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Evaluation of Clinical Utility of the Personal KinetiGraph® in the Management of Parkinson Disease

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Abstract

INTRODUCTION: Parkinson's disease (PD) is a disorder characterized by complex motor and non-motor symptoms that can be difficult for patients to accurately communicate. Wearable technologies portend improvements in assessment and monitoring of these symptoms, with their clinical utility currently being evaluated in routine clinical care. OBJECTIVE: To evaluate the clinical utility of the Personal KinetiGraph® (PKG®) Movement Recording System in the routine clinical care of persons with PD (PWP). METHODS: Clinically stable, non-demented PWP presented for two routine clinic visits that included: medication review, symptom review, neurological examination including the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III/IV, and completion of a clinical management plan by a movement disorder specialist prior to review of the PKG report. After reviewing the PKG report, the clinician completed a modified clinical management plan taking into consideration the findings of the PKG. This was repeated at a second visit to evaluate various outcome measures following PKG-enhanced management. RESULTS: The PKG improved the assessment of PD symptoms and the response to treatment, while increasing patient activity levels and compliance. Clinical management plans enhanced by PKG led to different recommendations in 29.4% of cases compared with standard of care due to higher rates of bradykinesia, dyskinesia, tremor, and fluctuations identified by PKG. Using the PKG in the clinical management plan led to a change in medications in 75% (21/28) of patients and both a statistically significant difference and a clinically meaningful reduction in MDS-UPDRS III score of 4.8 (p = 0.028). Additionally, positive changes in both the clinician (17/28; 61%) and patient-reported (13/24; 54%) Global Impression of Improvement were reported. CONCLUSION: The PKG is a valuable tool in augmenting clinical management when utilized along with a clinical assessment.

Keywords

Parkinson's Disease, Wearable, Objective Measurement, Clinical Management

1. Introduction

Parkinson's disease (PD) is a neurological disorder characterized by progressive loss of motor control and a host of non-motor symptoms including cognitive impairment, depression, and impulse control behaviors [1]. The prevalence of PD in the United States increases with patient age and the minimum case burden is estimated to be 930,000 by 2020 increasing to over 1.2 million cases by 2030 [2]. Medicare claims data reveal persons with PD (PWP) have increased health care utilization and spending with an annual, all-cause, per-patient cost of $55,033, a healthcare burden double that of the non-PD cohort [3]. PWP require various types of healthcare services with outpatient physician office visits being the mainstay of clinical management. In terms of overall office visits and healthcare utilization for any medical reason, PWP attended over 9 office visits per patient year [4]. Furthermore, a recent report commissioned by the Michael J. Fox Foundation showed a $51.9 billion per year total cost of PD, a substantial increase over previous estimates [5].

PD is a complex disorder with varying symptom frequency, severity and coexistence of motor and non-motor symptoms for each PD patient. Patients report challenges with articulating symptoms and treatment response because symptoms may be unpredictable, difficult to recognize, and vary within a given day and from day-to-day. Patients report that important goals for improving their care include reductions in "off" time, better symptom control, and less side effects [6].

Clinical management of PWP is similarly complex, symptom-based and requires individualization to address functional status and quality of life. Optimal management relies on patient/caregiver-reported assessments and clinic-based evaluations during physician office visits that commonly occur every 3 - 6 months, with frequency increasing as symptoms dictate. The patient's condition during a physician office visit may not reflect the range of or most troubling symptoms experienced during routine activities of daily living [7]. Therefore, an opportunity exists to obtain more thorough and accurate information clinicians can be used to evaluate patient symptomology, response to therapy, and monitor disease progression over time to support delivery of patient-centered care [8].

To address this unmet need, wearable technologies offering continuous objective measurement (COM) platforms have emerged [9] [10]. These new technologies provide clinicians with information about a patient's movement throughout the day during activities of daily living and variation in movement

from day-to-day. One of these technologies is the Personal KinetiGraph® (PKG®) Movement Recording System (Global Kinetics Corp, Australia; FDA Clearance #K140086), which consists of an interactive wrist-worn watch that collects movement data, proprietary analysis algorithms and multi-symptom report generation. Programmable vibration-based medication reminders can be used to monitor medication compliance and symptom response. Since 2012, the PKG System has undergone clinical validation studies [11]-[18] with more recent multi-national publications of its clinical applications [19]-[24]. The University of California San Diego (UCSD) Movement Disorder Center was among the first clinical sites in the United States to use the PKG System. The aim of this study was to formally evaluate the clinical utility of the PKG System in the routine clinical care of PWP. To do so, we integrated the PKG System into our Movement Disorder Specialist clinical practice and formally studied its impact on PD symptom assessment, clinical management optimization, and patient outcomes.

2. Methods

2.1. Population

Patients were enrolled from the UCSD Movement Disorder Center from 6/2/2016 to 3/16/2017. Inclusion criteria were a UK PD Brain Bank clinical diagnostic criteria [25], Hoehn and Yahr stages 1 - 3, ages 46 - 83 years, current use of levodopa, and ability to provide informed consent. Patients were excluded if they had a clinical diagnosis of dementia that could limit their ability to use the PKG.

2.2. Objectives

The primary objective of this study was to evaluate the clinical utility of the PKG System when used in routine clinical care of PD patients.

2.3. Design and Procedures

This was a prospective, single-arm, open-label study approved by the UCSD institutional review board and carried out during two routine successive office visits (Visit 1 and Visit 2) completed by the study Movement Disorder Specialist (MDS) neurologist. Established patients were identified either during a routine office visit or via telephone screening to determine their interest in study participation. Patients who met eligibility requirements provided written informed consent.

Prior to each clinic visit, a PKG Watch was configured by clinic staff and provided to the patient in advance of the clinic visit. Patients received instruction on PKG Watch use including placement of the watch on the side of the body most severely impacted by PD symptoms and wear, vibration-based medication alerts, and acknowledgement of medication intake. Following completion of a 6-day wear period, the patient returned the PKG Watch to the clinic for data download and automated PKG report generation. During each clinic visit, patients under-

went routine clinical evaluations by the study MDS including: structured symptom assessments, medication review, a neurological examination including Movement Disorder Society Unified Parkinson's Disease Rating Scale Motor Examination and Motor Complications (MDS-UPDRS III & IV, respectively), a commonly used assessment to measure progression of PD [26], followed by the development of a clinical management plan. The study MDS then reviewed the PKG report. Using the PKG data in addition to the information gained during usual care activities, the study MDS determined if the standard clinical management plan should be changed and discussed findings with the patient to arrive at a final clinical management plan the patient would then follow. At the end of each visit, the study MDS completed a survey on the impact of the PKG during that visit.

At the end of Visit 2, the patient received a survey to record his/her experience with PKG use and PKG impact on his/her care using a 5-point Likert scale (Strongly Disagree to Strongly Agree, and Not valuable to Very Valuable), respectively. The patient also completed the Patient Global Impression of Improvement scale (PGI-I) [27] in which the patient rates on a scale of 1 (Very Much Improved) to 7 (Very Much Worse) the status of his/her Parkinson's Disease at Visit 2 compared to Visit 1. The study MDS similarly completed a survey to record the global impact of the PKG on patient using the Clinician Global Impression of Improvement scale (CGI-I) [12] [28]. A REDCap database was utilized for data collection and management [29]. Quality control audits were carried out to ensure data accuracy and integrity.

