. However, early objective assessments of PD utilized existing instruments developed for other purposes (e.g. a strained gauge transducer connected to electroencephalogram and electromyography as outputs for tremor monitoring) to monitor an individual symptom of interest (e.g. tremor) under a specified protocol in a research setting [7]. With the development of movement sensors, it became possible to record movements in different axes, but initial applications focused on single parameter assessment (e.g. triaxial accelerometers/gyroscopes for quantifying tremor or dyskinesia), so limiting wider implementation as standardized tools of motor assessment in clinical trials [8,9]. Further sensor developments have evolved into home-based testing devices that are capable of assessing a set of defined outcomes (e.g. tremor, speech, reaction time, etc.) with good correlation with the UPDRS, and associated with high patient compliance and satisfaction [10]. Nevertheless, traditional portable sensor-based applications can be impractical in clinical practice as they usually require additional hardware and may lack of wireless capability necessitating hard wiring or docking for download of data. At-home use of unfamiliar devices may also be hampered by lack of technological preparedness and cost considerations among patients. In addition, these 'at-home' assessments are still sporadic and irregular, generally requiring active participation, making them inadequate for fully capturing the natural history of PD manifestations, which can change at varying and unpredictable times during both day and night [3,4]. The availability of accelerometers in most modern wearable smart devices and smartphones presents a possible solution to these limitations in terms of cost, duration of monitoring, and active participation from PD patients who are already familiar with these devices [11].

Advances in circuit technology have allowed sensors to become much smaller with low-power consumption, and expanded capability for quantifying various PD manifestations, not just tremor and dyskinesias [12]. A surge of interest in objective assessments in PD, by both investigators and developers, has led to various devices being developed for either research or commercial purposes, paralleled by an expansion in applications available to aid physicians monitor different motor and NMS ranging from cardinal motor features, dyskinesia, gait, balance, sleep, autonomic functions, activity levels, with the list continuing to grow [13,14]. Current technology now allows the continuous monitoring of an individual patient's phenotype, defined as *digital phenotyping*; a concept being proposed by Torous et al. as 'the moment-by-moment' quantification of the individual-level patient phenotype *in situ* using data from personal digital devices [15]. One's unique set of activities, recorded on digital devices, is referred to as your 'digital footprint'. Originally adopted in behavioral studies (e.g. psychosis), the concept of digital phenotyping is beginning to be seen in studies of movement disorders, particularly PD and Huntington's disease [16].

In order to comprehensively capture moment-by-moment symptoms of interest in PD, active participation from patients as "users" is essential. While wearable-based monitoring is feasible in the majority of PD patients, long duration of monitoring (>13 weeks), the number of reminder notifications for patients to provide ratings, and high disease severity (Hoehn & Yahr stage >3) can potentially influence patients' adherence [17–20]. Wearing multiple monitors when going out in public may also attract unwanted attention. Smartphones represent an attractive alternative to wearables due to their public acceptance as a personal device for daily use. They are equipped with multiple sensors, including motion sensors, touch screens and a camera, providing the opportunity for digitally phenotyping of various motor and non-motor behaviors in PD patients. Under proper conditions, smartphones can provide a rich set of tools for advancing our understanding of physiological and behavioral perspectives of PD, with scalability and individualization for both passive and active monitoring [21]. However, despite these advantages, the applicability of smartphone technologies in PD also depends on the affinity and capability of the target population (PD patients) to use these tools [18]. There are many parts of the world, like most of sub-Saharan Africa and certain areas in South America and Asia, where smartphone usage is far from commonplace. This is particularly true among the elderly where smartphone ownership varies widely by country, being highest in Scandinavian countries (41–43%) but lowest in certain countries in South Asia and South America (<10%) [22]. Moreover, motor and non-motor symptoms may also hinder proper handling of smartphones and the physical location of a smartphone on an individual patient potentially impacts on how symptoms are monitored and collected. Better integration of smartphones into functional clothing is needed to address requirements of the wearer and allow the optimal positioning of the smartphones. Background 'noise' and overload of data acquisition also makes meaningful analysis challenging. The term 'infobesity' is a portmanteau, based on the words *information* and *obesity*, referring to the situation of continually consuming large amounts of information, especially when there is a negative effect on a person's wellbeing and ability to concentrate [23]. Therefore, it is more practical if measurable outcomes that are clinically relevant to the individual patient and/or those involved in their care are identified first and simplified for both patients and neurologists to ensure valid interpretation. Such measures, that can be used for clinical decision making, have recently been termed 'clinically actionable phenotypes' [21]. Finally, it is important to identify outcomes that patients deem appropriate as not all patients want all their symptoms objectively monitored, even if found to be bothersome to them [24].

