

## Technology in Parkinson's Disease: Challenges and Opportunities

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**ABSTRACT:** The miniaturization, sophistication, proliferation, and accessibility of technologies are enabling the capture of more and previously inaccessible phenomena in Parkinson's disease (PD). However, more information has not translated into a greater understanding of disease complexity to satisfy diagnostic and therapeutic needs. Challenges include noncompatible technology platforms, the need for wide-scale and long-term deployment of sensor technology (among vulnerable elderly patients in particular), and the gap between the “big data” acquired with sensitive measurement technologies and their limited clinical application. Major opportunities could be realized if new technologies are developed as part of open-source and/or open-hardware platforms that enable multichannel data capture sensitive to the broad range of motor and nonmotor problems that characterize PD and are adaptable into self-adjusting, individualized treatment delivery systems. The International Parkinson and Movement Disorders Society Task Force on Technology is entrusted to convene engineers, clinicians, research-

ers, and patients to promote the development of integrated measurement and closed-loop therapeutic systems with high patient adherence that also serve to (1) encourage the adoption of clinico-pathophysiologic phenotyping and early detection of critical disease milestones, (2) enhance the tailoring of symptomatic therapy, (3) improve subgroup targeting of patients for future testing of disease-modifying treatments, and (4) identify objective biomarkers to improve the longitudinal tracking of impairments in clinical care and research. This article summarizes the work carried out by the task force toward identifying challenges and opportunities in the development of technologies with potential for improving the clinical management and the quality of life of individuals with PD. © 2016 International Parkinson and Movement Disorder Society

**Key Words:** digital health; digital biomarkers; eHealth; Parkinson's disease; precision medicine; remote monitoring; technology; wearable technology

During the past decade, a multitude of technology-based objective measures (TOMs) of parkinsonian impairments have been developed, bringing with them the promise of substantially changing the diagnostic, monitoring, and therapeutic landscape in Parkinson's disease (PD). Sensors, mobile communications, cloud computing, advanced analytics, and the Internet of Things (wireless connectivity of all electronic devices)<sup>1,2</sup> are among the innovations that have the potential to transform healthcare and our approach to patients with chronic, complex, and fluctuating disorders. With the abundance of new technologies, their growing power and versatility, and the smart algorithms on which they increasingly rely, our field needs to ponder the basic questions of why we should even consider adding alternative measures; what clinical needs should be addressed; what instruments should be used; how to deploy new technologies with minimal burden, disruption, and cost and maximal compliance; and whether they replace or complement existing resources. Unfortunately, technology develop-

ers appear to be operating in competing “islands of expertise” whose focus may be redundant, thus increasing the risk of duplicating rather than extending progress while potentially making their technologies incompatible with those of other developers. Also, not all technologies are primarily driven by burning questions from within the clinical field, sometimes creating technical solutions that—clever as they may be—remain in search of a clinical indication.

In the absence of well-established and validated biomarkers of diagnosis or disease progression, PD remains a clinically defined disease. Today, clinical scales and traditional patient-reported outcomes continue to be the primary assessment tools or endpoints in PD clinical care and research. However, there is a growing awareness that TOMs may improve the sensitivity, accuracy, reproducibility, and feasibility of objectively capturing the full complexity and diversity of changes in motor and nonmotor behaviors.<sup>3-7</sup> Examples include the difficulty to reliably evaluate fluctuating events (eg, the variable response to

medication), to capture rare incidents (eg, falls or freezing of gait), or to assess behaviors that, by definition, take place over long periods of time outside the clinical examination room (eg, physical activities in everyday life). The ability to remotely capture behavioral data and use it to optimize treatment strategies has the potential to finally “close the loop” and address critical knowledge gaps.<sup>8</sup> Despite multiple ongoing projects by stakeholders in academia and industry, it remains challenging to determine what initiatives have the capacity to be scaled up, and what type of deployment would ensure the highest yield in the future.

This review summarizes the deliberations of the International Parkinson and Movement Disorders Society Task Force on Technology. As a first step, we concentrated on assessing the landscape of wearable devices and other technologies for individualized assessments as well as the therapeutic and scientific uncertainties they stand to fill rather than on the clinical properties of any of the growing list of measurement technologies that have become available in the past 10 years. For the latter purpose, a number of reviews have been recently published.<sup>9-11</sup> The task force is entrusted with bringing together experts from the device and biopharmaceutical industry, clinicians, researchers, engineers, and patients to brainstorm on needed developments to advance PD research and care. We aim to appraise the extent to which technology and data analysis in general, and TOMs in particular, can bring robust granularity to the clinical complexity of PD to facilitate clinico-pathophysiologic phenotyping, the detection of prodromal symptoms, the improvement of diagnostic accuracy, and progression monitoring and to begin the process of integrating technology-based diagnostics and actionable pharmacological and nonpharmacological therapeutics for clinical applications.

