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REVIEW

Role of the Personal KinetiGraph in the routine clinical assessment of Parkinson's disease: recommendations from an expert panel

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ABSTRACT

Introduction: Evaluation of people with Parkinson's disease (PD) is often complex due to heterogeneity of symptoms and disease course, including the variability of motor fluctuations and dyskinesia. Routine clinical evaluations may be incomplete, may not accurately capture important symptoms, and may not reflect day-to-day variability. While significant advances have been made in wearable ambulatory continuous objective monitoring (COM) technologies, many clinicians remain uncertain of how to incorporate them in clinical practice, including the value to clinical decision-making. The Personal KinetiGraph™ (PKG) has FDA clearance in the United States, and has recently been used in several clinical studies.

Areas covered: An expert group of movement disorders neurologists convened to discuss the clinical utility of the PKG in the routine assessment of people with PD. Based on their experience, the group identified clinical scenarios where objective information gained from review of PKG reports can provide useful information to improve clinical management.

Expert commentary: PKG provides clinically meaningful data in patients with PD that can aid the clinician in evaluating patients and optimizing their pharmacologic therapy. Early clinical experience and expert opinion suggest that utilization of COM technologies such as the PKG have the potential to improve medical care in people with PD.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 1% of the population aged over 60 years old [1]. While the definition of PD is constantly evolving to encompass a wide range of pathologies and non-motor symptoms [2,3], the dopaminergic motor symptoms of bradykinesia, rigidity, and tremor remain the core features by which clinical PD is defined [3]. Dopaminergic replacement with levodopa, often with adjunctive medications, is the cornerstone of motor treatment paradigms [4]. However, 50% of patients will develop motor fluctuations and dyskinesia by 5 years and over 90% of patients by 10 years [5–7]. Motor fluctuations can be complex, variable day-to-day, and often reflect dose 'wearing-off', delayed-onset of therapeutic response and dose failures [6] – often with significant impact on quality of life [8,9]. Current American Academy of Neurology Practice guidelines [10] recommend querying patients once a year about motor fluctuation and dyskinesia but do not recommend any formal evaluations.

The Unified Parkinson's Disease Rating Scale (UPDRS) has been the most widely used standardized scale to quantify impairment and disability in PD, and was updated in 2007 [11]. With this scale, nonmotor (Part I) and motor (Part II) experiences of daily living are scored based on patient self-report, while motor function (Part III) is entirely scored by the clinician. However, it is only intended to provide a brief snapshot of Parkinsonian symptoms within the constrained environment of the clinic and does not address, nor have the capability to characterize, the normal biological variability that patients may experience over time (i.e. within and between days) [12].

Moreover, in routine practice, patients often time their medication intake so that they are in their best clinical state to attend the appointment, which can affect their clinical evaluation by the physician (with or without the use of scales such as the UPDRS). The other common method of assessment is a discussion with the patient/caregiver about 'how they are currently doing' [12]. This can also be problematic when patients lack a standard by which to compare their symptoms or may not recognize and report the full extent of their symptoms. There is a 'perceived normal' that is apparent in PD where patient may assume their uncontrolled symptoms are normal and/or uncorrectable. While home diaries are helpful, they typically include only categorical options (e.g. ON with or without dyskinesias or OFF), and do not capture the severity of the patients' OFF state or dyskinesia. Moreover, even patients participating in clinical trials will defer recording their clinical states in diaries to a more convenient time [13,14] leading to recall bias. This dependence on patient

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presentation at short appointments and self-report has led to the development of ambulatory COM technologies that can be administered at home, allowing for out-of-office continuous assessments both for routine care, as well as clinical trials.

While significant advances have been made in wearable ambulatory COM technologies, many clinicians do not yet view these technologies as capable of providing meaningful data to support their clinical practice [15]. A key reason for this is uncertainty of how to incorporate these technologies into clinical practice. For example, clinicians may not be sure of the various clinical scenarios where technology can be helpful in diagnosis and/or management, or they may lack awareness about the different kinds of data that can be measured and reported. Other barriers include questions about logistics (i.e. time needed in clinic, cost to practice, cost to patients, paperwork), timing (i.e. before/after visit), and whether the measurements are truly objective and reliable.

The Personal KinetiGraph™ (also known as the Parkinson's KinetiGraph™ or PKG™, Global Kinetics Corporation, Australia) is approved for use in Australia and Europe [16], and has FDA clearance in the United States [17]. This report summarizes the discussions of an expert group of US and Australian movement disorder specialist (MDS) neurologists who met to describe the clinical utility of the PKG in the management of PD. Each MDS in this group has 10–20+ years of experience treating patients with PD and, between the whole group, they have used over 2000 PKGs to inform patient treatment. They have also completed all PKG training programs. The overall aim of the expert group was to reach consensus on various clinical scenarios and provide practical guidance on how the PKG can be incorporated into routine practice as an aid to a comprehensive clinical evaluation of PD patients.

2. The Personal KinetiGraph

2.1. The technology

The PKG system was designed to collect real-time accelerometry data using a portable technology (wristwatch or data logger worn by the patient for a specified period of time) (Figure 1) that is analyzed using validated algorithms to measure and report bradykinesia and dyskinesia [18]. The term PKG refers to the output of these components in a clinically intuitive presentation comprised of graphical and numerical data in a chart form that is read and interpreted by the clinician to inform the clinical evaluation.

Bradykinesia is characterized by slowness in initiation and execution of movements that are typically of lower acceleration and amplitude than normal movements and with longer intervals between movements [19,20]. Reductions in acceleration are particularly apparent when subjects attempt rapid alternating movements [21]. The PKG logger, when worn by the patient, captures movement accelerations of the wrist and analyzes their spectral power to graphically and numerically quantify the kinematics of bradykinesia and dyskinesia [18].

The PKG logger is worn on the wrist for 6–10 days and, once the data is downloaded, proprietary algorithms provide a score of the likelihood of movements being either dyskinetic or bradykinetic in two-minute epochs (Figure 2). Frequency histograms show the proportion of the day spent across the range of bradykinesia and dyskinesia scores. A person with PD is assessed by comparing the extent to which the mean and distribution of their bradykinesia score (BKS) and dyskinesia score (DKS) deviate from standardized scores from a healthy, age-matched group. The BKS has been shown to closely correlate with UPDRS motor score (minus tremor item) and DKS correlates with the modified Abnormal Involuntary Movement (AIMS) score [18] (Supplementary Appendix).