3. Characterizing the clinical relevance of digital phenotyping for measurement-based care in a cohort of Parkinson's disease

When patients' perspectives were evaluated to understand what they really wanted from their treatment, it was clear that their wishes focused

not only on bothersome symptoms, but also whether their symptoms would objectively improve or worsen [25]. Indeed, monitoring patients' response to treatments is one of the top 10 PD research priorities as selected by PD patients and other stakeholders [26]. As the manifestation of PD is so individualized, determining clinically actionable phenotypes for digital phenotyping that lead to patient-centered digital outcome measures (PCDOs) in an individual patient should be based on a joint decision by a team that is involved in the care of that particular patient [27]. There is a transition from focusing on single symptom domains (e.g. tremor or dyskinesia) to patient-centered management of how motor and NMS impair activities of daily living (ADLs). Although not specifically performed in PD patients, self-reported ADLs in the elderly have been identified to reflect objective measures of functioning [28]. A particular advantage of employing PCDOs is that these outcomes can be used in measurement-based care, referring to the systematic administration of symptom assessment tools and use of the derived results that enable clinical decision making at the individual patient level [29].

Currently, for various reasons, there is no consensus on what defines PCDOs in PD [30]. However, there is a growing interest in utilizing multidisciplinary research to identify patient-centered outcomes that can be further applied to digital phenotyping [27,30]. A framework has been developed to define the scope of PCDOs that refers to technology-based outcomes that facilitate clinically important decision-making by the clinician and promote long-term adherence by the patient [30]. These digital outcomes should be sensitive to individual patient preferences, needs, and values, ensuring that patient values guide all clinical decisions [31]. Therefore, not everything that can be measured should be measured. In a questionnaire-based study on patient-centered outcomes, monitoring treatment response was considered as a preferable measure, with a 50% reduction of symptoms considered successful [25]. Another study summarized a list of PD-related domains that are known to influence well-being and health-related quality of life (HRQoL) including physical activity, social participation, sleep quality, autonomic dysfunction and even coping with stress, with a proposal that these domains could be objectively evaluated by employing mobile health technologies [32]. Another recent trial has involved a group of patients, clinicians and technologists agreeing on a set of symptomatic domains for continuous assessment, including hypokinesia/bradykinesia, tremor, sway, gait, sleep and cognition [33]. However, while these studies share the common principle of patient's involvement in the participatory design, they also reflect different viewpoints on what aspects of PD should be considered for objective monitoring, ranging from bothersome symptoms, and physical activities, to mood, well-being and HRQoL. Individual variability among patients with regards to their subjective perception of disability from various objective impairments can also present a challenge. Fortunately, with the advantage of machine learning, these

