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Validation and clinical value of the MANAGE-PD tool: A clinician-reported tool to identify Parkinson's disease patients inadequately controlled on oral medications

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ABSTRACT

Introduction: Making Informed Decisions to Aid Timely Management of Parkinson's Disease (MANAGE-PD) is a clinician-reported tool designed to facilitate timely identification and management of patients with advancing Parkinson's disease (PD) with suboptimal symptom control while on standard therapy. The objective of this study was to evaluate the validity and clinical value of the tool.

Methods: Driven by structured inputs from a steering committee and panel of PD experts, the tool was developed to classify patients into 3 categories. Validity and clinical value were elucidated using a two-pronged approach: (i) hypothetical patient vignettes (n = 10) developed based on the MANAGE-PD tool and rated by 17 PD specialists and 400 general neurologists (GN) and (ii) patients with PD (n = 2546) managed in real-world clinical settings. Vignette validity was based on concordance between PD experts' clinical judgement and MANAGE-PD vignette categorization. Patient-level data was used for known-group comparisons (validity) and discordant pair analysis (clinical value).

Results: The tool demonstrated strong validity and clinical value among PD specialists (intraclass coefficient [ICC] 0.843; Fleiss weighted kappa [$\kappa_{weighted}$] 0.79) and GN (ICC 0.690; $\kappa_{weighted}$ 0.65) using patient vignettes. MANAGE-PD also demonstrated real-world validity and clinical value based on ability to identify patients with incrementally higher clinical, economic, and humanistic PD burden across categories of the tool ($p < 0.01$).

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Conclusions: MANAGE-PD demonstrated robust validity and clinical value in identifying patients with suboptimal PD symptom control. Clinical use of MANAGE-PD may complement treatment decision-making and facilitate timely and comprehensive management of patients with advancing PD.

1. Introduction

Parkinson's disease (PD) is the fastest growing neurological disorder worldwide [1]. The increasing prevalence of PD is projected to lead to significant economic burden for patients, families, communities, and countries with aging populations [2,3]. The increase in prevalence has accelerated the demand for timely indication and adjustment of symptomatic treatment and optimal interventions to reduce the burden of advancing PD [1,3]. PD is a complex and diverse neurodegenerative condition that affects multiple body systems, resulting in several motor and non-motor symptoms as well as functional impairments [2]. Motor fluctuations (wearing off) are common in PD and remain the most bothersome problem among patients with advancing PD [4]. While prevalent in PD, motor fluctuations are under-recognized by routine neurological clinical evaluation [5].

Effective management of PD is critical at all stages of disease, requiring individual customization of therapy including optimization of oral regimens and consideration for non-oral treatments such as advanced device-aided therapies [6]. Given the differences in the mechanism of action and routes of administration, neurologists and patients with PD face complex decisions, choosing between available treatment options and selecting the one that best suits the patients' and their families' needs [7]. A lack of consensus around the definition of advanced disease leads to delays in identification of advancing PD, and the resulting heterogeneity of care compounds the challenges to managing disease progression and timely treatment [8,9]. Most patients with advancing PD report being unsatisfied with their current treatment and not being informed about advanced treatment options [10]. The 5- (≥5 times oral levodopa tablet taken/day) 2- (≥2 h of OFF time/day) 1- (≥1 h of troublesome dyskinesia/day) criteria have been proposed by a Delphi expert consensus panel for detection of advanced PD to ensure optimal and timely management [11–16]. However, the 5-2-1 criteria was not meant to differentiate between patients who can benefit from further optimization of oral treatment vs patients who can be considered for device-aided therapy.

This study reports on the continued efforts of a global multi-year research program focused on the development, validation, and assessment of clinical value of Making Informed Decisions to Aid Timely Management of Parkinson's Disease (MANAGE-PD). Building on robust multi-national consensus efforts for identifying the indicators of advancing PD [12,17], MANAGE-PD is a clinician-reported tool designed to facilitate timely identification and management of patients with advancing PD with suboptimal symptom control on their current treatment regimen and may require referral for device aided therapies. The MANAGE-PD tool assesses motor, non-motor, and functional impact symptoms to classify patients into 3 categories: 1) controlled on current treatment regimen, 2) inadequately controlled on current treatment regimen but may potentially benefit with further non-device aided treatment optimization, or 3) inadequately controlled on current treatment regimen and may benefit from device-aided therapy. The purpose of this study was to evaluate the validity and clinical value of the MANAGE-PD tool in identifying patients with advancing PD who are suboptimally controlled on oral medications.