## Definitions and Objectives

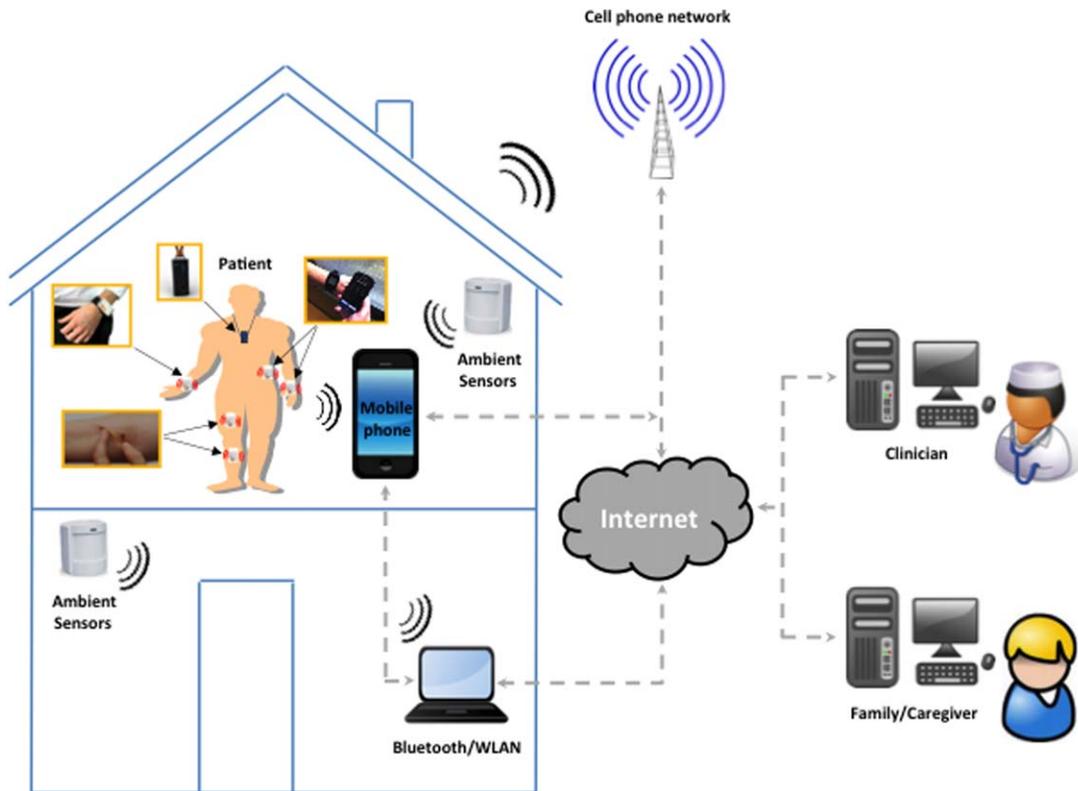
TOMs are the outcomes of device-based instrumented clinical tests conducted by clinicians in standardized environments to objectively measure specific behaviors or self-administered by patients to detect and monitor impairments in specific or overall function in everyday life. Initially, TOMs targeted motor phenomena, such as gait or balance, and were gathered in specialized movement laboratories.<sup>12</sup> More recently they have been extended to devices worn by the patient (ie, wearable sensors and systems) in the clinic and—for remote monitoring—in the home or community settings (Fig. 1).<sup>13-15</sup> The goal of wearable technologies is to maximize the “ecological” validity as well as the temporal and spatial resolution of capturing motor and nonmotor phenomena that are natu-

rally expected to change over time. As such, wearable technology may provide a more realistic portrayal of behaviors of interest in clinical and research settings.<sup>16</sup> In addition, in the research arena, increasing the temporal and spatial resolution of a targeted behavior is expected to reduce the sample size required to evaluate the effect of therapeutic interventions.<sup>17</sup>

Important goals of TOMs are to provide objective parameters in the detection and monitoring of motor and nonmotor functions, thereby enhancing the quality of treatment delivery and allowing for personalized care (Table 1). Currently available wearable technologies (such as inertial sensors and surface electromyography [EMG]) are—with variable success—capable of capturing the number and intensity of multiple activities, such as the frequency and amplitude of movements during the day and while asleep, the frequency with which tremor and dyskinesia appear and disappear during the day, and the fluctuations in the severity of gait and balance impairments.<sup>18-22</sup> The use of consumer wearable technologies in medicine is becoming increasingly more common. For instance, in the field of sleep medicine, the use of actigraphy for sleep monitoring may be used to supplant more traditional methods such as polysomnography because of its validity, lower cost, and ability to evaluate individuals in their homes during a longer period of time.<sup>23</sup> Advanced wearable technologies can also precisely monitor skin conductance, respiratory rate, blood pressure, and oximetry and provide surface EMG, electrocardiography, and electroencephalography tracings.<sup>24-29</sup> Furthermore, the ability to collect TOMs using smart devices (mobile phones, tablets, and smart watches) provides additional opportunities to collect and analyze numerous clinically relevant parameters (eg, posture, balance, dexterity, voice and speech patterns, facial expression, eye tracking, medication, and exercise compliance and adherence) and develop communication portals to improve patient engagement and self-management.

### Caveat Emptor: Why Measure at All?

The often-implied assumption that the sole existence of a PD symptom justifies its measurement and that all PD-related phenomena should be measured must be dispelled. A measure is justified if it enhances our understanding of a complex disease or aids in testing or delivering a therapy. The use of measurements to improve therapy is filled with rich examples from other branches of medicine (eg, glucose monitoring for insulin pumps, cardiac defibrillators). It should be remembered that every qualitative clinical assessment is a form of measurement and that the use of quantitative measures carries the potential for improving the decision-making process as to the need and dose of therapy. Implicit however is that what is being



**FIG. 1.** Schematic representation of a subject undergoing monitoring in the home setting using wearable and ambient sensors. The technology shown includes a wireless unit strapped around the wrist, Band-Aid-like sensors attached to the lower limbs, a wearable camera worn as a pendant, a smart watch, and a mobile phone clipped on the belt used as gateway to relay the data to the cloud to assess specific functions (using its embedded sensors) as well as to communicate with the patient (using customized apps). Ambient sensors and computer technologies are used in the home settings to gather additional information or replace wearable sensors when wearable sensors cannot be used. The integration of wearable technology with smart devices enables the remote monitoring of patients with PD and real-time feedback to clinicians, family/caregivers, and the patients themselves. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

**TABLE 1.** Examples of available and needed technologies relevant to the diagnosis and clinical management of patients with Parkinson's disease

Clinical problem	Available/needed technologies	Clinical objective
Improving diagnosis	Needed: sensors for prodromal features (e.g., constipation, REM sleep behavior, anosmia); blood sensors for biomarkers ( $\alpha$ -synuclein, proteinomics, etc.)	Enable population screening for PD, including the earliest possible (prodromal) stages
Monitoring response to therapy and motor complications (motor fluctuations, dyskinesia)	Available: accelerometers, gyroscopes, magnetometers, electrogoniometers, surface EMG sensors Needed: small patches onto the skin or other sensors that improve patient adherence	Collect ecologically valid data of motor fluctuations, falls, freezing of gait episodes Implement sensor-based closed-loop technologies capable of delivering treatments (eg, infusion pump)
Monitoring nonmotor symptoms and progression	Available (but requiring improvements): sweat sensors, skin conductance sensors, heart rate sensors, blood pressure sensors	Collect ecologically valid data of nonmotor symptoms and progression
Improving medical treatment	Available (but requiring improvements): oral capsules, subcutaneous and gastrointestinal infusion pumps	Implement adjustable extended-release drug formulations, smart (self-adjusting) levodopa delivery infusion systems
Enhancing surgical treatment	Available (but requiring improvements): STN DBS, GPi DBS, Vim thalamus DBS	Implement closed-loop STN and GPi DBS (variable stimulation based on local field potentials)
Improving rehabilitation interventions	Available: accelerometers, gyroscopes, magnetometers, electrogoniometers, surface EMG sensors, pulse oximetry sensors, respiratory rate sensors, blood pressure sensors	Implement closed-loop cueing and feedback systems validated for home use