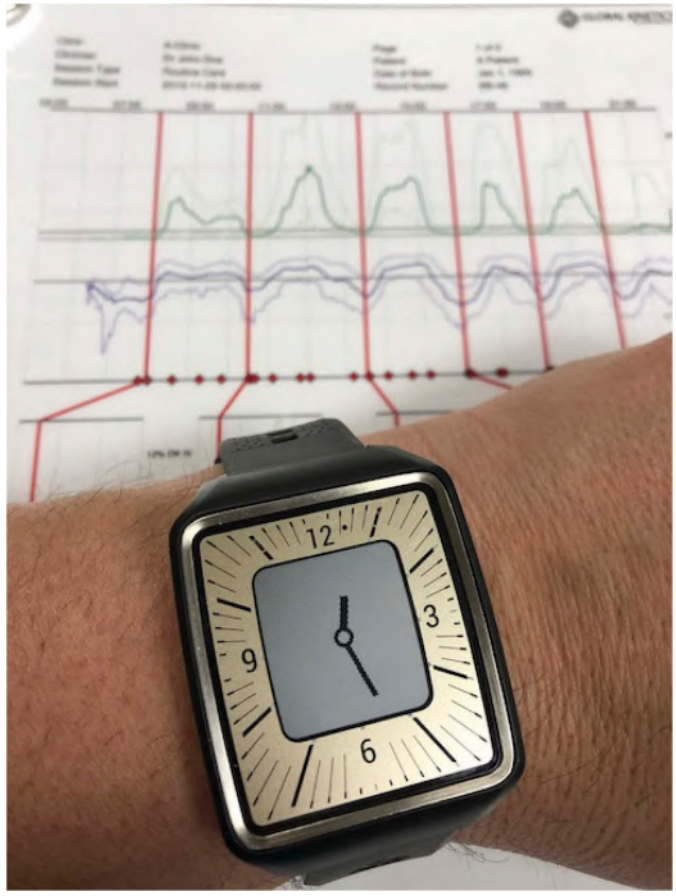

Figure 1. The Personal KinetiGraph logger.

The PKG logger also includes a medication reminder and acknowledgement. The logger is programmed to vibrate at appropriate medication times (medication reminder) and the patient swipes the smart screen once they have taken medications to stop the vibration (acknowledgement). The medication reminder/acknowledgement system not only enhances medication adherence and reports on compliance, but also is vital to identify the relationship of symptoms to medication intake. The PKG logger also contains a capacitance sensor to identify when the logger is not being worn, which is included graphically in the report.

2.2. PKG plots

Multiple days of recording is required to collect sufficient data to capture the natural variability of PD and response to medications, and to minimize artifact due to differences in daily activities over days (e.g. exercise, going shopping, to an

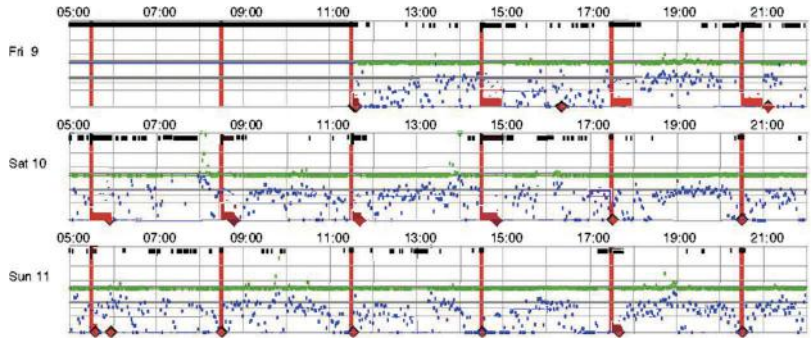

Figure 2. Example of a Personal KinetiGraph daily plot.
Legend: Each dot represents a 2-minute epoch of data.

appointment, etc.). The PKG provides a measure of severity and the proportion of time spent at various levels of dyskinesia and bradykinesia in relation to timing of medication. The summary plot of the PKG shows the median bradykinesia score (BKS, in blue) and dyskinesia score (DKS, in green) for the recording period, along with their respective interquartile ranges (light blue and light green), and this is presented in comparison to the BKS and DKS median, 75th and 90th percentiles for healthy age matched control group (46–83 years old) (Figure 3).

The peri-dose response curves provide a measure of BKS and DKS change in response to medication doses, adjusted for time medication acknowledged as taken, rather than time due. The daily plots provide a view of day-to-day variability in data and to help recognize artifact. The Fluctuation and Dyskinesia Score (FDS) has been developed as a summary score of motor fluctuation and dyskinesia, derived as the logarithm of the sum of the interquartile range of BKS and DKS across all days of recording and has been shown to differentiate clinical fluctuators from nonfluctuators, and to be significantly different in patients before and after deep brain stimulation (DBS) (Figure 4) [22].

In addition, a tremor algorithm assesses the presence of tremor (presented as the Percent Time with Tremor, PTI) and its relationship to bradykinesia and medication timing (presented as a tremor raster) [23] (Figure 5). Similarly, the PKG provides information about daytime immobility by way of a numerical score (Percent Time Immobile, PTI), and a raster plot showing immobile periods over the recording period (Figure 5). This sustained immobility has been shown to correlate with periods of sleep and somnolence [24].

3. Role of PKG in clinical practice

3.1. How can PKG data help with clinical assessment?

The PKG was designed to provide an objective measure of motor status over a 6-day period.

Although the data collection may have value in all types of PD patients, the expert group discussed clinical situations where use of the PKG has helped inform the clinical evaluation and affected medical management. These scenarios are summarized in Table 1 and the summary of the expert discussions is given in the following text.

3.2. Clinical situation 1: the poor historian

The assessment of motor fluctuations requires a good patient history to understand the relationship of the complication to the timing of medication intake. For example, the progressive shortening of the duration of levodopa therapeutic effect (wearing-off) means that symptoms re-emerge before the

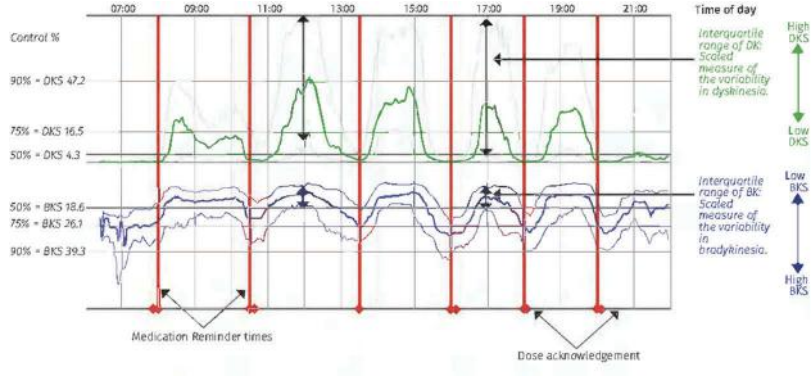

Figure 3. Example of a Personal KinetiGraph summary plot.
Legend: Data from all recording days aligned to the time of day. Shows when reminders were given via *red horizontal lines, median DKS (green line), median BKS (blue line) and their 25th and 75th percentiles plotted against time of day. Increasing/decreasing severity levels represented on right Y axis. Time patient acknowledged taking medications represented as red diamonds on X axis*