2. Methods

2.1. Study design

The research program involved a mixed-method approach, which included the development and validation of the MANAGE-PD tool. Internationally renowned PD experts formed the study Steering Committee and provided clinical guidance in the tool development. The validation was conducted using a two-step approach: (i) vignette-based validation using an online survey of selected movement disorder specialists (PD specialists) from 15 countries (Denmark, Greece, Austria, Germany, Netherlands, Israel, Finland, Norway, Turkey, France, United Kingdom [UK], Romania, Spain, Italy, and United States [US]) and an internet-panel of general neurologists (GNs) from the US and UK and (ii) real-world patient validation including a global sample of patients with PD receiving care in G7 countries (US, UK, Italy, Spain, France, Germany, Japan).

2.2. MANAGE-PD development

A panel of internationally renowned PD experts was selected based on their expertise in treating patients with advanced PD, experience in development of clinical guidelines, the conduct of research studies, and clinical use of multiple device-aided therapies. The tool was developed based on existing literature [12] and survey-derived and prioritized clinical indicators of suboptimal control on oral PD medications and eligibility to receive device-aided treatment.

2.3. Vignette-based assessment

A set of 10 hypothetical patient vignettes representing the full spectrum of PD severity were developed based on structured inputs from the steering committee. The vignettes were anchored on the items of the MANAGE-PD tool [12] and Delphi consensus-based clinical indicators of advancing PD. Each vignette included demographic characteristics such as age at diagnosis, gender, current PD medications, and description of the frequency and severity of current motor symptoms, non-motor symptoms, and functional impairment limiting activities of daily living [Appendix A. Fig. S1]. Patient vignettes were classified based on *a priori* steering committee assessment and the MANAGE-PD scoring algorithm (labeled as MANAGE-PD vignette category). The vignettes were assigned to MANAGE-PD tool categories such that: vignette 1 represented a patient in MANAGE-PD category 1 (anchor vignette), vignettes 2–5 represented a patient in MANAGE-PD category 2, and vignettes 6–10 represented a patient in MANAGE-PD category 3. The anchor vignette for category 1 served as a control vignette of a patient adequately controlled on oral therapy. Since the MANAGE-PD tool is designed to detect suboptimal symptom control, more vignettes were designed for categories 2 and 3. In addition, categories 2 and 3 represent more complex patient profiles spanning larger symptom types and ranges and thus needed more vignettes to ensure coverage of various symptom combinations.

Leveraging the designed vignettes, two web surveys were conducted: (i) with the selected panelists of international PD specialists and (ii) an internet-based anonymous panel of GNs. A randomized block design was used in both surveys to assign each participant a total of 4 vignettes; 1 anchor vignette and 3 randomly assigned vignettes. In addition, each PD specialist or GN participant independently rated the assigned vignettes using their own clinical judgment.

2.4. Real-world patient assessment

As part of the large, syndicated data collection effort through a PD-specific large observational survey of patients with PD and neurologists involved in their care in G7 countries (based on previously established methodology [18], data on MANAGE-PD assessment was

collected in 2019–2020). In the syndicated data source, data for all patients was collected based on clinical evaluation and chart reviews. For a subset of sample, additional self-reported data on patients and caregivers were also available (e.g., quality of life, disease burden, caregiver burden). For the analyses in this study, patients with MANAGE-PD assessment and receiving routine oral PD therapy (Device-aided therapy-naïve) were included. This real-world sample was leveraged to evaluate the validity and clinical value of MANAGE-PD based on known-group comparisons and discordant pair analyses.

2.5. Study measures

Demographics and practice characteristics were collected for PD specialists and GNs including country, gender, specialty, years in clinical practice, and experience in treating patients with PD. Demographic and clinical characteristics were captured for real-world patients including geographic location, age, gender, comorbidities, and specialty of treating physician. Patients were assessed using clinical measures of PD including physician perceived disease severity, daily duration of 'Off'-time and dyskinesia-time, Mini-Mental State Examination (MMSE) [19], and Unified Parkinson Disease Rating Scale (UPDRS) [20]. Economic measures included 12-month hospitalization rate and weekly caregiver utilization. Humanistic measures included Parkinson's Disease Questionnaire (PDQ-39) [21], EQ-5D health utility and visual analog scale (VAS), and Zarit Burden Index (ZBI) [22]. Patients were assigned into 3 categories based on MANAGE-PD. In addition, patients were independently classified based on the treating physicians' own clinical judgment.