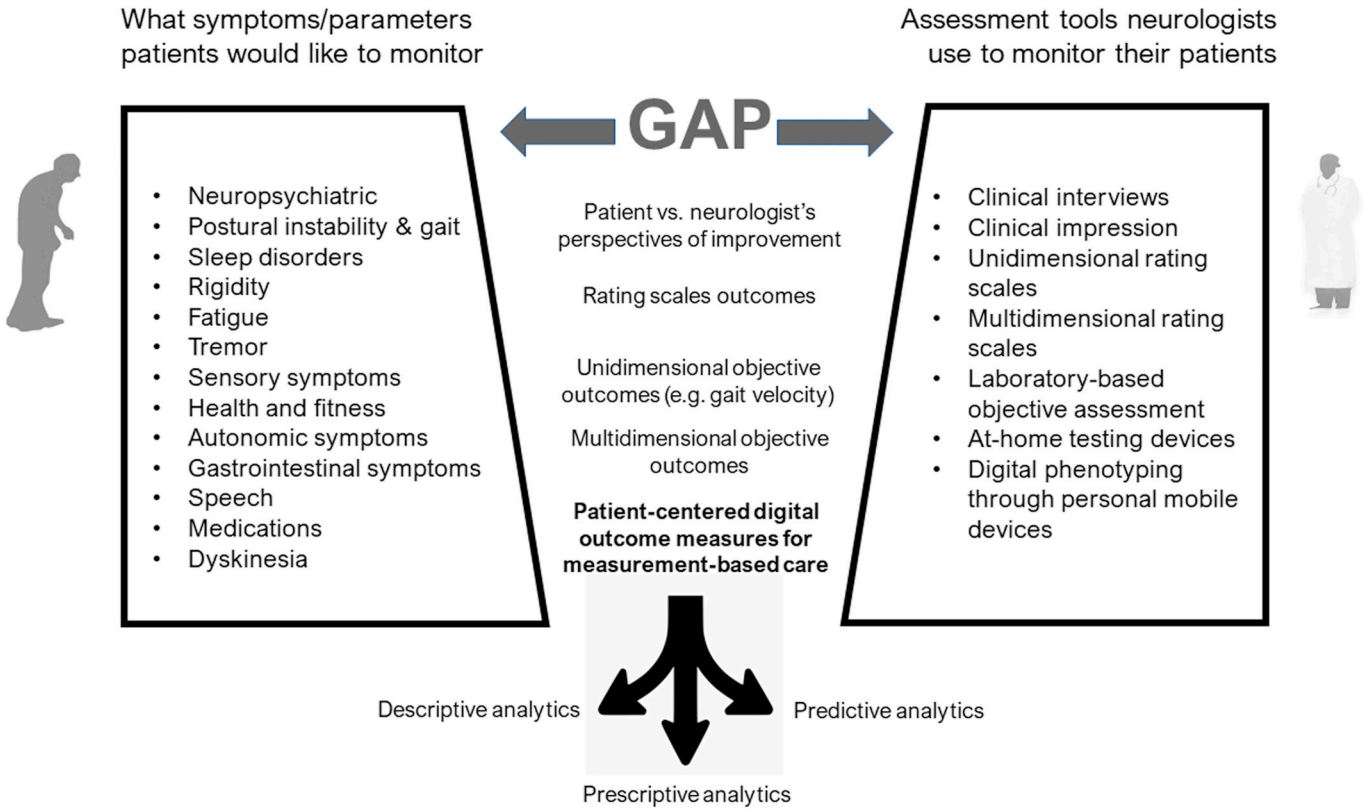

Fig. 1. The diagram demonstrates a gap between what symptoms or parameters Parkinson's disease patients would like to monitor and the assessment tools available for neurologists to implement in clinical practice. Symptoms or parameters in the left box refer to domains that patients would like to monitor according to the survey on 492 PD patients by Mathur et al. [24]. Symptoms or parameters are listed by the number of responses; neuropsychiatric symptoms receiving the most and dyskinesia the least. The right box refers to a list of assessment tools that neurologists can implement in their clinical practice, starting from clinical interviews and clinical impression evolving to rating scales and finally digital phenotyping being the most recent instrument. The gap between right and left boxes refers to the outcomes from assessment tools of patient's symptoms or parameters of interest that is unmet by the multidisciplinary care team. With advances in technologies in PD assessment, it is expected that this gap will narrow as a set of combined symptoms or parameters of interest can be continuously monitored with digital phenotyping, resulting in patient-centered digital outcome measures for measurement-based care. Under proper and well-planned settings, continuous flow of data from patient-centered digital outcome measures will evolve into a not only 'big', but also 'good' data that can be used for different types of analytics. *Descriptive analytics* brings insights to the past, focusing on the questions of what happened, through analyzing data from history while *predictive analytics* allows us to understand the future and predict the likelihood of a future outcome. *Prescriptive analytics* refers to decisions to be made for optimal outcomes: that is, to use all available data and analytics to inform and evolve a decision of what action to take—that is, smarter decisions.