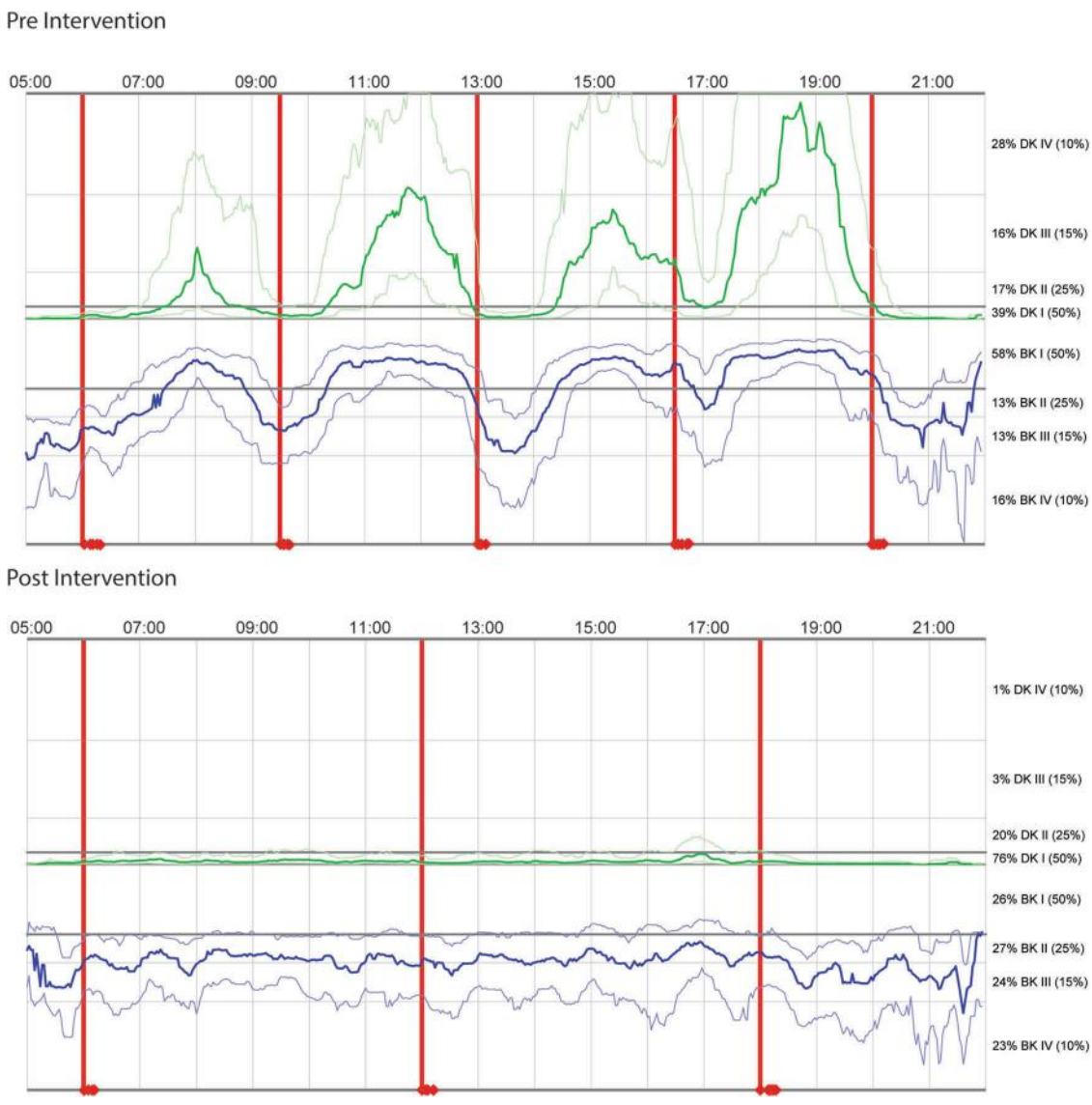

Figure 4. Examples of Personal KinetiGraph summary plots in patients (a) before and (b) after deep brain stimulation.

next dose is scheduled, and the most common fluctuating motor symptoms reported by the patient are tremor and 'slowness of movement' (bradykinesia) [25,26]. Many patients also experience a significantly delayed time to ON (e.g. when the effects of a levodopa dose take more than 30 min to kick in) [25–28]. Several self-report questionnaires exist to help understand the timing of the medication to wearing-off [26,29,30], but this requires an adequate recognition of the problem by the patient and proper recording of their clinical status. In one survey, whereas most people with PD and their care partners (87% and 74%, respectively) said that they understood what 'wearing-off' means, only 30% of patients and 17% of their care partners gave a correct answer on further questioning [31].

The term poor historian is often used to refer to a patient who is unable to express the history of their illness in a coherent fashion. This can be due to mild cognitive impairment (or dementia), limited understanding of the disease, etc. Patients may be unsure of how long they have experienced a symptom, what it feels like, its triggers, what makes it better or worse and whether it is constant or fluctuating. They may not be able to explain how it affects function, often because of associated non-motor symptoms that may or may not be medication responsive, just that *'it doesn't feel right'*. In the US, payers expect physicians to make all efforts in obtaining a reliable medical record (including information from another source, such as a family member, spouse, medical record), and if this is not possible, the physician should document the attempts made [32].

In such cases, the PKG can provide objective, documented information about the status of PD including motor fluctuations and dyskinesia. Using these data, the clinician can sensitively and accurately relate the timing of motor fluctuations to medication intake and observe whether there has been a gradual shortening of levodopa benefit and time to onset of medication benefit. For patients who have the cognitive capacity, the expert group agreed that the PKG data provides useful discussion points for patient education during consultations. The expert group also recognized that a minimum level