DBS, deep brain stimulation; EMG, electromyography; GPi, globus pallidus pars interna; PD, Parkinson's disease; REM, rapid eye movement; STN, subthalamic nucleus; Vim, ventrointermedial nucleus.

measured represents a therapeutic target and hence the measurement must be relevant to the treatment question (Table 1).

### The Case for Multidomain, Multisensor, Integrated Technology

PD is characterized by considerable inter- and intra-subject clinical variability in clinical symptoms. What matters most for one patient in the motor sphere may not be as important for another (eg, tremor vs. freezing of gait vs sleep disturbance) given the different levels of functional disability.<sup>30</sup> Fluctuations in daily functioning in some patients may only include nonmotor phenomena (eg, fatigue or anxiety).<sup>31</sup> Even if we were to accurately measure the most overt deficit, most patients display a repertoire of motor and nonmotor endpoints that vary within and between days, with varying impacts on their quality of life.<sup>32</sup> Thus, a multidomain, multisensor, smart technology is needed to determine the source of all relevant changes, identify individualized disease fingerprints, and develop truly personalized therapeutic approaches.

## Challenges

### The Need for Monitoring Nonmotor Symptoms

The development of wearable systems to monitor individuals with PD has focused heavily on motor aspects of the disease (eg, tremor, bradykinesia, gait impairment, and dyskinesia)<sup>33-35</sup> that are also, albeit with lower sensitivity and specificity, evaluated by clinical scales. Despite recent advances in the quantification of motor symptoms such as tremor, these endpoints often bear only modest quantitative agreement with measures of quality of life.<sup>36,37</sup> Indeed, patient priorities and sources of disability often arise from nonmotor deficits (eg, depression, anxiety, fatigue, orthostatic hypotension, sleep disturbance). Unfortunately, relatively few studies have thus far focused on capturing the fluctuations of these complex disease manifestations, marked by high variability within and between days.<sup>38,39</sup> The development of TOMs for nonmotor endpoints has relied on labor-intensive or computerized, laboratory-based measurements (eg, cognitive function, heart-rate variability, blood pressure changes, or sleep).<sup>40,41</sup> There is an urgent need for developing unobtrusive systems to monitor nonmotor endpoints in the home and community settings.

### Limitations of Sensors Used to Monitor Motor Symptoms

Biomechanical sensors such as accelerometers, gyroscopes, and magnetometers are well suited for the detection of tremor, bradykinesia, gait impairment, and motor complications, such as dyskinesia. However, data collected in the home and community

settings using these sensors do not always provide sufficient information to achieve a reliable clinical assessment of motor symptoms. For instance, it is difficult to infer from the sensor data alone if slowness of movement (as detected using biomechanical sensors) can be used as a proxy of bradykinesia or is the result of fatigue or other factors related to the context in which a motor task is performed (eg, slow walking because of fear of falling). Also, the resolution of biomechanical sensors is restricted to the anatomical area on which they are applied, which may yield low quantitative agreement with the wider range of motor disability, quality of life, and other measurable patient-relevant endpoints.<sup>36,37</sup>

### Discrepancy Between Clinical Needs and Research

Endpoints that may be ideally suited for a clinical study may not necessarily be relevant or applicable in clinical care. The relevance of specific TOMs to assessing the impact of parkinsonian symptoms on a patient's quality of life may be difficult to evaluate. For instance, fluctuations in motor symptoms and complications such as dyskinesia may have a complex quantitative relationship with measures of disability.<sup>42</sup> In addition, the measurement target and timeline of data capture differ depending on the goals of a study. For example, an instrumented test that captures finger tapping over several hours may suffice to track the immediate response to a dopaminergic therapy. However, monitoring disease progression over time involves more complex targets and longer data collection, such as physical activity levels, gait speed, frequency of falls and near fall events, as well as a variety of periodic or continuously gathered measures of motor, cognitive, or other nonmotor functions. In many cases, the accuracy and reliability of these TOMs may not yet be sufficient to justify their deployment in phase III clinical trials.

### Lack of Compatibility Among Wearable Systems

Most wearable systems developed to monitor individuals with PD are not compatible with one another. As a result, it may be cumbersome or impossible to combine data gathered by TOMs developed by different manufacturers. This makes it difficult to guide behavioral changes or therapeutic interventions. Furthermore, devices developed by different manufacturers for the same purpose may not always yield the same result, raising questions about the validity of the mathematical algorithms that govern the data processing. Few currently available systems gather synchronized data from multiple body segments before transfer to a computer for whole-body analysis<sup>43</sup> in a way that

**TABLE 2.** Limitations of existing technology-based objective measures (TOMs) and opportunities for the development of new TOMs using wearable technology

Limitations	Main roadblocks	Opportunities
Limited measurement	Low spatial resolution Single sensor data capture	Multiple sensors Recording multiple motor and nonmotor behaviors Measure their natural variability
Open-loop data capture	Failure to connect to other sensors or inform treatment	Continuous feedback into a closed-loop system that dictate treatment changes
High burden-to-value ratio	The larger the number of sensors used, the more significant is the negative impact on activities and adherence	Minimally obtrusive, continuously sensing systems Improve compliance Less missing data Lower cost of care
Noninteractivity	Off-line and unidirectional (ie, clinician to patient) feedback modalities are not effective	Increasing real-time interaction between patient and data and between patient and clinician Decrease need for in-person clinical visits Personalize and improve patient care
Multiplicity of technology platforms	Too many incompatible devices Duplicative efforts Poor comparability of measures Limited interoperability	Standardization of platform Increasing TOM sensitivity <sup>a</sup> Increasing TOM reliability Decreasing measurement errors More contextual information

<sup>a</sup>However, small changes of particularly sensitive measures may not necessarily be clinically relevant (eg, levodopa-induced, peak-dose dyskinesia could vary in amplitude but not bear a significant impact on disability because of the nonlinear relationship between amplitude of dyskinesic movements and disability).

is fully compatible with the simultaneous use of platforms developed by different manufacturers.