No restrictions were placed on the types of treatments that could be prescribed or changed by the MDS given the pragmatic nature of the study and the time elapsed between visits was per the standard of care. To reduce the potential for bias, at each visit, the routine clinic visit and clinical management plan were completed by the study MDS prior to reviewing the PKG report. Additionally, Visit 1 UPDRS data was not reviewed by the study MDS prior to completing the UPDRS for Visit 2.

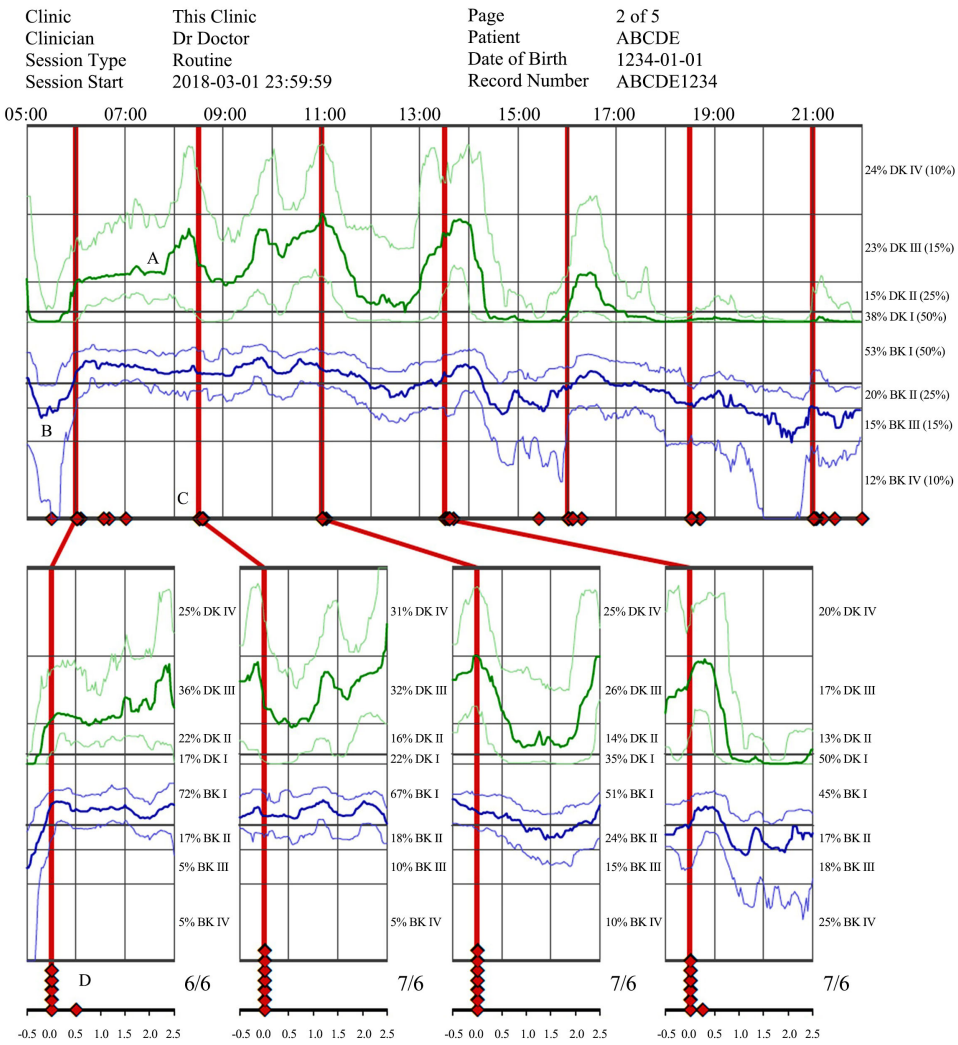
2.4. Information Provided by the PKG

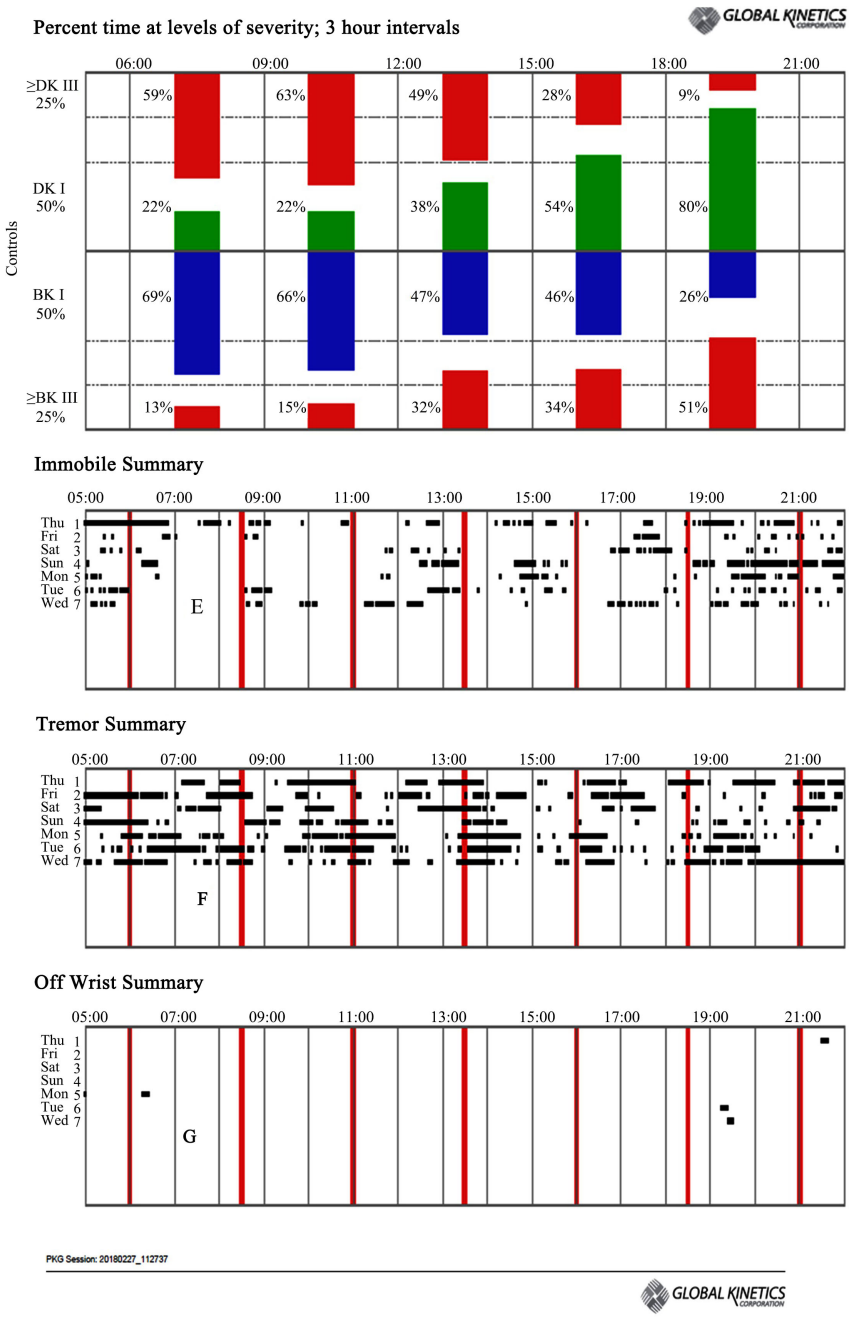
The PKG is a 4-page report depicting patient movement graphically and numerically, and includes the following information for each day of the wear period and summarized for all wear period days (**Figure 1**):