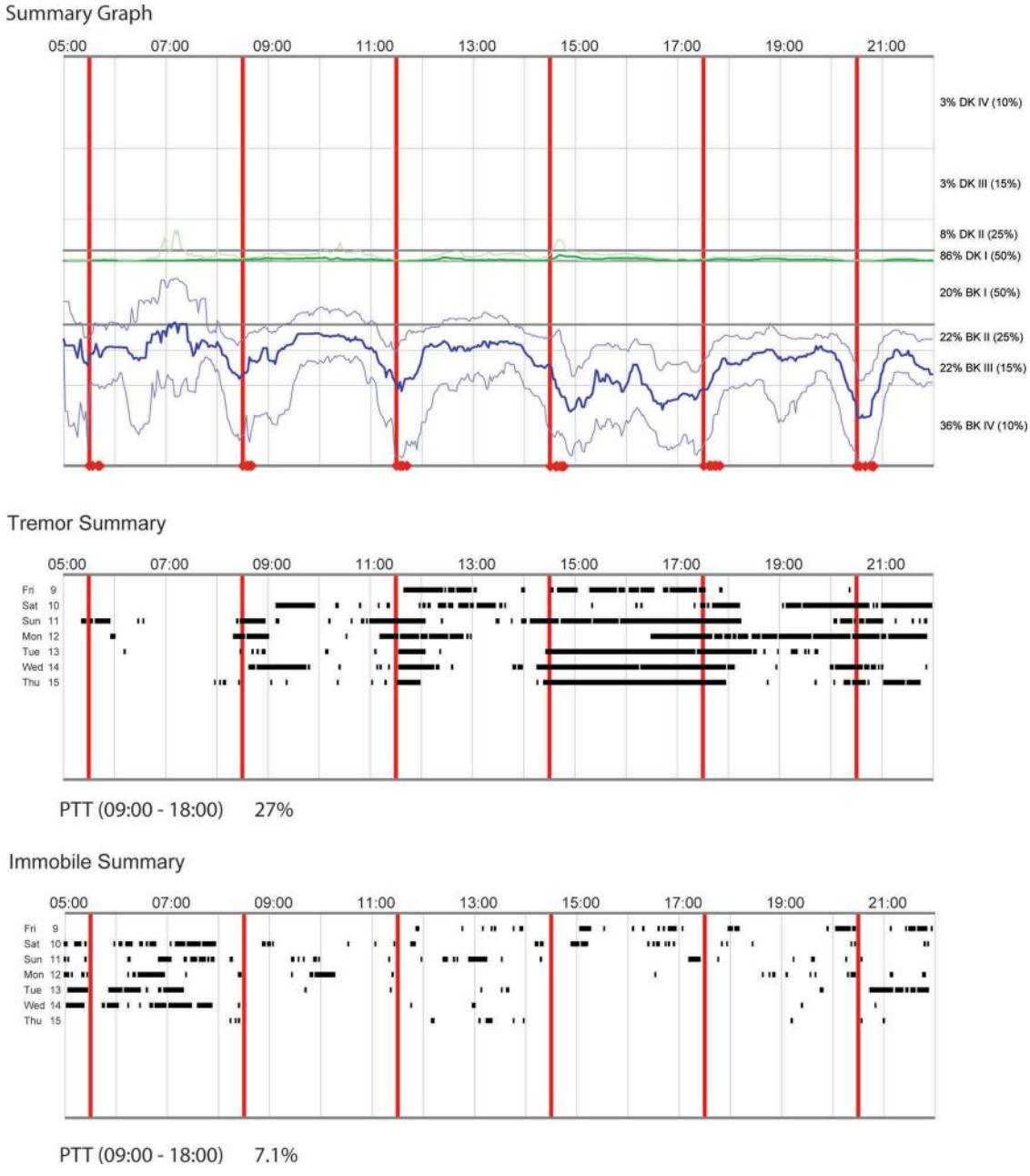

Figure 5. Example Personal KinetiGraph plots from the same patient showing (a) the overall summary plot, (b) tremor summary, and (c) time immobile summary.

Legend: tremor summary – X axis is time of day and Y axis is each day of recording. The raster is marked with a black dot for every 2 min epoch within which tremor is detected. Immobility summary – X axis is time of day and Y axis is each day of recording. The raster is marked with a black dot if a BKS epoch at the relevant time on the X axis is > 80. This is equivalent to the logger sitting on a table (i.e. Immobile for a 2 min epoch).

of cognitive capacity was required to properly use the PKG, making it less helpful in the setting of dementia unless a caregiver could assist with its use.

3.3. Clinical situation 2: patients with difficult to characterize motor fluctuations

As discussed earlier, the PKG is helpful in relating the timings of motor fluctuations to medication intake. Motor fluctuations are not a binary (ON-OFF) phenomenon. There are differences in the severity, onset and duration of OFF symptoms, and even if the patient is able to provide detailed information, this may not be sufficient to enable the clinician to gain a clear impression of fluctuation type, severity, duration of OFF periods, and the magnitude of response to medications. For example, in some cases, it might well be understood that the patient has poor symptomatic control but the severity is either over- or underestimated. Patients may report feeling better or worse since their last medication change, but the clinician's own observation does not match the self-report. Patients may also report unpredictable OFF symptoms while the clinician may suspect predictable OFF symptoms.

Without accurate information, this can result in the under- or overtreatment of symptoms – either perpetuating

Table 1. Summary of clinical situations discussed by the expert group.

Scenario	Example clinical presentations	PKG Utility
Poor historian	Patient is unable to identify or communicate PD symptoms or their report of the symptoms does not match the clinical impression	– Provides objective information on status of PD including fluctuations, dyskinesia, bradykinesia, tremor, and compliance -Provides discussion points for physician/patient education
Motor fluctuations	Patient presents with motor fluctuation symptoms of complex or uncertain pattern and severity, and/or increased OFF-time	– Identifies the type, timing, duration and severity of motor fluctuations- Displays the timing and magnitude of response to medications
Dyskinesia	Patient presents with dyskinesias of uncertain pattern or severity, clinical impression of dyskinesia does not match patient report, and/or movements of uncertain etiology	– Confirms the presence/absence of dyskinesias, timing in relation to medication dosing, variability, severity, and proportion of day with dyskinesias
Tremor	Patient over/under reports tremor, or denies any tremor response to medication	– Confirms the presence/absence of tremor, response to medication, duration of tremor, and relationship of tremor to bradykinesia
Dyskinesia vs. Tremor	Patient reports involuntary movement of unclear type, with inability to distinguish between tremor and dyskinesias over the day, or how they are affected by medications	– Differentiates between tremor and dyskinesia– Demonstrates the impact of medication on the involuntary movement
Excessive daytime sleepiness	Over/under reporting of daytime sleepiness by patient, or incongruences between patient/caregiver reports	– Immobility report demonstrates the presence/absence of excessive daytime immobility– Demonstrates potential medication effects on daytime immobility as a surrogate for somnolence
Response to therapy change	Patient is unclear about the benefits of a therapeutic change	– Provides a qualitative and quantitative assessment of various motor symptoms to determine the impact of a therapeutic change
Assessment for and optimization of advanced therapies	Assessing the need for advanced therapies such as deep brain stimulation in patients with suspected motor fluctuations, dyskinesias, and/or tremor. Advanced therapies also provide more complexity, making optimization more challenging	– Identifies motor fluctuations, dyskinesia, and medication-refractory tremors– Aids in the selection of appropriate patients for advanced therapies– Aids in the optimization of advanced therapies once instituted
Telemedicine	Patients who cannot be seen in the clinic in person, leading to more limited telemedicine-based assessments	– Provides an interim PD evaluation without an in-clinic visit or adds value to a telemedicine evaluation– Aids in determining whether an urgent clinic assessment is required. - Reduces the need for in-clinic visits in clinically stable patients
New patients	Any newly diagnosed PD patient or a new patient to the clinic	– Establishes a baseline– Aids in early detection of motor fluctuations and dyskinesias– Enhances patient education of their symptoms

the problem of suboptimal control (undertreatment) or worsening dyskinesia (overtreatment). In such cases, the PKG can provide accurate information about the severity of bradykinesia and how long the OFF periods are during the day. By looking at BKS over the day, the clinician can assess if the patient suffers suboptimal responses to medication dosing and if this changes over the course of the day (e.g. after a meal). By providing a baseline BKS, the impact of medication changes on symptom severity can also be assessed and monitored over time. In this respect, it is well known that the profile of motor fluctuations changes with advancing disease [25]. However, the rate and patterns of progression are highly variable between patients [33,34], and the clinician often has to make changes to the medication for optimal control of motor complications. The expert group agreed that recurring use of the PKG may be helpful in following the progression of motor fluctuations, thereby providing additional evidence that further medication changes are warranted.

The expert group further discussed the potential to use the PKG in the identification of early fluctuators who can be very difficult to recognize [6]. In a study conducted at a single expert center in Australia, objective assessment of 28 PD patients who were thought (by themselves and their general neurologist) to be doing well, identified 24/28 were, in reality, poorly controlled according to a combination of Movement Disorder Specialist (MDS) and PKG analysis. Of these, eight patients were identified by PKG but not by the MDS clinical assessment. In all 24 patients, a treatment change occurred, with improvement in PKG scores and significant improvements in UPDRS total and motor scores, with the greatest improvement seen in those eight poorly controlled patients only identified by PKG [35].

3.4. Clinical situation 3: patients with difficult to characterize dyskinesia

Like motor fluctuations, dyskinesias are a common complication of long-term treatment with levodopa. In one 10-year study of newly diagnosed patients, most (91%) exhibited dyskinesia with varying degrees of troublesomeness during their disease course [36]. Dyskinesias develop earlier in people with young-onset PD and they have a higher incidence of levodopa-induced dyskinesia [37].