### Limitations of Available Analytical Methods

Despite our ability to collect and store extremely large datasets of TOMs, our ability to algorithmically analyze and synthetically display clinically and disease-relevant information to physicians and patients remains limited. Here, clinical expertise is needed, for instance, to eliminate the “clinical noise” in the data analytical efforts. In addition, technical expertise is needed so that the field can take advantage of the tremendous advances that have been achieved during the past 2 decades in research areas such as signal processing and machine learning. Data analysis techniques that leverage advances in these research areas are important to achieving clinically meaningful TOMs.

### Practical Limitations in User Engagement

Software and hardware components of wearable systems are often not as user friendly or compelling to adopt as they should be.<sup>44</sup> Currently, patient and caregiver engagement with wearable and mobile technology is modest, as shown by a recent study demonstrating that 32% of users stop using wearables after 6 months, and 50% after slightly more than a year.<sup>45</sup> Similarly, there is a high dropout rate among smartphone apps users: 26% of apps are used only once and 74% of apps are not used more than 10 times.<sup>45,46</sup> Lack of motivation to use wearables/self-monitoring systems should not be underestimated, particularly in the absence of meaningful feedback provided to their users. Preliminary evidence suggests

that patient empowerment and their inclusion as active players in the development of research activities may favorably impact compliance.<sup>47</sup> Research is needed to determine the characteristics of wearable systems for long-term monitoring of motor and non-motor symptoms that would be acceptable to patients. In particular, we need to ascertain the number of sensors needed to accurately monitor PD symptoms without negatively affecting compliance in a clinical context.

## Opportunities

Wearable systems provide the opportunity to measure and monitor the individual variability of motor and nonmotor phenomena, minimize rater bias, and increase sensitivity to subclinical but possibly relevant physiologic changes (Table 2).<sup>4,10,48,49</sup>

### Standard Measurement Platform

Several companies have tested or are in the process of assessing a variety of methods to probe individual motor and nonmotor constructs. To avoid duplication of investments and efforts, an opportunity exists to identify the technologies and approaches with most versatility, greatest ease of deployment, least patient and physician encumbrance, and lowest cost. It should no longer be a question of whether a given motor phenomenon can be measured in yet a different manner (which it can), but how to choose a standard platform of TOMs behind which developers and end-users can coalesce. Efforts toward standardization—guided by the Movement Disorders Society Task Force on

Technology but endorsed or sanctioned by regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA)—will greatly facilitate technology adoption and the integration of different systems.

### Multidomain Measurements

With different types of disabilities comes the need for tailored measurement approaches to support the design of individualized interventions. Tremor measurement may be completely irrelevant to individuals with an akinetic or postural-instability gait-disorder phenotype of PD. Continuous step monitoring to capture freezing of gait episodes would be futile in patients without gait impairment. Systems that are designed for multidomain data capture could provide researchers and clinicians with the flexibility of choosing the sensors to monitor individuals with different phenotypes of PD. In exploratory studies, an approach based on multidomain data capture would increase the likelihood of finding relevant changes in one of the many channels of the system. This approach would also provide the opportunity for assessing correlated effects of symptoms of interest across other domains.

### Better Phenotyping and Subtyping

Tremor and tremorless (akinetic/postural-instability gait-disorder) variants of PD are grossly defined clinical phenotypes based on mainly observational evidence, with substantial heterogeneity.<sup>50</sup> Besides these clinical phenotypes, there likely exist several disease subtypes defined by autonomic, cognitive, or other domains of disability that could be captured by multi-channel systems.<sup>51</sup> In addition, it is conceivable that the greater resolution of TOMs may detect novel phenomena that could serve to more sensitively stratify certain PD subtypes and serve as (or assist in the development of) biomarkers of disease progression.

### Precision Medicine

By identifying areas of dysfunction and their relationship with therapy, TOMs can be used to provide customized feedback to individual patients and possibly stratify criteria that predict the responsiveness to distinct treatment paradigms in a way that is similar to how consumer-based wearable devices already measure level of activity, sleep disturbances, and so on. Smart algorithms could be developed to generate specific recommendations that would be made available directly to patients and clinicians to motivate changes in treatment and lifestyle-related behaviors, tailored to each person's specific individual needs and disabilities. This approach would provide value for end-users (both patients and their care team) and thereby improve adherence.

### Closed-Loop (Feedback) Systems

Data collected using wearable sensors could be used to trigger device-based interventions. Much as electrocardiography sensing is used in cardiac defibrillators to trigger the delivery of stimulation pulses, data collected from sensors positioned on the limbs and trunk could be used to predict, for instance, the onset of a freezing episode. The system may detect an increase in cadence with a corresponding decrease in step length or a change in frequency of the lower leg oscillations.<sup>34</sup> The detection of such motor behaviors could trigger a device designed to deliver proprioceptive cues that could lead to a change in postural control and stepping pattern, which in turn could prevent a fall.<sup>43,52,53</sup>

### Real-Time Symptom Tracking

TOMs could offer real-time, continuously captured, rater-independent data in contrast with clinical assessments that rely on subjective information gathered during sporadic, in-clinic evaluations.<sup>54</sup> Continuous monitoring of parkinsonian symptoms could replace diary-based recordings of fluctuations and be used to track periods of OFF, OFF with dystonia or dyskinesia (not currently captured using the Hauser diary), ON, and ON with dyskinesia over the time span of several days.