- A: Validated dyskinesia score (DKS) representative of hyperkinetic movements plotted against time of day for individual days over the full recording period [14]
- B: Validated bradykinesia score (BKS) representative of the degree of slowed movements plotted against time of day for individual days over the full recording period [14]
- C: Record of the patient's self-reported acknowledgement of taking levodopa relative to the patient's prescribed medication times

- D: Peri-dose response curves graphically depicting summary bradykinesia and dyskinesia summary data with each dose aligned with the time when the patient acknowledged taking their PD medications
- E: Record of periods of immobility, which may be indicative of periods of daytime sleep and somnolence, plotted against time of day and a validated summary percent time immobile score (PTI) [15]
- F: Record of periods of tremor for each day and a validated summary percent time with tremor score (PTT) [16]
- G: Record of periods when the patient was not wearing the PKG Watch
- H: Validated fluctuation and dyskinesia score (FDS) representative of motor fluctuations characterized by wearing-off and complications in the form of dyskinesia [17]

Use of the median BKS and DKS scores helped to characterize whether patient symptoms were considered to be "controlled" or "uncontrolled" in relation to target ranges that were defined based on normal reference ranges and modified according to expert opinion [14] [21] [27] [30] [31].





PKG Session: 20180227_112737

GLOBAL KINETICS

Session Type	Routine
Session Start	2018-03-01 23:59:59
Session Duration	6 days (05:00 - 22:00)
Reminders	06:00, 08:30, 11:00, 13:30, 16:00, 18:30, 21:00
Deep Brain Stimulator	0
Session Comment	
Prescription Details	Madopar 125mg 2 -2.5 hourly from 06:00 (x7 per day) opicapone 50 mg Neupro patch 10mg daily Please check medications, timings and most affected side

	ABCDE Patient	Control	(Percentiles)
BK (09:00 - 18:00) **B**	10.8 - 17.5 - 26.7	12.7 - 18.6 - 26.1	25 - 50 - 75
DK (09:00 - 18:00) **A**	0.8 - 13.7 - 42.6	0.9 - 4.3 - 16.5	25 - 50 - 75
FDS (09:00 - 18:00)	17.5 **H**		
PTI (09:00 - 18:00)	11.6% **E**		
PTT (09:00 - 18:00)	22.0% **F**		

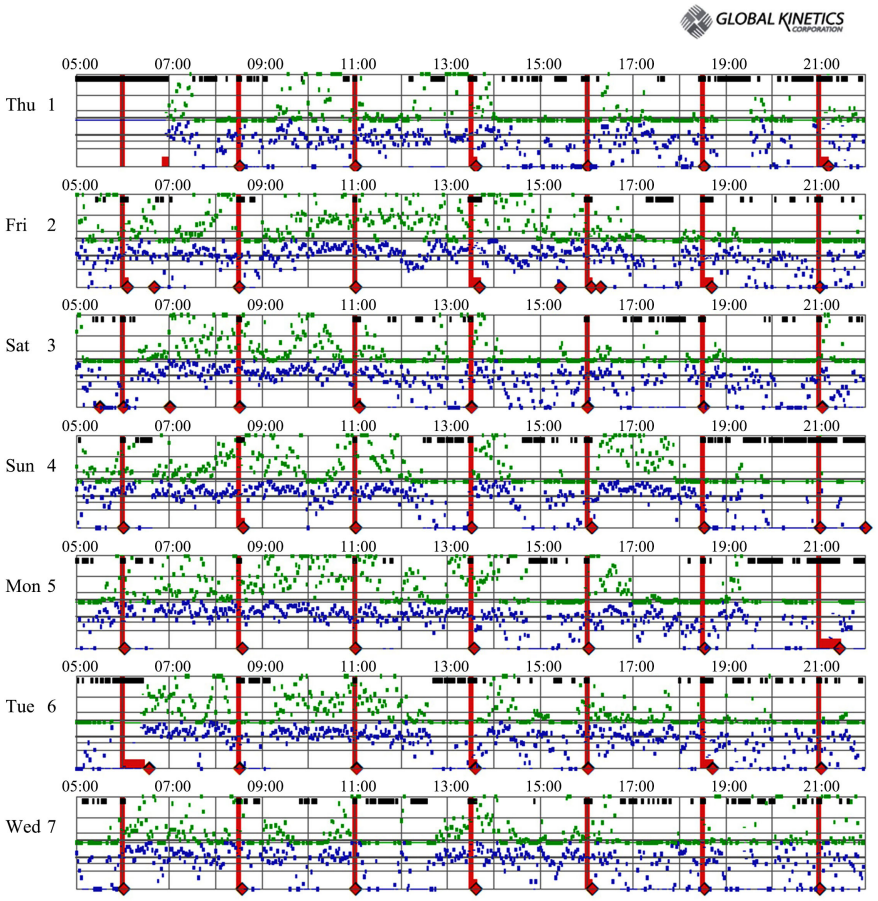


Figure 1. PKG report. A: Dyskinesia Score (DKS), B: Bradykinesia Score (BKS), C: Medication acknowledgment, D: Peri-Dose response, E: Percent Time Immobility (PTI), F: Percent Time Tremor (PTT), G: Off-wrist, H: Fluctuation and Dyskinesia Score (FDS).

2.5. Outcome Measures

Outcome measures of interest included:

- Patient PD symptom assessment: bradykinesia, on-off fluctuations, dyskinesia, somnolence, and medication non-compliance
- Clinical management optimization: clinical management plan changes, PD medication management, MDS survey
- Patient outcomes: MDS-UPDRS III [26] [27], MDS-UPDRS IV [26] [27], PKG scores [11]-[18], Hoehn & Yahr rating scale for PD staging [32], CGI-I, PGI-I, patient survey [28]

2.6. Statistical Analysis

An accrual size of up to 40 patients was empirically selected to allow for potential drop-outs. Given the intended design of this study, relevant summary descriptive statistics are reported for all outcome measures of interest at each visit and we did not correct for multiple comparisons. Levodopa-equivalent dose (LED) was calculated for each PD medication dose using a standardized protocol [33] because the amount of levodopa included in each PD medication varies.

MDS-UPDRS III and IV scores were calculated using previously published and validated procedures [26]. A paired t-test was used for comparisons of continuous measures between study visits, and Wilcoxon signed rank test for ordinal data. Subgroup analyses were not carried out due to small sample sizes. All P values are two-sided, with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in SPSS version 26 (Armonk, NY: IBM Corp).

3. Results

3.1. Study Population and Demographics

A total of 35 PWPs fulfilling inclusion/exclusion criteria provided informed consent and were enrolled into the study between 6/2/2016 and 2/28/2017 with 28 completing both study visits and were included in the final analyses. Seven patients were withdrawn from the study prior to completion by the investigator. One patient admitted to using a walker after enrollment (exclusion criterion), one patient changed his own medication schedule during a PKG Watch wear period, one was non-compliant with PKG wear, one PKG led to inadequate data collection and the patient was unable to repeat, one patient became bedridden due to an unrelated illness, and two were lost to follow up. Table 1 outlines the demographics and baseline characteristics of the 28 patients who completed the study.

Table 1. Patient characteristics.