Dyskinesias are clinically heterogeneous. They can present as chorea or choreoathetosis, though dystonia, myoclonus, akathisia, ballism, and other forms of abnormal movements have also been described [25]. Based on their relationship with levodopa dosing, dyskinesias can be classified as peak-dose (related to peak levodopa plasma levels), biphasic (which develop when plasma levodopa levels are rising or falling, but not with the peak levels), OFF state, ON state, and yo-yo dyskinesias [38]. While patients might easily recognize when they have overt (severe) involuntary movements, accumulating evidence suggests that at least a proportion of PD patients are either partially or totally unaware of the presence of dyskinesia [39]. Studies have shown poor self-awareness when dyskinesias are mild [40], and denial of dyskinesias even with longer symptom durations [41].

Differentiating between the types of dyskinesia is important as, for example, biphasic dyskinesias do not respond to levodopa dose reduction (but peak dose dyskinesias do) and may instead improve with higher dose of levodopa [38]. When patients (and their caregivers) are unsure of the pattern of their dyskinesia, or when the clinical impression of dyskinesia does not match the patient report, the PKG can provide important information on the relationship of the dyskinesia to medication intake (helping to differentiate between peak dose and diphasic dyskinesia) and can also help distinguish the relationship to OFF and ON periods (for OFF and ON state dyskinesia).

Key indicators of severity of dyskinesias include the amplitude and duration of the dyskinesia and, here, the DKS provides important objective information about the severity of the complication. This can be especially helpful in the face of conflicting reports from patients (who often prefer being ON with dyskinesia to being OFF with no dyskinesia) and their caregivers (who may be more concerned with their presence). The expert group also noted that it is helpful when there are conflicts with self-report and the clinical exam, and noted that dyskinesia often increases during stress-related events – which would include a visit to a PD specialist. The use of the PKG in the latter scenario can help to reduce over-treatment of dyskinesias seen in clinic that are not present to any significant degree otherwise.

3.5. Clinical situation 4: patients with difficult to characterize tremor

Tremor is recognized as one of the cardinal symptoms of PD and occurs in approximately 75% of people with PD [42]. There are several forms of tremor associated with PD, and classification is based on the distinction between rest, postural, kinetic, and intention tremor [43]. The classic asymmetric, resting tremor of PD has a frequency of 4–6 Hz, is inhibited by movement and may re-emerge with posture. Postural/kinetic tremors are typically 1.5 Hz greater than rest tremor and there are also other postural and kinetic tremors in PD whose frequencies are between 4 and 9 Hz [43].

In clinical practice, tremor may not always respond as well as bradykinesia and rigidity to treatment [44]. In those that do respond, the tremor variably presents over the day. The expert group discussed that the PKG is helpful in identifying the patterns of tremor, and whether they are related to OFF episodes or under treated bradykinesia. In the validation study of the Tremor Summary (TS) score the authors noted that an advantage of the PKG is that the *'threshold of bradykinesia associated with emergence of tremor can be established'* for individual patients [23].

The PKG has been used in a nurse-led study where PD patients also completed pre- and post- PKG questionnaires to identify information that may improve understanding of tremor and its relationship to other PD symptoms. In all cases, the patients agreed that the PKG had facilitated communication and understanding of their tremor, and how it might be affected by other factors such as timing of medication and degree of bradykinesia [45]. The expert group also discussed that the PKG tremor profile can help establish whether disabling tremor is truly 'treatment resistant' and requires referral for advanced therapies or if increasing the dose of medication may help better manage this symptom.

3.6. Clinical situation 5: differentiating between dyskinesia and tremor

Another common problem is that patients can find it difficult to distinguish the 'shaking' caused by tremor from dyskinesia over the day and in response to medications. This is an important distinction because tremor is usually a symptom of OFF whereas dyskinesia can be a symptom of dopaminergic overload. For example, a PKG that shows tremor reemerging when medications are due can be helpful in recognizing 'wearing-off' which is treated by adjusting (frequently up-titrating or adding another medication) the dopaminergic treatment regimen. Such a treatment change would likely only worsen symptoms, if the patient is, in fact, experiencing dyskinesia.

In the validation study reported by Braybrook et al. [23], the authors reported that the PKG can discriminate between tremor (spectral analyses showed obvious dominant peaks greater than 3Hz although sub-harmonics were apparent) and dyskinesia (spectral analyses showed energy across a broad range of frequencies from 0.1 to 8 Hz, usually without a clear peak). Analysis of a database including data from > 1000 PKGs estimated only a 3% risk of tremor contaminating the DKS [23]. Such contamination can be recognized because high DKS activity is associated with low BKS in dyskinetic states, while high DKS activity is associated with high BKS in tremor states that contaminate the DKS algorithm.

3.7. Clinical situation 6: patients with excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is common in PD, and has been estimated to occur in 20–50% of patients [46]. PD medications, including the dopamine agonists and levodopa, can significantly contribute to EDS as well as the disease itself. It is recommended that due to the high risk of accidents in sleepy drivers, levels of daytime sleepiness must be regularly checked in PD patients, especially when the dopaminergic treatment is changed [47,48]. However, the presence of EDS is often under-recognized and therefore underreported by the patient, with many PD patients failing to perceive daytime naps lasting minutes and involving slow wave sleep [49] and many patients are also unaware of how long they sleep. Such problems have also limited the clinical study of EDS because existing methods of detection and quantification are largely based on self-report through diaries or other subjective measures.

The PKG quantifies immobility to provide a surrogate marker of daytime sleep, confirmed by correlation with daytime polysomnography and the Epworth Sleepiness Scale; the Sleep Score validation study showed that BKS> 80 were associated with daytime sleep [24]. The expert group discussed that patients and caregivers often give conflicting information at the office visit as the patient does not realize their own daytime sleeping pattern. In many cases, having a better understanding of the relationship of excessive sleepiness to

recently introduced medications (e.g. a dopamine agonist) has led to adjustments to the therapy regimen.

3.7 Clinical situation 7: patients with a changing response to therapy or uncertainties with dose titration

For many PD medications, optimal titration refers to increasing the dose for maximal efficacy without unacceptable side effects. During the course of the disease, clinicians frequently have to make dose adjustments to account for changes in patient presentation due to underlying disease progression. In the case of new drug initiations, each of the available PD medications has a widely differing titration schedule, ranging from an immediate start for drugs that are given at a fixed dose (e.g. rasagiline) to several weeks (e.g. with higher doses of pramipexole and ropinirole). However, in daily practice, many clinicians are unable to see the patient face-to-face with enough frequency to evaluate whether the medication change or titration is optimal and instead rely on telephone call follow-up.

The expert group discussed that the PKG has utility in quickly helping to understand if a recent medication change has improved the patient condition in the intended way (e.g. better symptomatic control, reduction in OFF time, improvement in tremor). New emergence of dyskinesia (with information regarding its frequency and severity) can easily be picked up following the introduction of adjunct therapies. In cases of uncertain titration, the PKG provides an objective way of quantifying the improvements afforded by each incremental increase in dose.