### The Promise of Remote Monitoring

TOMs based on the use of wearable systems could improve healthcare delivery by providing assessment data when patients are not in the clinic. This possibility is particularly relevant for individuals with PD who live in areas with limited access to care. TOMs could provide ecologically valid data to help clinicians monitor responses to therapy and individualize management to optimize outcomes.<sup>49</sup> Remote monitoring also offers the opportunity for healthcare cost reduction.<sup>8</sup>

### Better Monitoring, Better Patient Engagement, Better Outcomes

Innovation in sensor and communication technologies alongside mobile connectivity has enabled a process of medical democratization.<sup>1</sup> The creation or support of TOMs for remote, continuous monitoring provides an opportunity for healthcare providers to scale and extend services offered to patients to better manage their health.<sup>55</sup> TOMs can capture meaningful aspects of function that improve personalized patient care through an intuitive, interconnected, and energy-efficient interface.<sup>56,57</sup>

### Potential Pitfalls in Developing TOMs

#### Clinimetric Validation Pitfall

A number of studies have focused on developing methods to derive TOMs that parallel the clinical

assessment scales commonly used in clinics. These are important but potentially misguided efforts toward validating new TOMs in the clinic or home settings by attempting to force a simple quantitative agreement with widely used, previously validated subjective rating scales or questionnaires. However, it could be argued that, in theory, a “perfect” objective measurement should have a complicated quantitative match with an “imperfect” subjective one. This is because a clinical rater integrates many sources of information to produce a subjective score, including prior experience and expectations. So there is no a priori reason to believe that assessments performed by clinical raters would lead to a simple quantitative agreement with data features derived from sensor data. Indeed, the relationship between TOMs and subjective clinical scores may be highly complex and extremely difficult to ascertain in practice.

To the extent that we are seeking more sensitive and ecologically valid technologies, TOMs may agree only loosely with clinical scales. An important aim of TOMs is to improve on, rather than act as surrogates of, previously developed clinical scales. As these are developed, clinicians and regulatory agencies will need to consider that a new TOM that appears to provide clinically relevant measures of movement characteristics, but which does not correlate with the motor section of the Unified Parkinson Disease Rating Scale, for example, could be accepted as valid on the basis of its own merits if it can accurately represent patient-relevant endpoints. Engineers and clinicians alike should be reminded to think outside the box and use the power of the technology to develop new scoring paradigms rather than solely generate sensor-based versions of existing clinical scores.

### Ecological Validity Pitfall

Efforts in ensuring validity, or the degree to which we are truly measuring what we intend to measure, increase in complexity with proliferating technologies, evolving in different platforms and on different targets with unclear ecological and clinical relevance. To this end, before developing new TOMs, researchers would need to determine which constructs generated by routine clinical observations, and standardized by clinical scales and medical devices, are truly relevant to patients within such domains and are meaningful contributors to the performance of activities of daily living. For example, if “dyskinesia” is not relevant as a construct to patients and is not a significant contributor to the performance of activities of daily living in their ecological environment, do we invest in maintaining its primacy in future technologies? Efforts to ensure system interoperability and to build open data repositories will help distinguish relevant from futile TOMs.

### “Big Data” Pitfall

It has been demonstrated that an abundance of behavioral data can be captured from individuals and populations using largely unstructured, crowd-sourced efforts. These data may differentiate populations of loosely defined PD (on the basis of generic measures of movement abnormalities) from healthy individuals. However, although these measures can provide valuable background information at the population and community levels, they cannot substitute for a careful neurological examination, deep clinical phenotyping, and assessment via laboratory studies. At best, they complement but do not replace the phenomenological and pathophysiological granularity required for PD subtyping, much less predict the response of an individual to treatment. Ultimately, the reproducibility and responsiveness of individually selected TOMs confirmed beyond small pilot studies and accounting for contextual information and confounders, should prevail over simply obtaining a large body of population-level data.

### Preparing for TOMs in Clinical Care and the Research Setting

Wearable systems that are used to gather TOMs in the home and community settings could generate real-time, accurate, sensitive, and rich datasets including contextual information and data such as the time of medication, food intake, and location information. Although TOMs are typically derived from wearable sensors, contextual information is captured using companion applications (eg, mobile apps and web-based applications). Wearable systems that are used to gather TOMs also provide an opportunity for multi-directional interactions among investigators/clinicians and patients/caregivers at a reasonable cost. In the clinical care setting, the use of wearable systems to generate TOMs could decrease the need for outpatient visits while maintaining high-quality care and high patient engagement. Likewise, the integration of TOMs with virtual-visit interfaces has the potential to greatly improve the accuracy and value of telemedicine visits. In the clinical research setting, the use of wearable systems could enhance protocol adherence and patient compliance, leading to fewer missing data points. Also, an appropriate choice of TOMs could lead to prospectively collecting data with a high signal-to-noise ratio (with regard to the effect size of interest) hence reducing the required sample size and the resulting study costs. The composite of TOMs, companion applications designed to gather contextual information and pharmacogenomics could enable precision medicine interventions.<sup>58</sup>

## Integrating Technologies

The development of new TOMs is currently advancing in isolated silos rather than as part of concerted actions aimed to implement open platforms. The development of open platforms would be highly desirable in the context of obtaining comprehensive information on patients and populations of interest. An open platform may not yet be fostered by the brave new world of health-driven technologies. However, there are reasons for optimism. Although in the traditional medical device market, short-term financial forces drive the creation of proprietary measuring instruments at the expense of multichannel, interconnected systems, consumer-driven market forces are pushing heavily in the opposite direction, that is, toward the development of open technology platforms. As consumer technologies evolve to achieve the clinimetric sophistication required for application in the clinical management of individuals with PD, the move toward shared, interoperable software and hardware for applications in research and clinical practice is also emerging.