Characteristic	Mean ± SD or N (%)
Gender	
Male	19 (68%)
Female	9 (32%)
Age in years	71 ± 10
Age at diagnosis of Parkinson's disease (years)	65 ± 11
Years with Parkinson's disease	6 ± 5
Body side most affected by Parkinson's disease symptoms	
Right	14 (50%)
Left	14 (50%)
Hoehn and Yahr scale	
Stage 1	10 (36%)
Stage 2	14 (50%)
Stage 3	4 (14%)
Medications used	
Carbidopa/Levodopa Immediate Release	23 (82%)
Carbidopa/Levodopa Controlled Release	6 (21%)
Rasagiline	4 (14%)
Carbidopa/Levodopa Extended Release (Rytary™)	3 (11%)
Selegiline	3 (11%)
Ropinirole	2 (7%)
Number of Parkinson's disease medications used per patient	
1	19 (68%)
2	6 (21%)
3	2 (7%)
4	1 (4%)
Levodopa equivalent dose (mg)	486 ± 288

3.2. PD Symptom Assessment

Table 2 summarizes patient PD symptoms found during routine clinical history as reported by the patient and/or caregiver, and those found using qualitative and quantitative data from the PKG. Bradykinesia was the most commonly reported symptom by both assessment methods. PD symptom assessment by clinical history resulted in more frequent reports of on-off fluctuations, daytime somnolence, and dose-related somnolence compared to the PKG. Conversely, PD symptom assessment by the PKG identified more patients with bradykinesia, dyskinesia, and medication non-compliance (defined as not taking the prescribed PD medicines at scheduled times). Of note, five of nine patients with no clinical history of bradykinesia at one or both visits and showed evidence of uncontrolled bradykinesia based on the PKG. Presence of tremor was found in 86% (24/28) of the patients with high concordance between clinical history and PKG. Despite all patients reporting consistent medication use, non-compliance was found on the PKG in 4 patients at Visit 1 and 1 patient at Visit 2.

Table 2. PD symptom assessment: clinical history and PKG.

Symptoms/Findings	Visit 1		Visit 2	
	Clinical History	PKG	Clinical History	PKG
Bradykinesia	50%	79%	43%	68%
On-off fluctuations	36%	21%	25%	25%
Dyskinesia, peak-dose	4%	25%	11%	29%
Tremor	86%	86%	86%	96%
Daytime somnolence	32%	29%	57%	11%
Dose-related somnolence	14%	0%	21%	0%
Medication non-compliance	4%	14%	7%	4%

3.3. Clinical Management Optimization

The addition of the PKG to the clinical assessment revealed a higher degree of symptom severity than was noted by the clinical history alone in 18 patients (64%) at Visit 1 and 8 patients (29%) at Visit 2, resulting in 21 (75%) and 9 (32%) clinical management plan changes at Visit 1 and Visit 2, respectively (Table 3). These medication changes included one or more of the following: add a new medication, stop a mediation, increase a medication dose, decrease a medication dose or adjust dose timing.

Table 4 provides a summary of the clinical management plan for PD medication management from the clinical assessment alone and the clinical assessment with the PKG for Visits 1 and 2. Management plans were changed after review of the PKG in 76% (26/34) of cases with PD medication dose increases being the most common change. When the PKG was added to the clinical assessment, 8 cases that would not have otherwise had a clinical management change went on to have a change.

Table 3. Clinical management plan changes.

Clinical Management Changes*	Visit 1	Visit 2
	N (%)	N (%)
Add Medication	5/28 (18%)	1/28 (4%)
Stop Medication	2/28 (7%)	0 (0%)
Increase Medication	10/28 (36%)	4/28 (14%)
Decrease Medication	1/28 (4%)	0 (0%)
Adjust Medication Dose Timing	3/28 (11%)	2/28 (7%)
Other Changes	0 (0%)	2/28 (7%)**
Total # Clinical Management Changes	21/28 (75%)	9/28 (32%)
Total Patients with Management Change	18/28 (64%)	8/28 (29%)

*Multiple changes possible, **PKG indicated no treatment change (n = 1) or recommendation for deep brain stimulation (n = 1).

Table 4. PD medication management: clinical assessment alone and clinical assessment with the PKG.

		Based on Clinical Assessment with the PKG					
		Add	Stop	Increase Dose	Decrease Dose	Adjust Timing	No Change
Based on Clinical Assessment Alone	Add	1					1
	Stop			7			
	Increase Dose						
	Decrease Dose						
	Adjust Timing			1		5	
	No Change	4	2	9	1	3	2

*Light gray shading indicates an incongruency in the management plan between clinical assessment and the PKG. Dark gray shading signifies agreement between clinical assessment alone and the clinical assessment with the PKG.

We also compared the type and magnitude of changes in PD medications that resulted from the PKG-based recommendations. Reviewing the LED data, 21 of 28 patients (75%) had a change in medication dose with 64% increasing dose (LEDmean = +223 mg) and 11% decreasing dose (LEDmean = −117 mg). A total of 7/28 patient (25%) had no change in LED. All four patients receiving Rytary had their dose changed; two patients had an increase and two had a decrease.

The MDS survey indicated patient care benefited from the PKG being added to the clinical assessment and resulted in improved patient dialogue and education (Table 5). The MDS also reported the PKG improved the ability to assess the impact of therapy in 93% of patients at Visit 1 and 89% at Visit 2.

Table 5. MDS survey: Global impact of PKG use on patient care.

Survey Element	Visit 1	Visit 2
	N (%)	N (%)
Improved dialogue with patient	28 (100%)	25 (89%)
Improved ability to assess impact of a therapy	26 (93%)	25 (89%)
Improved patient education about symptoms	26 (93%)	22 (79%)
Improved patient education about illness	25 (89%)	23 (82%)
Improved patient education about treatment use	18 (64%)	19 (68%)
Improved ability to assess need for additional tests or treatments	3 (11%)	1 (4%)

4. Patient Outcomes

Table 6 summarizes overall outcome measures of MDS-UPDRS-III and IV, PKG Scores, and Hoehn and Yahr Scale ratings for the study cohort. At the start of the study, a majority of patients had clinically significant PD symptoms based on the MDS-UPDRS and PKG Scores: 54% had a MDS-UPDRS-III score > 27, 82% reported motor fluctuations with 44% spending > 50% of the waking day in the OFF state, 82% had a PKG PTI > 5%, 82% had a PKG PTT > 1%, 79% had a PKG BKS score > 25, and 18% reported dyskinesias. Among patients with uncontrolled motor symptoms per MDS-UPDRS-III, 12/15 (80%) also had a median BKS score > 25.

At Visit 2, overall mean motor function assessed by MDS-UPDRS-III were reduced (improved) which was statistically significant and clinically meaningful [34] [35] and most notably, the proportion of patients with motor fluctuations, >50% of waking day in the OFF state, and fluctuations of moderate to severe complexity was reduced (Table 6). Overall, PKG scores were similar between Visit 1 and 2. At Visit 2, 16 (57%) had improvement and 12 (43%) had worsening median BKS scores and this finding was similar across the PKG scores. Two patients had medication changes due to higher than desired DKS (2.5 and 2.8) with both having improvement in DKS at Visit 2 (2.1 and 1.3 respectively). Overall, Hoehn and Yahr ratings were similar between Visit 1 and 2. At Visit 2, 5 (18%) patients were rated as having improved one Hoehn and Yahr stage and 6 worsened one stage.