3.8. Clinical situation 8: optimization of advanced therapies

While the suitability of PD patients for advanced therapies is readily recognized in specialized centers, they may be overlooked by clinicians who have less experience with these therapies. In this respect, the expert group agreed that use of the PKG is helpful in quantifying the frequency and severity of motor complications thereby complementing the selection of appropriate patients referred for consideration of advanced therapies. It also provides objective evidence of uncontrolled motor complications that some payers require before approving an expensive advanced treatment.

For example, recent machine learning approaches using PKG data have been shown to be useful in sorting patients into those 'suitable for deep brain stimulation (DBS) on motor grounds' or 'not ready for DBS' [50]. The PKG has also been shown to provide a more reliable picture of the reductions in motor fluctuations and dyskinesia afforded by DBS than patient diaries [51] – thereby providing potential utility in patient follow-up following the surgery. If the decision is to try an infusion-based therapy, titration protocols for both duodenal levodopa and apomorphine infusion often require a period of hospitalization to ensure the patient is safely titrated to the correct dose. However, these in-patient titration periods are often no longer than a week – whereas it can take several weeks to reach the best individualized dose for the patient [52]. Here, the group agreed that the PKG can aid in the optimization of advanced therapies once instituted.

3.9. Clinical situation 9: telemedicine

It has been established that PD patients who see a neurologist live longer and are less likely to require nursing home care than those who do not see a neurologist. However, only about 60% of PD patients in the US Medicare system receive neurologist care [53]. There are many reasons for this, but difficulties with access (e.g. distance to neurologist, difficulties with travelling long distances, costs of transport and/or lodging, etc.) are a particular problem in the United States and Australia because PD specialists tend to work at academic medical centers located only in major urban areas. Telemedicine is a fast-growing field, and many schemes for PD are currently in development [54,55]. The expert group discussed that while the PKG could easily be integrated with web-based technologies into future telemedicine programs [56], it is already proving useful as an interim PD evaluation to help decide if a patient who has difficulties attending the clinic requires an in-clinic assessment. Use of the PKG in this way reduces the need for in-clinic visits, saving time and the significant costs that can be associated with attending visits.

3.10. Clinical situation 10: new patients

As the PKG is increasingly accepted into clinical practice, the group discussed that it will have increasing clinical utility in newly diagnosed PD patients or patients who are new to the clinic. It can be used to establish a baseline presentation and continued (repeated) use would allow early detection of fluctuations.

4. PKG targets

PKG algorithms are based on a comparison of the extent to which the mean and distribution of their BKS and DKS for PD patients deviate from standardized scores for healthy individuals. Thus, clinicians starting to use the PKG often ask about 'target ranges' for a person with PD. A recent study conducted in an Australian movement disorders clinic experienced with the technology, tested the utility of predefined target PKG ranges when assessing motor function in a representative sample of 103 people with Parkinson's disease [57]. The authors found that using PKG targets to guide treatment decisions led to a change of oral therapy in 74% of patients, of which 43% benefited from significant improvements in UPDRS total scores (effect size of 8) and in patient quality of life (as assessed by the PDQ-39). The unmet need for proposed COM target ranges was also addressed by a group of European Movement Disorder Specialists [58]. The US expert group reviewed the proposed targets from both these publications, tested them in routine care, and agreed that the suggested targets in Table 2 are a reasonable starting point, which should continue to be refined over time with further research.

5. Current limitations of PKG in clinical practice

While the PKG provides important objective information, there are current limitations to the technology that should

Table 2. Proposed PKG target scores.

PKG Score	Optimal	Acceptable	Treatment Considerations
Bradykinesia Score (BKS)	• Median BKS < 23 and FDS > 8.0	• Median BKS 23–25 and/or FDS > 7.5 and no fluctuations Consider treatment in this range if: (1) Observable dose related fluctuations with peak > BKS 25 (2) FDS > 10.0	• Median BKS > 25 • Any single dose related fluctuation (even if parameters are OK) IF: (1) Not due to sleep and peak > BKS 25 (2) Due to sleep if possible hypotension contributing (i.e. treat the hypotension, spread morning dose, etc.) • FDS < 6.0 potential under treatment or poor responder • Any indication of unpredictable wearing off or other OFF times
Dyskinesia Score (DKS)	• Median DKS < 7 and FDS < 10.8	• Median DKS 7–9 and FDS < 13 and no fluctuations Consider treatment in this range if there are: (1) Observable dose related fluctuations (2) FDS > 13.0	• Median DKS > 9 • Single dose related dyskinesia peak (even if other parameters are ok) IF: (1) Peak is > 13 (2) Not due to exercise (3) Not due to tremor artifact

be clearly understood. At present, while the main graphical plot of the PKG shows bradykinesia and dyskinesia scores from 05:00 to 22:00 h daily (excluding periods when the PKG logger was off wrist), the summary bradykinesia and dyskinesia scores are based on data analysis between 09:00 and 18:00 h. This is regardless of the patient's personal timings, and was chosen because these timings were considered likely to capture much of the waking and active day for most PKG users. It is also important to understand that 5 days of recording are recommended to overcome potential artifact. For example, in the validation studies, the dyskinesia scores were shown to be at risk of artifacts from exercise (particularly when exercise occurs at the same time each day) [59]. Strategies to identify artifacts in the process of report review are available to limit misinterpretation, alongside the summary DK scores.

The PKG watch is worn on the most affected upper limb. While, the results of PKG analysis from one upper limb usually correlate well with whole body scores (except in more strictly unilateral disease), the PKG doesn't provide information on axial symptoms, such as freezing of gait. While the PKG is used in 'real-life' situations (i.e. at home), its use does promote compliance with the timing of medication intake and clinicians should consider that compliance with medication timing is typically poor in people with PD [60]. Although the PKG does not provide information about common non-motor symptoms of PD such as depression, anxiety, dementia and pain, it can be helpful in linking these symptoms to motor ON or OFF periods when patients keep a diary of the time that these symptoms occur.

Although the time taken to write a physician PKG interpretation report can be initially time consuming, the expert group agreed that it provides a standardized development structure for reviewing the data and a platform for more rapid data analysis with experience. Finally, it should be noted that PKG sessions can end early due to mechanical difficulties, user discontinuation or premature connection to the tablet (i.e. upload of a partial session). The off-wrist summary and the daily plots should be reviewed to check for significant periods off-wrist or an early end of the session, in which case there is suboptimal data for analysis, and consideration must be taken when interpreting the PKG.

6. Conclusion

In summary, the PKG is a readily available wearable ambulatory COM technology designed to provide objective information of an individual patient's motor status over 6 days. It is approved for use in Australia and Europe, and has FDA clearance in the United States. Early clinical experience and expert opinion suggest that, in several routine clinical scenarios, use of the PKG can provide clinically meaningful data to aid clinical decision-making.

7. Expert commentary

The validity of the PKG as a tool to measure motor function in PD has been established through several clinical studies [18,22–24,61–63] and, with increased adoption, this evidence base will continue to grow. As highlighted by the broad variety of routine clinical scenarios discussed earlier, the utility of the PKG can be summarized as an enhancement to standard medical care of PD, including a more ecologically valid assessment of symptoms, patient compliance, and treatment efficacy. Early clinical evidence and expert opinion suggest a role for the PKG in influencing and enhancing clinical decision-making. For example, objective measurement helps detect uncontrolled patients and provide data to help decide on which treatments should be introduced or changed to optimize therapy. With increased understanding of the heterogeneity of PD, there is a move to a more personalized medicine approach to treating this disease [64], and the PKG will fit with this approach.