## Smart Delivery of Treatment

Justification for the development and adoption of TOMs is strongest when presented in the context of improving the clinical management of individuals with PD. TOMs can be used as part of closed-loop systems designed to assist in the controlled delivery of medications. The development of such systems requires manufacturing high-performance, energy-efficient, and energy-harvesting sensors and storage modules.<sup>59</sup> In this context, the development of nanomembranes and stretchable electronics on a polymeric substrate for intimate mechanical contact with soft tissue has been proposed.<sup>60</sup> A critical unmet need is the ability to connect multisensor diagnostics to self-guided therapies in a closed-loop system. In the field of neuromodulation, deep brain stimulation (DBS) electrodes may also act as sensors capable of recording local field potentials (for the presence or absence of beta-band oscillations) to automatically program the amplitude and frequency of stimulation, thus effectively closing the loop between measuring and treating.<sup>61</sup>

Objective measures of specific movement impairments can also be used to tailor therapy. Proof of concept systems have been developed to predict the onset of pathological tremor using surface electromyographic and acceleration data, which could inform the design of the next generation of noninvasive closed-loop predictive ON-OFF controllers for DBS.<sup>62,63</sup> In the realm of physical rehabilitation, subtle asymmetries in gait, limitations in joint range of motion, or excessive postural sway indicating poor balance may be difficult to observe clinically but can be addressed by rehabilitation specialists when identified using

TOMs. Through TOMs, therapists could personalize the therapy prescribed to each individual.<sup>43</sup> A simple clinical measure such as the time needed to walk a specified distance does not provide the therapist with an understanding of the spatial and temporal gait performance or the musculoskeletal and dynamic balance characteristics that cause poor mobility. These factors could be captured using TOMs and hence guide the choice of appropriate therapeutic approaches. Longitudinal monitoring of TOMs also has the potential for identifying small improvements or declines related to the intervention or the progression of the disease that could lead to changes in the prescribed rehabilitation intervention.

## Regulatory Needs and Commercialization

We anticipate that TOMs will eventually be routinely used in both clinical practice and research settings. Despite the promise of greater sensitivity and the presumed accuracy of collected data, regulatory validation of TOMs as efficacy and safety measures will require dedicated studies. The path to marketing for TOMs appears long and risky considering the short lifecycle of technological innovation and the costs associated with their development. Unlike drug development, where there is substantial precedent and a regimented path for marketing authorization, commercialization, and license protection, the path for TOMs and digital health solutions remains to be defined. It is critical that key stakeholders share the costs and financial rewards of technology development, implementation, and maintenance to accelerate and preserve innovation and growth. Despite opportunities to meet all stakeholder needs, the business model for development and deployment of TOMs in healthcare remains to be determined. Currently, healthcare payers show little incentive to financially reimburse TOMs despite the promise for healthcare cost reduction, population management, and delivery of high-quality, efficient care. The lack of incentive may be driven by initial expenditures and the complexity of a rapidly evolving, but not yet fully integrated, technology market. Providers are also reluctant to fully adopt TOMs despite early evidence that they can improve patient outcomes and lead to overall improved care and patient satisfaction. Clinicians may not yet view TOMs as an opportunity to support clinical decision making and increase productivity. Patients are also reluctant to pay out of pocket despite opportunities for improved access to better care and better outcomes. Building a solid business case—including properly designed cost-effectiveness studies—is much needed. A value-based care approach could be an attractive solution in which deployment of TOMs is funded as part of an integrated care solution where providers are rewarded for good outcomes per

invested dollar and in which the decision to engage TOMs is left to the providers and patients. Finally, in addition to funding agencies, regulatory bodies such as the FDA and the EMA should increase efforts toward establishing programs that encourage the adoption of standards aimed to assure interoperability of wearable systems and the development of open data repositories.

### Integration Into Medical Care and Reimbursement

Payers do not yet provide reimbursement for medical services provided by TOMs and companion apps. This limits the rate of innovation and the opportunities for integration of TOMs into medical care. Establishing reimbursement mechanisms will require demonstration that, along with the enhancements in diagnostics and therapeutics, TOMs can be integrated in quality-control concepts, help reduce costs and time, and improve the quality of life for patients while guarding against privacy concerns. Quantifying clinical benefits of interventions using TOMs is anticipated to become increasingly important in healthcare as the allocation of resources is expected to be tied to objective outcome measures.

### Conclusions and Next Steps

Despite challenges, the continuous improvements in technological sophistication, versatility, and wearability of sensors have created opportunities to collect disease-relevant data using targets consequential to patients and sensitive to PD-specific symptoms and milestones. To translate these opportunities into enhanced care, better self-management options for PD patients, and overall improved healthcare outcomes, technologies will need to be (1) developed as open platforms and integrated with electronic medical record systems, (2) suitable for the acquisition of data that captures motor and nonmotor phenomena, and (3) integrated in treatment delivery systems. The International Parkinson and Movement Disorders Society Task Force on Technology aims at reversing the current model of simply adapting available technologies to meet patient management and research endpoints. As such, the task force will assist in improving the academic and regulatory environments for technology developers by encouraging the sanctioning of open standard platforms for technology-based measurements and treatments by, for example, the FDA and EMA. This collaborative endeavor will encourage the development of integrated, multichannel, and in many instances closed-loop feedback systems that can achieve more sophisticated clinico-pathophysiologic characterization, better informed tailoring of symptomatic therapy, greater patient engagement and self-

assessment, and better subgroup targeting of patients for testing of future disease-modifying treatments. ■