outcomes can be grouped and analyzed to produce new objective scores or indices to measure PD severity, a concept that has been tested in a few clinical trials in PD with promising results [34,35]. Recently, a roadmap for implementation of PDCOs has been proposed to facilitate the adoption of mobile health technologies in order to match the need for identifying patient-centered and clinically relevant digital outcomes and the availability of technology-based tools that are reliable, accessible, and scalable by health care organizations [30].

Digital phenotyping offers a promising strategy to close the gap between what PD patients would like to know, and the various objective PD characteristics that we are able to monitor continuously for measurement-based care (Fig. 1). Measurement-based care using data from wearables has recently been demonstrated in PD clinical trials, where automated optimization of individualized treatment with medications and deep brain stimulation settings was accomplished with the aid of ambulatory accelerometry [36,37]. However, there are limitations to consider, especially on validity in 'free-living' environments, where minimal intra-individual variability with long-term assessments and inter-individual variability among patients needs to be established for selected PCDOs. While akinesia, dyskinesias and motor fluctuations seem relatively close to the specifications described, clinimetric properties of gait and balance in free-living environments are still limited [14]. Recent high-quality reviews have evaluated the latest developments and validity of these outcome measures [13,14,32,38–41]. However, more work is needed to clarify the validation process of PCDOs where correlations between PDCOs and clinical scales may be considered unsuitable due to the substantial inter- and intra-rater variability of clinical scales [30]. To be validated, PDCOs may need to be tested against direct patient input or another robust measure of clinical meaningfulness. Issues related to sensor standardization for common sets of PCDO, outputs that are understandable for end users (e.g. neurologists) and regulatory approval for adoption into health care systems need to be overcome for a successful implementation of PDCOs in a measurement-based care [30].

There are several areas in PD where digital phenotyping can play a significant role in measurement-based care, including monitoring responses to medical or surgical treatments and rehabilitation interventions, and treatment-related motor complications. Also, applications could be extended to identification of adverse events and longitudinal monitoring to assess disease progression, but as digital phenotyping refers to the monitoring of individual-level patient phenotypes, not biological subtypes, its role should be restricted to determining symptomatic interventions or progression, and not evaluating disease modifying effects. To achieve valid outcomes, we need to ensure "good data" is collected. First, data from digital phenotyping is largely unstructured so requires processing to be of clinical value. Secondly, clinimetric properties of data from digital phenotyping needs to be validated with health outcomes. In contrast to classic programming, where analysis is provided by rigid rules created by humans which limits performance, it is now possible to employ machine learning, so-called big data analytics, where computers adapt the programming while performing specific tasks on the basis of previous results and established parameters, resulting in judgments that are likely to surpass rule-based approaches. Descriptive analytics brings insight into the past, based on analyzing data from history, predictive analytics allows us to understand the future, predicting the likelihood of future outcomes, such as the likelihood of developing PD from a prodromal stage, motor complications, and cognitive impairment. Machine learning also lends unforeseen potential in phenotyping PD at the individual patient level. Recently, model-free big data machine learning-based classification methods have been shown to outperform model-based techniques in forecasting the diagnosis of PD with accuracy of more than 80% [42]. However, predictive analytics remains elusive as it requires access to real-time data that allows near real-time clinical decision making, with digital phenotyping from mobile devices fully integrated providing up-to-the moment information on a PD patient's health. Also, neurologists need to be experienced with interpreting and utilizing such data. Recently, the utility of machine learning-based analytics has been shown at a clinical level. The Mobile Parkinson Disease Score, derived from a rank-based machine learning algorithm and disease severity score learning of five tasks (voice, finger tapping, gait, balance, and reaction time) on a smartphone application, was able to detect intraday symptom fluctuations and objectively determine responses to dopaminergic medications with significant correlations to standard clinical measures [34]. Another study used a set of digital biomarkers in a clinical trial setting and demonstrated the effectiveness of commercially available smartphones for in-home active testing and passive monitoring in the home environment [35]. A model-free machine learning-based technique has also forecast falls in PD with a classification accuracy of 70–80% [43]. So, digital phenotyping should enable the instigation of meaningful analytics to inform and improve decision making in the measurement-based care of PD. The ability to make informed and evolving decisions for optimal outcomes, using all available data and analytics will lead to smarter choices (Prescriptive analytics).