8. Five-year view

Objective measurements are standard in other disease management areas. For example, Holter monitors are routinely used to diagnose slow, fast or irregular heartbeats, observing occasional cardiac arrhythmias that would otherwise be difficult to identify, and to assess how well medications and devices manage these symptoms. While the adoption of ambulatory COM technologies in PD has thus far been slow, it is predicted that they will become standard practice within

the next few years. The increasing adoption of 'smart watches' as a life-style choice to monitor fitness and health will also increase patient acceptability of such technologies. Finally, the development of treatment guidelines that incorporate objective treatment targets such as provided by the PKG will aid uptake. Such guidelines will provide vital advice for choosing advanced therapies and how to assess success of treatment.

From the clinical research perspective, there is already keen interest in using technologies as an objective way of quantifying the response to new therapies. Such work will rely on the understanding the clinimetrics of what the objective scores mean to the patient. There is also huge potential to use PKG data as a surrogate biomarker and outcome biomarker. In this respect, researchers need to develop their abilities in handling the amount of data that the PKG provide [15].

Key issues

- Evaluation of patients with Parkinson's disease is often complex due to the heterogeneity of symptom presentation, and the variability of motor fluctuations and dyskinesia. Routine clinical evaluations based on patient and caregiver query, and clinical examination at the time of the clinic visit may not provide a complete picture of the patient in their daily life.
- The Personal KinetiGraph™ (PKG) is a readily available ambulatory COM technology designed to provide objective information of an individual patient's motor status over 6 days. It is approved for use in Australia and Europe, and has FDA clearance in the United States.
- In routine clinical practice, the clinical utility of the PKG is reflected in clinical situations where it provides clinically meaningful data that aid the clinician in evaluating PD patients and optimizing their pharmacologic therapy.
- Early clinical experience and expert opinion suggest that utilization of ambulatory COM technologies such as the PKG have the potential to improve the medical care of people with Parkinson's disease.

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm. 2017;124:901–905.
2. Titova N, Padmakumar C, Lewis SJG, et al. Parkinson's: a syndrome rather than a disease? J Neural Transm. 2017;124:907–914.
3. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591–1601.
4. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology. 2009;72:S1–136.
5. Olanow CW, Agid Y, Mizuno Y, et al. Levodopa in the treatment of Parkinson's disease: current controversies. Mov Disord. 2004;19:997–1005.
6. Stocchi F, Jenner P, Obeso JA. When do levodopa motor fluctuations first appear in Parkinson's disease? Eur Neurol. 2010;63:257–266.
7. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord. 2001;16:448–458.
8. Chapuis S, Ouchchane L, Metz O, et al. Impact of the motor complications of Parkinson's disease on the quality of life. Mov Disord. 2005;20:224–230.
9. Hechtner MC, Vogt T, Zollner Y, et al. Quality of life in Parkinson's disease patients with motor fluctuations and dyskinesias in five European countries. Parkinsonism Relat Disord. 2014;20(9):969-974.
10. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. 2006. Neurology.
11. Goetz CG, Tilley BC, Shaftman SR, et al. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129–2170.
12. Saha RA, Worth PF, Stamford J. Assessing quality of life in Parkinson's in routine clinical settings. ACNR. 2015;14:12–14.

13. Stone AA, Shiffman S, Schwartz JE, et al. Patient non-compliance with paper diaries. BMJ. 2002;324:1193–1194.
14. Papapetropoulos SS. Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. CNS Neurosci Ther. 2012;18:380–387.
15. Espay AJ, Bonato P, Nahab FB, et al. Technology in Parkinson's disease: challenges and opportunities. Mov Disord. 2016;31:1272–1282.

• **Review paper outlining the opportunities and challenges for wearable technologies in Parkinson's disease.**

16. Press release: CE mark awarded to second generation PKG™ system. [cited 2018 May 1]. Available from: https://www.globalkineticscorporation.com.au/news-and-events/ce-mark-awarded-to-second-generation-pkg-system?page=4
17. Press release: FDA clearance received for second generation Parkinson's KinetiGraph™. [cited 2018 May 1]. Available from: https://www.globalkineticscorporation.com.au/news-and-events/fda-clearance-received-for-second-generation-parkinsons-kinetigraph?page=4
18. Griffiths RI, Kotschet K, Arfon S, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. J Parkinsons Dis. 2012;2:47–55.

•• **Original paper describing assessment of bradykinesia and dyskinesia using the Personal KinetiGraph.**

19. Yanagisawa N, Fujimoto S, Tamaru F. Bradykinesia in Parkinson's disease: disorders of onset and execution of fast movement. Eur Neurol. 1989;29(Suppl 1):19–28.
20. van Hilten JJ, van Eerd AA, Wagemans EA, et al. Bradykinesia and hypokinesia in Parkinson's disease: what's in a name? J Neural Transm. 1998;105:229–237.
21. O'Boyle DJ, Freeman JS, Cody FW. The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson's disease. Brain. 1996;119(Pt 1):51–70.
22. Horne MK, McGregor S, Bergquist F. An objective fluctuation score for Parkinson's disease. PLoS One. 2015;10:e0124522.

•• **Original paper describing the Fluctuation and Dyskinesia Score.**

23. Braybrook M, O'Connor S, Churchward P, et al. An ambulatory tremor score for Parkinson's disease. J Parkinsons Dis. 2016;6:723–731.

•• **Original paper describing assessment of tremor using the Personal KinetiGraph.**

24. Kotschet K, Johnson W, McGregor S, et al. Daytime sleep in Parkinson's disease measured by episodes of immobility. Parkinsonism Relat Disord. 2014;20:578–583.

•• **Original paper describing assessment of daytime sleep using time immobile as a proxy measure.**