On the CGI-I survey, the MDS ranked 17/28 (61%) as having improvement, with one patient very much improved. Nine patients had no change and 2 were rated as minimally worse from the start of the study. On the PGI-I survey, 13/24 (54%) patients indicated their PD was improved, 9/24 (38%) no change and 2/24 (8%) minimally worse, four patients did not respond.

On the patient survey, patients indicated the PKG was easy to use (93%), performed as expected (96%) with all 28 (100%) patients stating they would use it again if given the opportunity. Patients assessed the PKG as having an overall positive impact on their care with 79% of patients reporting the device assisted with explaining symptoms to the physician. All patients indicated the PKG me-

dication reminders assisted with taking medication on time. In addition, they thought it was valuable in providing data to the physician they could not provide (89%), in providing additional data about their normal daily activities (96%), in providing addition data that assisted the physician with making decision about

Table 6. Patient outcomes: MDS UPDRS III and IV, PKG scores, and Hoehn and Yahr scale.

Outcome	Visit 1	Visit 2	P Value
	Mean ± STD (Range) or N (%)	Mean ± STD (Range) or N (%)	
MDS-UPDRS, Part III			
Summary Score	28.9 ± 14.1 (6 - 67)	24.1 ± 13.5 (6 - 61)	0.028*
Score > 27 [30]	15 (54%)	12 (43%)	
MDS-UPDRS, Part IV			
Summary Score	4.1 ± 3.3 (0 - 16)	3.0 ± 2.9 (0 - 9)	0.07*
Dyskinesias	5 (18%)	5 (18%)	
Functional Impact Moderate or Severe	1 (20%)	0 (0%)	
Motor fluctuations	23 (82%)	21 (75%)	
>50% time spent in off state	10 (44%)	4 (19%)	
Complexity Moderate or Severe	4 (17%)	0 (0%)	
PKG Scores [All Patients]			
Total Scores (Mean± SD; Range)			
BKS	31.7 ± 7.1 (20.2 - 51.1)	31.6 ± 7.0 (20.5 - 52.3)	0.86
DKS	1.8 ± 2.2 (0.0 - 7.2)	1.5 ± 1.6 (0.0 - 8.0)	0.21
FDS	8.0 ± 2.6 (3.3 - 15.4)	8.1 ± 2.2 (4.3 - 13.4)	0.82
PTI (%)	12.6 ± 9.7 (0 - 42.4)	12.8 ± 8.3 (1.1 - 33.5)	0.88
PTT (%)	12.5 ± 11.9 (0.7 - 44.3)	12.2 ± 12.1 (0.2 - 44.6)	0.78
Hoehn and Yahr Scale	1.79	1.82	0.76
[Controlled Bradykinesia (BKS ≤ 25)]	6 (21%)	5 (18%)	
BKS	22.5 (20.2 - 25.0)	22.5 (20.5 - 24.9)	
DKS	4.5 (1.0 - 7.2)	3.3 (1.2 - 8.0)	
FDS	9.1 (3.3 - 15.4)	9.3 (4.3 - 13.4)	
PTI (%)	2.2 (0.0 - 6.4)	4.9 (2.3 - 9.6)	
PTT (%)	9.9 (0.7 - 23.4)	3.9 (0.2 - 10.8)	
[Uncontrolled (BKS > 25)]	22 (79%)	23 (82%)	
BKS	34.2 (25.4 - 51.1)	33.6 (26.7 - 52.3)	
DKS	1.1 (0 - 6.9)	1.1 (0 - 2.9)	
FDS	7.7 (4.8 - 13.2)	7.8 (4.4 - 11.1)	
PTI (%)	15.5 (1.1 - 42.4)	14.5 (1.1 - 33.5)	
PTT (%)	13.3 (0.7 - 44.3)	14.1 (0.8 - 44.6)	
[Uncontrolled Dyskinesia (DKS > 9)]	0 (0%)	0 (0%)	
[Other]			
FDS > 13 [30] [31]	2 (7%)	1 (4%)	
PTI > 5% [16]	23 (82%)	20 (71%)	
PTT >1% [17]	23 (82%)	26 (93%)	

*Statistically significant ($\alpha \leq 0.05$).

their care (93%) and in providing data that contributed to the overall management of their PD (93%). When asked whether they would be willing to pay for the device if their insurance didn't cover the cost, 32% of patients stated they would, 25% stated it would depend on the cost and 43% said they would not pay if their insurance did not cover the cost.

Case Study

A 60-year old man with 1-year history of slowed movements, rest tremor and rigidity was diagnosed with PD. Carbidopa/levodopa 1 tablet every 4-hours (QID) had been initiated and produced subtle improvements in tremor and bradykinesia according to the patient who was unable to discern shifts in on-off status. Work-up included a normal brain MRI and positive DaTscan demonstrating reduced dopamine transporter binding on the right more than the left. During visit 1, the patient reported symptoms of bradykinesia, freezing and tremor, with onset of levodopa effect in ~1 hour and no clear wearing off which he reported were "unpredictable". MDS-UPDRS showed moderate bilateral rigidity, bradykinesia, mild gait dysfunction, slight freezing, moderate postural instability, moderate global bradykinesia, and slight rest tremor of left leg. Based on the history and exam, the patient appeared undermedicated and the management plan included increasing the frequency of levodopa to every 3-hours (5/day). After reviewing the PKG results, the bradykinesia and tremors were confirmed along with medication compliance, though no dose-response was observed over the 6-day wear suggesting the patient was globally bradykinetic and always "off". This was confirmed by the high median BKS of 35.1 (severe bradykinesia), low FDS of 6.1 (minimal fluctuations), and PTT of 4.7% (moderate tremor). Based on the PKG, the patient was considered severely undermedicated and the plan was to increase to 1-tab every three hours for 1-week, then increase again to 2-tabs every 3 hours as tolerated after 2-weeks.

The patient returned approximately 3-months later for follow up again noting onset of levodopa effect in 1-hour, no fluctuations, and now reported peak-dose dyskinesia on 2-tabs taken 5-times daily. The patient also reported daytime somnolence. MDS-UPDRS now showed mild rigidity, slight bradykinesia, mild gait dysfunction, slight freezing, moderate postural instability, and no tremor or dyskinesia. The clinical management plan included a change to carbidopa/levodopa 2 tabs taken every 4-hours to reduce symptoms of dyskinesia that the patient reported were occurring > 75% of the day and causing at least a mild impact on his daily activities. A review of the PKG report showed improved bradykinesia (BKS = 29.8), evidence of fluctuations (FDS = 8.1), no dyskinesia (DKS = 2.9), and improvement in tremors (PTT = 2.4%) (**Figure 2**).

The case illustrates a routine challenge encountered in the clinical management of PD, including the over-reliance on the medical history, the limitations of a brief examination without ecologically valid corroborating evidence, and the complexity of PD symptoms the further exacerbate these challenges. In this case, both the standard of care and the additional PKG findings correctly identified

the patient to be bradykinetic, though the quantitative nature of the PKG emphasized the severity of the symptoms and led to a potentially more aggressive levodopa titration schedule. On follow up, the standard of care and PKG management plans diverged due to the reliance on the patient's history of peak-dose bothersome dyskinesias that were not seen on the PKG. Clinicians often encounter similar scenarios whereby a potentially unnecessary dose adjustment is carried out due to patient report that subsequently leads to a clinical decline.