It is also important to acknowledge that subjective and objective measures in PD complement each other as each method has unique strengths and weaknesses [4]. In clinical situations, no assessment methods can replace the clinical acumen of an individual neurologist, which involves detailed history taking, and thorough examination, surpassed by observing skills. It is usually a physician's judgement to determine which method, scales or monitoring devices or a combination of both, is most appropriate to individual patient to address a particular clinical question. Therefore, we, as neurologists should be aware and ready to adopt appropriate technologies to improve the care of PD patients.

4. Future directions towards a digital health pathway in Parkinson's disease

While recent evidence has demonstrated that mobile health technologies, including wearable sensors and smartphone applications can measure targeted parameters in a more accurate and objective way, questions often arise about the extent to which such technologies can be considered a better choice than more established means of data capture. The adoption of these technologies will require complex assessment by multidisciplinary teams, with experts identified and involved as needed, while continuity and knowledge transfer within assessment teams is supported [44]. Therefore, a 'digital health pathway' has recently been proposed to support the integration of innovative healthcare technologies into the complex healthcare workflow, providing data-driven personalized decision support that is based on a combination of big data sources, including the knowledge derived from mobile health technologies [45]. This patient-centered pathway aims to support the clinical decisions of medical professionals, particularly neurologists, acting as facilitators, with other stakeholders, in the adoption of patient-centered clinically relevant digital outcomes and device selection to deliver reliable, clinically relevant insights for measurement-based care. In order to implement such a pathway in PD, dialogue is needed between patients and providers to develop understanding, action plans, and key results at different stages. Once a pathway is in place, it should provide the long-term standardization of real-life longitudinal multidimensional data from individual patients for individualized prediction, with benefits extending to individualized benchmarking, not only for the patient (individual disease status along the disease course), but also for the healthcare provider (to control for quality and efficacy of the chosen treatment paradigm), and for our PD communities (to secure best medical or surgical care for its citizens) [45].

5. Conclusion

PD is a heterogeneous disorder comprising of complex and dynamic

motor and NMS, making it difficult for clinicians to accurately measure them in spot assessments, which are ecologically invalid and dependent on often unreliable patient reports. However, PD is one of the disorders whose primary motor manifestations can be comprehensively captured in free-living environments using current smartphone technologies. Therefore, it is now theoretically possible to quantify, moment-by-moment, an individual's phenotype by using their own personal devices in their own environments. This concept of 'digital phenotyping' is proposed as an optimal tool for individualized, continuous, and reliable objective assessment in PD. However, in order to implement such digital phenotyping into the PD ecosystem, a step-wise approach is recommended by first validating a set of PDCOs with technologically affine patients who may be accustomed to this new development. While unprecedented and previously impossibly vast amounts of data can now be collected relatively easily, extracting clinically relevant information from big data emerges as one of our greatest challenges. The goal is to have ultimate outcomes that are patient-centered, with clinical relevance for measurement-based care. Machine-learning based analytics coupled with continuous data from digital phenotyping will provide a powerful new tool in the treatment of PD. Implementing PCDOs will require large collaborative efforts, but neurologists and patients working together, embracing digital technologies, will define how these new tools can be most powerfully employed in PD management.

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