25. Aquino CC, Fox SH. Clinical spectrum of levodopa-induced complications. Mov Disord. 2015;30:80–89.
26. Stacy M, Bowron A, Guttman M, et al. Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. Mov Disord. 2005;20:726–733.
27. Melamed E, Bitton V, Zelig O. Delayed onset of responses to single doses of L-dopa in parkinsonian fluctuators on long-term L-dopa therapy. Clin Neuropharmacol. 1986;9:182–188.
28. Isaacson S, Lew M, Ondo W, et al. Apomorphine subcutaneous injection for the management of morning Akinesia in Parkinson's disease. Mov Disord Clin Pract. 2017;4:78–83.
29. Stacy M, Murck H, Meng X. COMPASS-1: a validation study of the 9-question, wearing off questionnaire (WOQ-9). Mov Disord. 2006;21:S590.
30. Antonini A, Martinez-Martin P, Chaudhuri RK, et al. Wearing-off scales in Parkinson's disease: critique and recommendations. Mov Disord. 2011;26(12):2169-2175.
31. Matthews H, Stamford J, Saha R, et al. Off-park survey steering g. Exploring issues around wearing-off and quality of life: the OFF-PARK survey of people with Parkinson's disease and their care partners. J Parkinsons Dis. 2015;5:533–539.
32. AAPC: What to do when your patient is a "Poor Historian". 2014 [cited 2017 Nov]. Available from: https://www.aapc.com/blog/27881-what-to-do-when-your-patient-is-a-poor-historian/
33. Rascol O, Hauser RA, Stocchi F, et al. Long-term effects of rasagiline and the natural history of treated Parkinson's disease. Mov Disord. 2016;31:1489–1496.
34. Evans JR, Mason SL, Williams-Gray CH, et al. The natural history of treated Parkinson's disease in an incident, community based cohort. J Neurol Neurosurg Psychiatry. 2011;82:1112–1118.
35. Farzanehfar P, Braybrook M, Kotschet K, et al. Objective measurement in clinical care of patients with Parkinson's disease: an RCT using the PKG [abstract]. Mov Disord. 2017;32(suppl 2). [cited 2018 May 1]. Available from: http://www.mdsabstracts.org/abstract/objective-measurement-in-clinical-care-of-patients-with-parkinsons-disease-an-rct-using-the-pkg/
36. Garcia-Ruiz PJ, Del Val J, Fernandez IM, et al. What factors influence motor complications in Parkinson disease?: a 10-year prospective study. Clin Neuropharmacol. 2012;35:1–5.
37. Kumar N, Van Gerpen JA, Bower JH, et al. Levodopa-dyskinesia incidence by age of Parkinson's disease onset. Mov Disord. 2005;20:342–344.
38. Thanvi B, Lo N, Robinson T. Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment. Postgrad Med J. 2007;83:384–388.
39. Pietracupa S, Latorre A, Berardelli A, et al. Parkinsonian patients and poor awareness of dyskinesias. Front Neurol. 2014;5:32.
40. Vitale C, Pellecchia MT, Grossi D, et al. Unawareness of dyskinesias in Parkinson's and Huntington's diseases. Neurol Sci. 2001;22:105–106.
41. Sitek EJ, Soltan W, Wieczorek D, et al. Assessing self-awareness of dyskinesias in Parkinson's disease through movie materials. Funct Neurol. 2011;26:121–126.
42. Hughes AJ, Ben-Shlomo Y, Daniel SE, et al. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology. 2001;57: S34–S38. 1992.
43. Deuschl G, Bain P, Brin M. Consensus statement of the movement disorder society on tremor. Ad Hoc scientific committee. Mov Disord. 1998;13(Suppl 3):2–23.
44. Nonnekes J, Timmer MH, de Vries NM, et al. Unmasking levodopa resistance in Parkinson's disease. Mov Disord. 2016;31:1602–1609.
45. Price J, Martin H, Ebenezer L, et al. Evaluation of the clinical use of Parkinson's KinetiGraph (PKG) movement recording system in the assessment of Parkinson's disease patients with tremor [abstract]. Mov Disord. 2017;32(suppl 2). [cited 2018 May 1]. Available from: http://www.mdsabstracts.org/abstract/a-service-evaluation-of-the-clinical-use-of-parkinsons-kinetigraph-pkg-movement-recording-system-in-the-assessment-of-parkinsons-disease-patients-with-tremor/
46. Arnulf I. Excessive daytime sleepiness in Parkinsonism. Sleep Med Rev. 2005;9:185–200.
47. Arnulf I, Leu-Semenescu S. Sleepiness in Parkinson's disease. Parkinsonism Relat Disord. 2009;15(Suppl 3):S101–S104.
48. Jitkritsadakul O, Bhidayasiri R. Physicians' role in the determination of fitness to drive in patients with Parkinson's disease: systematic review of the assessment tools and a call for national guidelines. J Clin Mov Disord. 2016;3:14.
49. Merino-Andreu M, Arnulf I, Konofal E, et al. Unawareness of naps in Parkinson's disease and in disorders with excessive daytime sleepiness. Neurology. 2003;60:1553–1554.
50. Horne M, Volkmann J, Sanneli C, et al. An evaluation of the Parkinson's Kinetigraph (PKG) as a tool to support deep brain stimulation eligibility assessment in patients with Parkinson's disease [abstract]. Mov Disord. 2017;32(suppl 2). [cited 2018 May 1]. Available from: http://www.mdsabstracts.org/abstract/an-evaluation-of-the-parkinsons-kinetigraph-pkg-as-a-tool-to-support-deep-brain-stimulation-eligibility-assessment-in-patients-with-parkinsons-disease/
51. Koivu M, Scheperjans F, Pekkonen E. Ambulatory movement measurement in evaluating deep brain stimulation effect in patients with advanced Parkinson's disease [abstract]. Mov Disord. 2017;32(suppl 2). [cited 2018 May 1]. Available from: http://www.mdsabstracts.org/abstract/ambulatory-movement-measurement-in-evaluating-deep-brain-stimulation-effect-in-patients-with-advanced-parkinsons-disease/
52. Willows T, Dizdar N, Nyholm D, et al. Initiation of levodopa-carbidopa intestinal gel infusion using telemedicine (Video communication

system) facilitates efficient and well-accepted home titration in patients with advanced Parkinson's disease. J Parkinsons Dis. 2017;7:719–728.
53. Willis AW, Schootman M, Evanoff BA, et al. Neurologist care in Parkinson disease: a utilization, outcomes, and survival study. Neurology. 2011;77:851–857.
54. Schneider RB, Biglan KM. The promise of telemedicine for chronic neurological disorders: the example of Parkinson's disease. Lancet Neurol. 2017;16:541–551.
55. Beck CA, Beran DB, Biglan KM, et al. National randomized controlled trial of virtual house calls for Parkinson disease. Neurology. 2017;89:1152–1161.
56. Pasluosta CF, Gassner H, Winkler J, et al. An emerging era in the management of Parkinson's disease: wearable technologies and the internet of things. IEEE J Biomed Health Inform. 2015;19:1873–1881.
57. Farzanehfar P, Woodrow H, Braybrook M, et al. Objective measurement in routine care of people with Parkinson's disease improves outcomes. NPJ Parkinsons Dis. 2018;4:10.
58. Odin P, Chaudhuri KR, Volkmann J, et al. Viewpoint and practical recommendations from a movement disorder specialist panel on objective measurement in the clinical management of Parkinson's disease. Npj Parkinson's Dis. 2018;4. Article number: 14. DOI:10.1038/s41531-018-0051-7
59. Farzanehfar P, Horne M. Evaluation of the Parkinson's KinetiGraph in monitoring and managing Parkinson's disease. Expert Rev Med Devices. 2017;14:583–591.
60. Grosset KA, Bone I, Grosset DG. Suboptimal medication adherence in Parkinson's disease. Mov Disord. 2005;20:1502–1507.
61. Horne M, Kotschet K, McGregor S. The clinical validation of objective measurement of movement in Parkinson's disease. CNS. 2016;2:16–23.
62. Evans AH, Kettlewell J, McGregor S, et al. A conditioned response as a measure of impulsive-compulsive behaviours in Parkinson's disease. PLoS One. 2014;9:e89319.
63. Ossig C, Gandor F, Fauser M, et al. Correlation of quantitative motor state assessment using a Kinetograph and patient diaries in advanced PD: data from an observational study. PLoS One. 2016;11:e0161559.
64. Titova N, Martinez-Martin P, Katunina E, et al. Advanced Parkinson's or "complex phase" Parkinson's disease? Re-evaluation is needed. J Neural Transm. 2017;124:1529–1537.