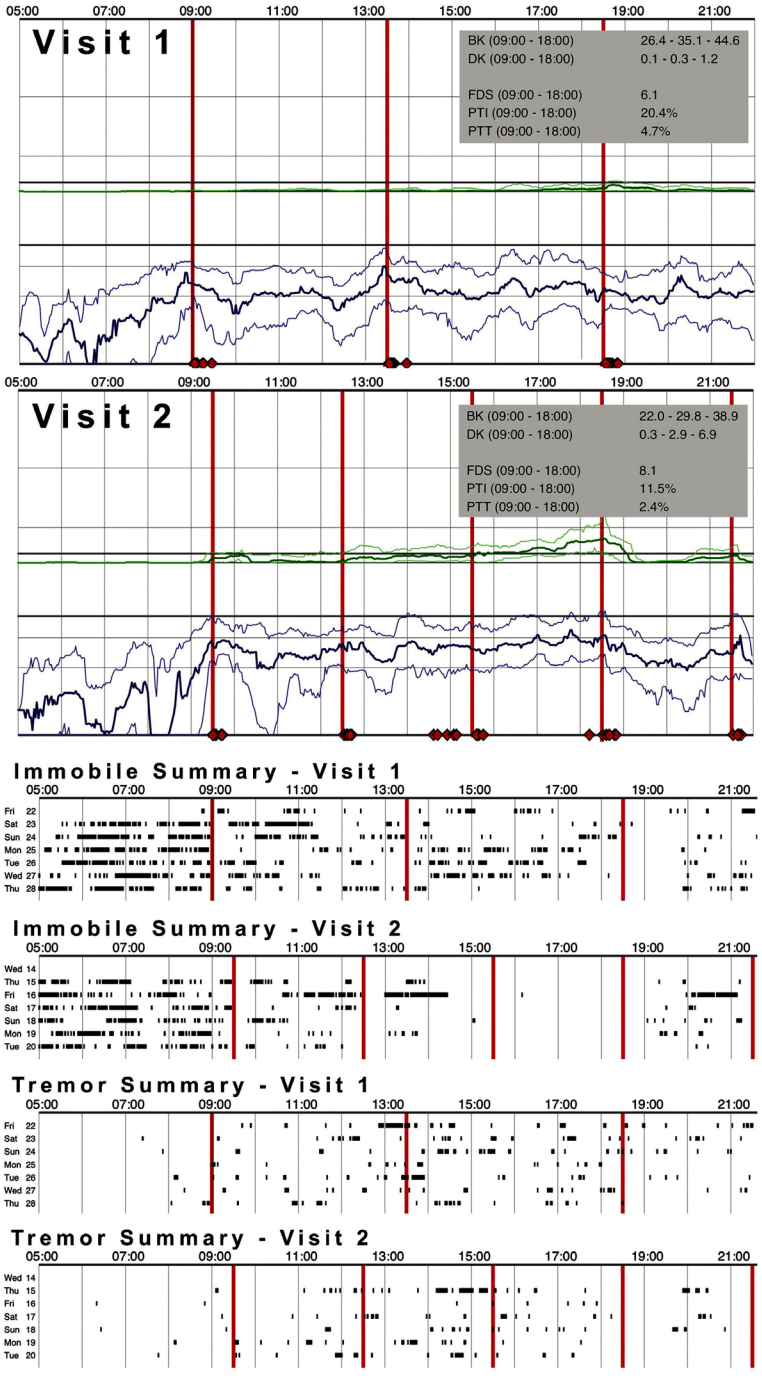


Figure 2. PKG findings from case study comparing visit 1 and visit 2.

Having the corroborating objective data from the PKG helped the clinician to avoid a scenario that may have led to an additional office visit or an adverse event.

5. Discussion

Continuous objective measurement technologies are of significant interest across the healthcare community for the potential to improve healthcare quality and efficiency as well as serve as a catalyst for accelerating the pace of innovation [36] [37] [38]. These technologies are driving a paradigm shift from sole use of in-clinic subjective measurements to in-home continuous monitoring during activities of daily living, a transformation in health care delivery of particular importance in prevalent, heterogeneous, and chronic disease states like diabetes, cardiovascular disease, and asthma [39] [40] [41] [42].

COM use in the care of PWP is following this growing trend and holds promise for earlier diagnosis, improved accuracy of symptom detection, especially for bradykinesia which is difficult for patients to articulate, enhanced disease monitoring, patient engagement, therapy selection, and treatment optimization [43] [44]. COM technologies have the potential to improve upon assessments done in the artificial, constrained environment of the clinic and provide new insights into the impact of medication intake on PD symptoms. The expansion in time and environment that COMs provide has the potential to better inform the clinician of the true state and range of the patient's symptoms. Moving these technologies from research interests to the routine clinical care armamentarium requires clinical validation and ongoing study of clinical utility. In recent years, early adopters have published consensus statements that define how COM data can augment clinical decision making as in the care of patients who are poor historians or have difficulty articulating symptoms, have excessive daytime sleepiness, and in the optimization of new therapies [30] [31].

In this study, we integrated the PKG System into our busy tertiary care PD clinic and evaluated how augmentation of clinical care with the new information this system provides impacts care delivery. One unexpected finding was the divergence of patient-reported symptoms compared to objective measurements of the PKG System. For example, a patient may recall periods of hypersomnolence while the PKG shows accelerometry patterns consistent with wakefulness or a patient reports he/she is experiencing worsening tremors while the PKG shows dyskinesia and no tremor. A number of possibilities may explain these disparities, including poor quality of sleep, mild cognitive impairment limiting recall, and limitations in the patient or caregiver ability to differentiate the complex phenomenology of various motor symptoms in PD. It is not surprising that patients under-reported their medication non-compliance. More importantly though was the observation that compliance rates improved at Visit 2 with the use of the PKG and the patient's presumed awareness that their compliance was being monitored. A similar and equally important observation occurred with regard to patient activity levels. While seemingly trivial and difficult for physi-

cians to accurately assess, the combination of improved medication compliance and increased physical activity in PWP are key factors in the management of PD. These findings also highlight the pitfalls of assuming that patient's consistently under- or over-report their symptoms, with the use of the PKG augmenting the history obtained. An important aspect of this study was the capturing of patient qualitative information regarding the use of COM.

Our findings showed that the use of the PKG System yielded more actionable information than could be obtained by an MDS performing a medical history and neurological examination alone. It is therefore not surprising that PKG-guided management led to a change in treatment in 75% of patients. While it could be argued that improvements in motor-based outcome measures such as the MDS-UPDRS III would improve regardless of the treatment, our findings argue that the type of recommendation depends on the patient and their particular symptom(s). In other words, an increase in levodopa dose across the group may have led to reductions in bradykinesia and tremor scores, while worsening dyskinesia measures. Instead, the use of the PKG System led to significant improvements in the UPDRS-III without exacerbating motor complications as evidenced by a small but non-significant improvement in UPDRS-IV scores. Furthermore, while it makes rational sense that increasing medication leads to positive effects on motor scores, Farzanehfar and colleagues [21] found that 22% of 103 study participants managed with the PKG System were well controlled at the onset of the study and did not require medication adjustment. Unfortunately, limitations in the standard of care prevent both patients and clinicians from accurately predicting whether the PWP is adequately treated.