2.6. Statistical analysis

In the vignette-based approach, univariate analyses were conducted to understand the item distributions, subjective characteristics of vignettes, and clinical category ratings for each vignette by survey respondents. Validity of MANAGE-PD classification was based on concordance between clinician judgement and *a priori* assigned classification of the vignettes based on steering committee assessment and MANAGE-PD scoring algorithm. Concordance was measured using intra-class correlation co-efficient (ICC) and Fleiss unweighted ($\kappa_{unweighted}$) and weighted kappa ($\kappa_{weighted}$) statistics. ICC values were interpreted as follows: <0.50 poor agreement, 0.50–0.74 moderate agreement, 0.75–0.90 good agreement, and >0.90 excellent agreement [23]. Fleiss kappa statistics were interpreted as follows: ≤0.40 fair to minimal agreement, 0.41–0.60 moderate agreement, and >0.60 substantial agreement [24].

In the real-world patient approach, construct validity was evaluated with known-group comparisons between patients in the 3 MANAGE-PD-assigned categories based on established measures assessing PD severity and burden, using analysis of variance, Wilcoxon rank sum, and chi square tests as appropriate. Concordance between MANAGE-PD and clinician judgment of patient category was evaluated. Among the discordant pairs, clinical value was assessed based on comparing measures of disease severity and burden between patients scored as higher severity by MANAGE-PD/lower severity by clinician judgment and higher severity by clinician judgment/lower severity by MANAGE-PD. SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC) was used to perform the analyses.

3. Results

3.1. MANAGE-PD development

The MANAGE-PD tool allows for the clinical evaluation of a patient to support treatment decision-making by classifying a patient into 1 of 3 categories: 1) controlled on current treatment regimen, 2) inadequately controlled on current treatment regimen but may potentially benefit with further non-device aided treatment optimization, or 3) inadequately controlled on current treatment regimen and may benefit from device-aided therapy. The tool consists of two sections, evaluating the frequency and severity of PD-related motor, non-motor, and functional symptoms across 10 domains. [Fig. 1]. The tool is also available in a paper [Appendix B] and web-based version [US: www.managepd.com; Outside-US: www.managepd.eu]. The questions in the tool follow a skip logic for each domain as well as between sections. Based on 5 yes/no questions, section 1 evaluates if the patients are adequately controlled on current oral medications (Category 1). If patients are inadequately controlled on current oral medications, Section 2 allows for further investigation of 10 domains assessing frequency and/or severity level of PD-related symptoms to classify between Category 2 and 3. The classification to Category 3 is based on taking ≥4 times oral levodopa/day and domain-specific threshold of frequency and severity. The MANAGE-PD scoring algorithm is included in Appendix C. Among domains evaluated by MANAGE-PD, dystonia with pain and impulse control disorder do not impact the tool categorization. Irrespective of the level of severity, while standalone, these individual domains do not call for an initiation of a device-aided therapy. Evaluation of these domains was deemed necessary to guide optimization of treatment choices (with or without a device-aided therapy).

3.2. Sample characteristics

A sample of 17 PD specialists and 400 GNs participated in the vignette-based assessment. The PD specialists had an average of 24.4 ± 7.6 years of experience treating patients with PD and managed an average of 73.2 ± 45.4 patients with PD/month. GNs reported an average of 15.6 ± 8.2 years of experience treating patients with PD and managed an average of 36.4 ± 20.8 PD patients/month. Among the GN sample, 63% practiced in the US and 37% in the UK. About two-thirds (68%) of US GNs reported working in a private practice. Most (63%) GNs reported having experience in treating PD patients with device-aided therapies.

The real-world assessment sample included 2546 patients from 7 countries [Appendix D. Table S1]. The patients had a mean age of 69.9 ± 10.1 years and time since diagnosis of 4.8 ± 4.8 years. In terms of PD severity, 15.4% were advanced as deemed by their physician. Approximately 37.2% reported experiencing off-time with an average of 1 ± 1.8 h per day. Most (81.5%) treating physicians had received movement disorders training, with remaining physicians identifying as GNs (15.4%).

3.3. Vignette-based assessment of validity

PD specialist ratings of the vignettes demonstrated excellent agreement with MANAGE-PD vignette category ratings (86%; ICC 0.843; $\kappa_{unweighted} = 0.77$; $\kappa_{weighted} = 0.79$) [Fig. 2]. The percent concordance of vignettes ratings ranged from 67% to 100% with 9 out of 10 vignettes demonstrating ≥70% concordance. The overall category agreement was 88% for Category 1, 83% for Category 2, and 86% for Category 3.