### References

1. Pasluosta CF, Gassner H, Winkler J, Klucken J, Eskofier BM. An emerging era in the management of parkinson's disease: wearable technologies and the internet of things. *IEEE J Biomed Health Inform* 2015;19(6):1873–1881.
2. Wang H, Jafari R, Zhou G, et al. Guest Editorial: Special Issue on Internet of Things for Smart and Connected Health. *IEEE IoT J* 2015;2(1):1–4.
3. Ozinga SJ, Machado AG, Miller Koop M, Rosenfeldt AB, Alberts JL. Objective assessment of postural stability in Parkinson's disease using mobile technology. *Mov Disord* 2015;30(9):1214–1221.
4. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Mov Disord* 2013;28(11):1544–1551.
5. Mariani B, Jimenez MC, Vingerhoets FJ, Aminian K. On-shoe wearable sensors for gait and turning assessment of patients with Parkinson's disease. *IEEE Trans Biomed Eng* 2013;60(1):155–158.
6. Cavanaugh JT, Ellis TD, Earhart GM, Ford MP, Foreman KB, Dibble LE. Capturing ambulatory activity decline in Parkinson's disease. *J Neurol Phys Ther* 2012;36(2):51–57.
7. Rahimi F, Bee C, Duval C, et al. Using ecological whole body kinematics to evaluate effects of medication adjustment in Parkinson disease. *J Parkinsons Dis* 2014;4(4):617–627.
8. Papapetropoulos S, Mitsi G, Espay AJ. Digital health revolution: is it time for affordable remote monitoring for Parkinson's disease? *Front Neurol* 2015;6:34.
9. Shull PB, Jirattigalachote W, Hunt MA, Cutkosky MR, Delp SL. Quantified self and human movement: a review on the clinical impact of wearable sensing and feedback for gait analysis and intervention. *Gait Posture* 2014;40(1):11–19.
10. Maetzler W, Domingos J, Sruojis K, Ferreira JJ, Bloem BR. Quantitative wearable sensors for objective assessment of Parkinson's disease. *Mov Disord* 2013;28(12):1628–1637.
11. Bonato P. Wearable sensors and systems. From enabling technology to clinical applications. *IEEE Eng Med Biol Mag* 2010;29(3):25–36.
12. Espay AJ, Giuffrida JP, Chen R, et al. Differential response of speed, amplitude, and rhythm to dopaminergic medications in Parkinson's disease. *Mov Disord* 2011;26(14):2504–2508.
13. Goetz CG, Stebbins GT, Wolff D, et al. Testing objective measures of motor impairment in early Parkinson's disease: feasibility study of an at-home testing device. *Mov Disord* 2009;24(4):551–556.
14. Klucken J, Barth J, Kugler P, et al. Unbiased and mobile gait analysis detects motor impairment in Parkinson's disease. *PLoS ONE* 2013;8(2):e56956.
15. Chen BR, Patel S, Buckley T, et al. A web-based system for home monitoring of patients with Parkinson's disease using wearable sensors. *IEEE Trans Biomed Eng* 2011;58(3):831–836.
16. Stamford JA, Schmidt PN, Friedl KE. What engineering technology could do for quality of life in Parkinson's disease: a review of current needs and opportunities. *IEEE J Biomed Health Inform* 2015;19(6):1862–1872.
17. Guo Y, Graber A, McBurney RN, Balasubramanian R. Sample size and statistical power considerations in high-dimensionality data settings: a comparative study of classification algorithms. *BMC Bioinformatics* 2010;11:447.
18. Roy SH, Cole BT, Gilmore LD, et al. High-resolution tracking of motor disorders in Parkinson's disease during unconstrained activity. *Mov Disord* 2013;28(8):1080–1087.
19. Mera TO, Burack MA, Giuffrida JP. Quantitative assessment of levodopa-induced dyskinesia using automated motion sensing technology. *Conf Proc IEEE Eng Med Biol Soc* 2012;2012:154–157.
20. Das S, Trutoiu L, Murai A, et al. Quantitative measurement of motor symptoms in Parkinson's disease: a study with full-body motion capture data. *Conf Proc IEEE Eng Med Biol Soc* 2011;2011:6789–6792.
21. Shen X, Mak MK. Technology-assisted balance and gait training reduces falls in patients with Parkinson's disease: a randomized