In addition to enhancing the history and neurological exam findings in PWP, the widening use of COMs such as the PKG System in clinical management will accelerate the debate to define what adequate treatment entails. In the management of diabetes mellitus and hypertension, managing patients to established targets is the standard of care. In the management of PD, these targets are starting to be defined by expert consensus [30] [31] though further studies are needed to demonstrate that treating PWP to particular targets will impact their clinical outcomes.

Given the exploratory nature of this study, some limitations deserve mention. A key limitation of the study was that patients were not followed through medication optimization; therefore, the two visits captured in this study offered a brief snapshot in the care continuum of these patients. As such, while the clinical outcomes observed here are encouraging, overall clinical outcomes achieved when COM is used to optimize medical management of PD patients could not be fully assessed. Additionally, this study did not have a control group; therefore, we cannot directly attribute results seen here to the PKG System. However, the study aimed to isolate the impact of the new information provided by the PKG System by reviewing the PKG after completion of routine clinical care activities and at that time the study MDS determined whether the new information would change the established clinical plan. While clinical assessments completed in this

project are the clinical acumen of one MDS and patients were not always able to be evaluated in the ON state, the project reflects real-world clinical practice of a patient population that is typically encountered in a tertiary MDS clinic.

6. Conclusion

Based on the data collected in this study, we found the PKG System to be a valuable tool in augmenting clinical management planning and decisions, and when utilized along with a clinical assessment. The device was well received by both physicians and patients, scoring high in survey results as a tool to assess impact of therapy and indicating the device had an overall positive impact on patient care and outcomes. Further research is needed to continue the important work of creating evidence-based guidance for the role of COM in the clinical management of PWP.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] International Parkinson and Movement Disorder Society Parkinson's Disease & Parkinsonism. http://www.movementdisorders.org/MDS/About/Movement-Disorder-Overviews/Parkinsons-Disease--Parkinsonism.htm

[2] Marras, C., Beck, J.C., Bower, J.H., Roberts, E., Ritz, B. and Ross, G.W. (2018) Prevalence of Parkinson's Disease across North America. *NPJ Parkinson's Disease*, **4**, Article No. 21. https://doi.org/10.1038/s41531-018-0058-0

[3] Hermanowicz, N. and Edwards, K. (2015) Parkinson's Disease Psychosis: Symptoms, Management, and Economic Burden. *American Journal of Managed Care*, **21**, s199-s206.

[4] Mantri, S., Fullard, M., Beck, J. and Willis, A. (2019) State-Level Prevalence, Health Service Use, and Spending Vary Widely among Medicare Beneficiaries with Parkinson Disease. *NPJ Parkinson's Disease*, **5**, Article No. 1. https://doi.org/10.1038/s41531-019-0074-8

[5] Michael J. Fox Foundation (2019) Parkinson's Disease Economic Burden on Patients, Families and the Federal Government Is $52 Billion, Doubling Previous Estimates. https://www.michaeljfox.org/publication/parkinsons-disease-economic-burden-patients-families-and-federal-government-52-billion

[6] U.S. Food and Drug Administration (FDA) (2016) The Voice of the Patient, Parkinson's Disease. https://www.fda.gov/media/124392/download

[7] Bergquist, F. and Horne, M. (2014) Can Objective Measurements Improve Treatment Outcomes in Parkinson's Disease? *European Neurological Review*, **9**, 27-30. https://doi.org/10.17925/ENR.2014.09.01.27

[8] Espay, A., Bonato, P., Nahab, F.B., *et al.* (2016) Technology in Parkinson's Disease: Challenges and Opportunities. *Movement Disorders*, **31**, 1272-1282. https://doi.org/10.1002/mds.26642

[9] Sánchez-Ferro, A., Elshehabi, M., Godinho, C., *et al.* (2015) New Methods for the Assessment of Parkinson's Disease (2005 to 2015): A Systematic Review. *Movement Disorders*, **31**, 1283-1292. https://doi.org/10.1002/mds.26723

[10] Ossig, C., Antonini, A., Buhmann, C., *et al.* (2015) Wearable Sensor-Based Objective Assessment of Motor Symptoms in Parkinson's Disease. *Journal of Neural Transmission*, **123**, 57-64. https://doi.org/10.1007/s00702-015-1439-8

[11] Ossig, C., Gandor, F., Bosredon, C., Fauser, M., Reichmann, H., Horne, M.K., *et al.* (2016) Correlation of Objective Measurement of Motor States Using a Kinetograph and Patient Diaries in Advanced Parkinson's Disease. *PLoS ONE*, **11**, e0161559. https://doi.org/10.1371/journal.pone.0161559

[12] Horne, M., Kotschet, K. and McGregor, S. (2016) The Clinical Validation of Objective Measurement of Movement in Parkinson's Disease. *CNS*, **1**, 15-22.

[13] Klingelhoefer, L., Rizos, A., Sauerbier, A., *et al.* (2016) Night-Time Sleep in Parkinson's Disease—The Potential Use of Parkinson's KinetiGraph: A Prospective Comparative Study. *European Journal of Neurology*, **23**, 1275-1288. https://doi.org/10.1111/ene.13015

[14] Griffiths, R.I., Kotschet, K., Arfon, S., *et al.* (2012) Automated Assessment of Bradykinesia and Dyskinesia in Parkinson's Disease. *Journal of Parkinson's Disease*, **2**, 47-55.

[15] Kotschet, K., Johnson, W., McGregor, S., Kettlewell, J., Kyoong, A., O'Driscoll, D.M., *et al.* (2014) Daytime Sleep in Parkinson's Disease Measured by Episodes of Immobility. *Parkinsonism & Related Disorders*, **20**, 578-583. https://doi.org/10.1016/j.parkreldis.2014.02.011

[16] Braybrook, M., O'Connor, S., Churchward, P., *et al.* (2016) An Ambulatory Tremor Score for Parkinson's Disease. *Journal of Parkinson's Disease*, **6**, 723-731. https://doi.org/10.3233/JPD-160898

[17] Horne, M.K., McGregor, S. and Bergquist, F. (2015) An Objective Fluctuation Score for Parkinson's Disease. *PLoS ONE*, **10**, e0124522. https://doi.org/10.1371/journal.pone.0124522

[18] Evans, A.H., Kettlewell, J., McGregor, S., Kotschet, K., Griffiths, R.I. and Horne, M. (2014) A Conditioned Response as a Measure of Impulsive-Compulsive Behaviours in Parkinson's Disease. *PLoS ONE*, **9**, e89319. https://doi.org/10.1371/journal.pone.0089319

[19] Price, J., Martin, H., Ebenezer, L., Cotton, L., Shuri, J., Martin, A. and Sauerbier, A. (2016) A Service Evaluation by Parkinson's Disease Nurse Specialists, of Parkinson's KinetiGraph (PKG) Movement Recording System Use in Routine Clinical Care of Patients with Parkinson's Disease. 4*th World Parkinson's Congress*, Portland, 20-23 September 2016. http://content.iospress.com/articles/journal-of-parkinsons-disease/jpd169900

[20] Spengler, D., Velez-Aldahondo, V.A., Singer, C. and Luca, C. (2016) Initial Deep Brain Stimulation Programming Optimization Using the Personal Kineti Graph (PKG) Movement Recording System. AAN Annual Meeting Abstract. http://www.abstractsonline.com/pp8/#!/4046/presentation/8131