- controlled trial with 12-month follow-up. *Neurorehabil Neural Repair* 2015;29(2):103–111.
22. Weiss A, Herman T, Giladi N, Hausdorff JM. Objective assessment of fall risk in Parkinson's disease using a body-fixed sensor worn for 3 days. *PLoS ONE* 2014;9(5):e96675.
  23. McCall C, McCall WV. Comparison of actigraphy with polysomnography and sleep logs in depressed insomniacs. *J Sleep Res* 2012;21(1):122–127.
  24. Liu G, Ho C, Slapetty N, et al. A wearable conductivity sensor for wireless real-time sweat monitoring. *Sensors Actuat B Chem* 2016; 227:35–42.
  25. Caldara M, Colleoni C, Guido E, Re V, Rosace G. Optical monitoring of sweat pH by a textile fabric wearable sensor based on covalently bonded litmus-3-glycidoxypropyltrimethoxysilane coating. *Sensors Actuat B Chem* 2016;222:213–220.
  26. Cazalé A, Sant W, Ginot F, et al. Physiological stress monitoring using sodium ion potentiometric microsensors for sweat analysis. *Sensors Actuat B Chem* 2016;225:1–9.
  27. Solla P, Cadeddu C, Cannas A, et al. Heart rate variability shows different cardiovascular modulation in Parkinson's disease patients with tremor dominant subtype compared to those with akinetic rigid dominant subtype. *J Neural Transm* 2015:1–6.
  28. Sommerauer M, Imbach LL, Jarallah M, Baumann CR, Valko PO. Diminished event-related cortical arousals and altered heart rate response in Parkinson's disease. *Mov Disord* 2015;30(6):866–870.
  29. Hellman AM, Shah SP, Pawlowski SM, Duda JE, Morley JF. Continuous non-invasive monitoring to detect covert autonomic dysfunction in Parkinson's disease. *Parkinsonism Relat Disord* 2015; 21(7):723–728.
  30. Nieuwboer A, De Weerd W, Dom R, Lesaffre E. A frequency and correlation analysis of motor deficits in Parkinson patients. *Disabil Rehabil* 1998;20(4):142–150.
  31. Brun L, Lefaucheur R, Fetter D, et al. Non-motor fluctuations in Parkinson's disease: prevalence, characteristics and management in a large cohort of parkinsonian outpatients. *Clin Neurol Neurosurg* 2014;127:93–96.
  32. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. *Mov Disord* 2005;20(suppl 11):S11–S16.
  33. Patel S, Lorincz K, Hughes R, et al. Monitoring motor fluctuations in patients with Parkinson's disease using wearable sensors. *IEEE Trans Inf Technol Biomed* 2009;13(6):864–873.
  34. Moore ST, Yungher DA, Morris TR, et al. Autonomous identification of freezing of gait in Parkinson's disease from lower-body segmental accelerometry. *J Neuroeng Rehabil* 2013;10:19.
  35. Lee SI, Daneault J-F, Golabchi FN, et al. A novel method for assessing the severity of levodopa-induced dyskinesia using wearable sensors. In: *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE. Conf Proc IEEE Eng Med Biol Soc*; 2015:8087–8090.
  36. Ellis T, Cavanaugh JT, Earhart GM, Ford MP, Foreman KB, Dibble LE. Which measures of physical function and motor impairment best predict quality of life in Parkinson's disease? *Parkinsonism Relat Disord* 2011;17(9):693–697.
  37. Berganzo K, Tijero B, Gonzalez-Eizaguirre A, et al. Motor and non-motor symptoms of Parkinson's disease and their impact on quality of life and on different clinical subgroups. *Neurologia* 2014; pii: S0213-4853(14)00233-3, doi: 10.1016/j.nrl.2014.10.010.
  38. Dubey H, Goldberg JC, Abtahi M, Mahler L, Mankodiya K. Echo-Wear: smartwatch technology for voice and speech treatments of patients with Parkinson's disease. In: *Proceedings from the Conference on Wireless Health*. ACM, New York, NY, USA; 2015.
  39. Bayestehtashk A, Asgari M, Shafran I, McNames J. Fully automated assessment of the severity of Parkinson's disease from speech. *Comput Speech Lang* 2015;29(1):172–185.
  40. Maetzler W, Liepelt I, Berg D. Progression of Parkinson's disease in the clinical phase: potential markers. *Lancet Neurol* 2009;8(12):1158–1171.
  41. Valappil RA, Black JE, Broderick MJ, et al. Exploring the electrocardiogram as a potential tool to screen for premotor Parkinson's disease. *Mov Disord* 2010;25(14):2296–2303.
  42. Hung SW, Adeli GM, Arenovich T, Fox SH, Lang AE. Patient perception of dyskinesia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2010;81(10):1112–1115.
  43. Horak F, King L, Mancini M. Role of body-worn movement monitoring technology for balance and gait rehabilitation. *Phys Ther* 2015; 95(3):461–470.
  44. Fisher JM, Hammerla NY, Rochester L, Andras P, Walker RW. Body-worn sensors in Parkinson's disease: evaluating their acceptability to patients. *Telemed J E Health* 2016;22:63–69.
  45. Ledger D, McCaffrey D. Inside wearables: how the science of human behavior change offers the secret to long-term engagement. In: LLC EP, Dan Ledger and Daniel McCarey, eds. *Endeavour Partners LLC*; Cambridge, MA, 2014;1–17.
  46. Consumer Intelligence Series: The Wearable Future. Pricewaterhouse Coopers. <http://www.pwc.com/us/en/retail-consumer/publications/assets/pwc-cis-wearable-future.pdf>
  47. Ferreira JJ, Godinho C, Santos AT, et al. Quantitative home-based assessment of Parkinson's symptoms: the SENSE-PARK feasibility and usability study. *BMC Neurol* 2015;15:89.
  48. Lieber B, Taylor BE, Appelboom G, McKhann G, Connolly ES Jr. Motion sensors to assess and monitor medical and surgical management of Parkinson disease. *World Neurosurg* 2015;84(2):561–566.
  49. Arora S, Venkataraman V, Zhan A, et al. Detecting and monitoring the symptoms of Parkinson's disease using smartphones: a pilot study. *Parkinsonism Relat Disord* 2015;21(6):650–653.
  50. Thenganatt MA, Jankovic J. Parkinson disease subtypes. *JAMA Neurol* 2014;71(4):499–504.
  51. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB. New clinical subtypes of parkinson disease and their longitudinal progression: a prospective cohort comparison with other phenotypes. *JAMA Neurol* 2015;72(8):863–873.
  52. Mazilu S, Calatroni A, Gazit E, Mirelman A, Hausdorff JM, Troster G. Prediction of freezing of gait in parkinson's from physiological wearables: an exploratory study. *IEEE J Biomed Health Inform* 2015;19(6):1843–1854.
  53. Bachlin M, Plotnik M, Roggen D, et al. Wearable assistant for Parkinson's disease patients with the freezing of gait symptom. *IEEE Trans Inf Technol Biomed* 2010;14(2):436–446.
  54. Rampp A, Barth J, Schulein S, Gassmann KG, Klucken J, Eskofier BM. Inertial sensor-based stride parameter calculation from gait sequences in geriatric patients. *IEEE Trans Biomed Eng* 2015; 62(4):1089–1097.
  55. Mendiola MF, Kalnicki M, Lindenauer S. Valuable features in mobile health apps for patients and consumers: content analysis of apps and user ratings. *JMIR Mhealth Uhealth* 2015;3(2):e40.
  56. Hubble RP, Naughton GA, Silburn PA, Cole MH. Wearable sensor use for assessing standing balance and walking stability in people with Parkinson's disease: a systematic review. *PLoS ONE* 2015; 10(4):e0123705.
  57. Del Din S, Godfrey A, Rochester L. Validation of an accelerometer to quantify a comprehensive battery of gait characteristics in healthy older adults and Parkinson's disease: toward clinical and at home use. *IEEE J Biomed Health Inform* 2015 [Epub ahead of print].
  58. FirstWord. *Patient-Centric Mobile Apps: Key Opportunities and Challenges for Pharma*. Doctor's Guide Publishing Limited; 2015. [http://www.fwreports.com/patient-centric-mobile-apps-key-opportunities-and-challenges-for-pharma/#.Vw1\\_mWQrL-Y](http://www.fwreports.com/patient-centric-mobile-apps-key-opportunities-and-challenges-for-pharma/#.Vw1_mWQrL-Y)
  59. Zheng YL, Ding XR, Poon CC, et al. Unobtrusive sensing and wearable devices for health informatics. *IEEE Trans Biomed Eng* 2014;61(5):1538–1554.
  60. Son D, Lee J, Qiao S, et al. Multifunctional wearable devices for diagnosis and therapy of movement disorders. *Nat Nanotechnol* 2014;9(5):397–404.
  61. Quinn EJ, Blumenfeld Z, Velisar A, et al. Beta oscillations in freely moving Parkinson's subjects are attenuated during deep brain stimulation. *Mov Disord* 2015;30:1750–1758.
  62. Basu I, Graupe D, Tuninetti D, et al. Pathological tremor prediction using surface electromyogram and acceleration: potential use in "ON-OFF" demand driven deep brain stimulator design. *J Neural Eng* 2013;10(3):036019.
  63. Shukla P, Basu I, Tuninetti D. Towards closed-loop deep brain stimulation: decision tree-based essential tremor patient's state classifier and tremor reappearance predictor. *Conf Proc IEEE Eng Med Biol Soc* 2014;2014:2605–2608.