[21] Farzanehfar, P., Woodrow, H., Braybrook, M., McGregor, S., Evans, A., Nicklason, F., *et al.* (2018) Objective Measurement in Routine Care of People with Parkinson's Disease Improves Outcomes. *NPJ Journal of Parkinson's Disease*, **4**, Article No. 10.

https://doi.org/10.1038/s41531-018-0046-4

[22] Berghuis, E., Van Harten, B., Van Kesteren-Biegstraaten, M., Rutgers, W. and Verwey, N. (2018) Parkinson Kinetic Graph: Are Motor Fluctuations in Parkinson Disease Related with Disease Duration? *Advances in Parkinson's Disease*, **7**, 1-6. https://doi.org/10.4236/apd.2018.71001

[23] Santiago, A., Langston, J.W., Gandhy, R., Dhall, R., Brillman, S., Rees, L. and Barlow, C. (2019) Qualitative Evaluation of the Personal KinetiGraphTM Movement Recording System in a Parkinson's Clinic. *Journal of Parkinson's Disease*, **9**, 207-219. https://doi.org/10.3233/JPD-181373

[24] Khodakarami, H., Farzanehfar, P. and Horne, M. (2019) The Use of Data from the Parkinson's KinetiGraph to Identify Potential Candidates for Device Assisted Therapies. *Sensors* (*Basel*, *Switzerland*), **19**, 2241. https://doi.org/10.3390/s19102241

[25] Hughes, A.J., Daniel, S.E., Kilford, L. and Lees, A.J. (1992) Accuracy of Clinical Diagnosis of Idiopathic Parkinson's Disease. A Clinic-Pathological Study of 100 Cases. *Journal of Neurology*, *Neurosurgery*, *and Psychiatry*, **55**, 181-184. https://doi.org/10.1136/jnnp.55.3.181

[26] Goetz, C.G., Tilley, B.C., Shaftman, S.R., *et al.* (2008) Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. *Movement Disorders*, **23**, 2129-2170. https://doi.org/10.1002/mds.22340

[27] Martínez-Martín, P., Rodríguez-Blázquez, C., Alvarez, M., *et al.* (2015) Parkinson's Disease Severity Levels and MDS-Unified Parkinson's Disease Rating Scale. *Parkinsonism & Related Disorders*, **21**, 50-54. https://doi.org/10.1016/j.parkreldis.2014.10.026

[28] Busner, J. and Targum, S. (2007) The Clinical Global Impressions Scale Applying a Research Tool in Clinical Practice. *Psychiatry*, **4**, 28-37.

[29] Harris, P.A., Taylor, R., Thielke, R., *et al.* (2009) Research Electronic Data Capture (REDCap)—A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support. *Journal of Biomedical Informatics*, **42**, 377-381. https://doi.org/10.1016/j.jbi.2008.08.010

[30] Odin, P., Chaudhuri, K.R., Volkmann, J., *et al.* (2018) Viewpoint and Practical Recommendations from a Movement Disorder Specialist Panel on Objective Measurement in the Clinical Management of Parkinson's Disease. *NP Journal of Parkinson's Disease*, **4**, 14. https://doi.org/10.1038/s41531-018-0051-7

[31] Pahwa, R., Isaacson, S.H., Torres-Russotto, D., Nahab, F.B., Lynch, P.M. and Kotschet, K.E. (2018) Role of the Personal KinetiGraph in the Routine Clinical Assessment of Parkinson's Disease: Recommendations from an Expert Panel. *Expert Review of Neurotherapeutics*, **18**, 669-680. https://doi.org/10.1080/14737175.2018.1503948

[32] Goetz, C., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G.T., *et al.* (2004) Movement Disorder Society Task Force Report on the Hoehn and Yahr Staging Scale: Status and Recommendations. *Movement Disorders*, **19**, 1020-1028. https://doi.org/10.1002/mds.20213

[33] Tomlinson, C., Stowe, R., Patel, S., *et al.* (2010) Systematic Review of Levodopa Dose Equivalency Reporting in Parkinson's Disease. *Movement Disorders*, **25**, 2649-2685. https://doi.org/10.1002/mds.23429

[34] Shulman, L.M., Gruber-Baldini, A.L., Anderson, K.E., *et al.* (2010) The Clinically Important Difference on the Unified Parkinson's Disease Rating Scale. *Archives of Neurology*, **67**, 64-70. https://doi.org/10.1001/archneurol.2009.295

[35] Makkos, A., Kovács, M., Pintér, D., Janszky, J. and Kovacs, N. (2019) Minimal Clinically Important Difference for the Historic Parts of the Unified Dyskinesia Rating Scale. *Parkinsonism & Related Disorders*, **58**, 79-82. https://doi.org/10.1016/j.parkreldis.2018.08.018

[36] Atluri, V., Rao, S., Rajah, T., *et al.* (2015) Unlocking Digital Health: Opportunities for the Mobile Value Chain. https://healthcare.mckinsey.com/sites/default/files/Healthcare_WhitePaper_screen_April17.pdf

[37] Al-Eidan, R., Al-Khalifa, H. and Al-Salman, A. (2018) A Review of Wrist-Worn Wearable: Sensors, Models, and Challenges. *Journal of Sensors*, **2018**, Article ID: 5853917. https://doi.org/10.1155/2018/5853917

[38] Cho, J. (2019) Current Status and Prospects of Health-Related Sensing Technology in Wearable Devices. *Journal of Healthcare Engineering*, **2019**, Article ID: 3924508. https://doi.org/10.1155/2019/3924508

[39] Wan, W., Skandari, M.R., Minc, A., *et al.* (2018) Cost-Effectiveness of Continuous Glucose Monitoring for Adults with Type 1 Diabetes Compared with Self-Monitoring of Blood Glucose: The DIAMOND Randomized Trial. *Diabetes Care*, **41**, 1227-1234. https://doi.org/10.2337/dc17-1821

[40] Ong, M.K., *et al.* (2016) Effectiveness of Remote Patient Monitoring after Discharge of Hospitalized Patients with Heart Failure: The Better Effectiveness after Transition Heart Failure (BEAT-HF) Randomized Clinical Trial. *JAMA Internal Medicine*, **176**, 310-318. https://doi.org/10.1001/jamainternmed.2015.7712

[41] Lee, Y.H., *et al.* (2013) Impact of Home-Based Exercise Training with Wireless Monitoring on Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *Journal of Korean Medical Science*, **28**, 564-568. https://doi.org/10.3346/jkms.2013.28.4.564

[42] Ryan, D., *et al.* (2012) Clinical and Cost Effectiveness of Mobile Phone Supported Self-Monitoring of Asthma: Multi-Center Randomized Controlled Trial. *BMJ*, **344**, e1756. https://doi.org/10.1136/bmj.e1756

[43] Monje, M., Foffani, G., Obeso, J. and Sanchez-Ferro, A. (2019) New Sensor and Wearable Technologies to Aid in the Diagnosis and Treatment Monitoring of Parkinson's Disease. *Annual Review of Biomedical Engineering*, **21**, 111-143. https://doi.org/10.1146/annurev-bioeng-062117-121036

[44] Rovini, E., Maremmani, C. and Cavallo, F. (2018) Automated Systems Based on Wearable Sensors for the Management of Parkinson's Disease at Home: A Systematic Review. *Telemedicine and e-Health*, **25**, 167-183. https://doi.org/10.1089/tmj.2018.0035