GN ratings of the vignettes demonstrated adequate agreement with MANAGE-PD vignette category ratings (71%; ICC 0.690; $\kappa_{unweighted} = 0.57$; $\kappa_{weighted} = 0.65$). The percent concordance of vignettes ratings ranged from 33% to 98% with 5 out of 10 vignettes demonstrating ≥75% concordance. The overall category agreement was 98% for Category 1, 40% for Category 2, and 78% for Category 3. We observed geographic differences between GNs from US ($\kappa_{weighted} = 0.61$) vs UK ($\kappa_{weighted} = 0.72$). There were relatively small differences in overall agreement between GN panelists based on previous experience with device-aided therapy or number of years of PD experience. PD specialists and GN panelists reported no major issues with clarity and usage of the tool in open-ended feedback.

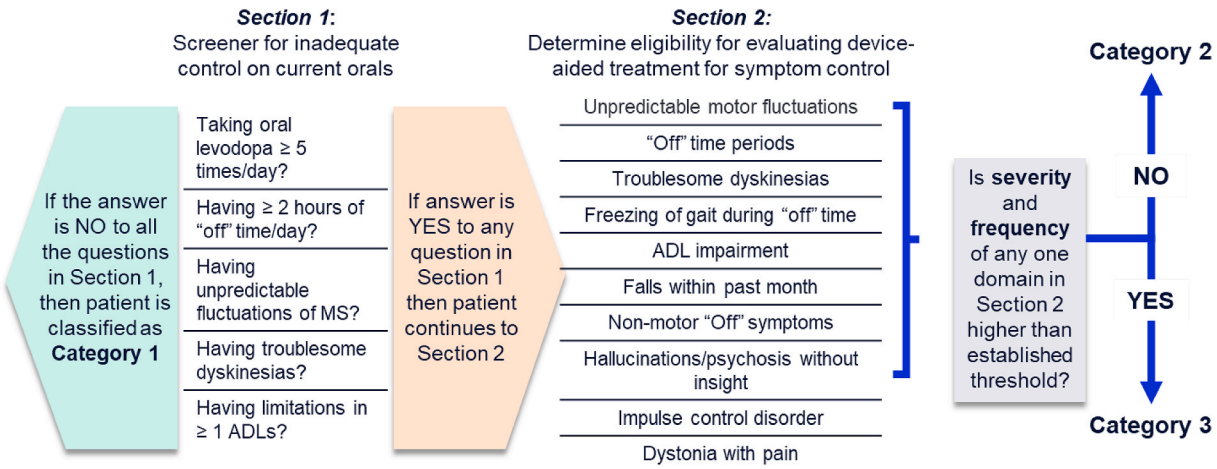

Fig. 1. Overview of the MANAGE-PD Tool. **Notes:** Frequency of domains measured as: (i) none of the time/never, (ii) rarely, (iii) frequent/some of the time, and (iv) most/all of the time (daily); Severity of domains measured as: (i) mild, i.e., detectable to clinician but not interfering with daily life (not or minimally troublesome to the patient), (ii) moderate, i.e., detectable to clinician and influences daily life (troublesome to the patient), and (iii) severe, i.e., detectable to clinician and significantly influences daily life (very troublesome to the patient). **Category 1:** Patient is adequately controlled on current oral therapy; Category 2: Patient is inadequately controlled on current oral therapy and optimization of oral therapy is recommended; Category 3: Patient is inadequately controlled on current oral therapy and along with optimization of oral therapy, evaluation for device-aided therapies is recommended. **Abbreviations:** MS, motor symptoms; ADLs, activities of Daily Living.

Fig. 2. Concordance between MANAGE-PD vignette category and PD-Specialist clinician judgment in identifying patients with inadequate PD symptom control*. *MANAGE-PD vignette category was based on *a priori* steering committee assessment and MANAGE-PD scoring algorithm. Clinician judgement was based on independent assessment of patient vignettes by PD-specialists. **Notes:** Due to incomplete responses, 1 PD-specialist was excluded from the vignette-based validation (analytical sample n = 17).

3.4. Real-world patient assessment of validity and clinical value

Based on the MANAGE-PD scoring in the analytical sample, 1180 (46%) of patients were classified as Category 1, 707 (28%) as Category 2, and 659 (26%) as Category 3. The tool demonstrated strong construct validity based on significant differences between the patients in the different MANAGE-PD categories in the order of increasing disease severity [Table 1]. The duration of off-time (0 ± 0.2 h/day; 1.3 ± 2.2 h/day; 2.4 ± 2 h/day), UPDRS score (20.9 ± 18.5; 36.8 ± 31.8; 44 ± 29.4), PDQ-39 score (18.4 ± 14.7; 28.4 ± 16.8; 40.2 ± 18.9), and ZBI score (22.6 ± 16.5; 31.6 ± 16.1; 36.3 ± 18.6) were all observed to be significantly higher ($p < 0.0001$) for more severe MANAGE-PD categories (higher burden for Category 3 > 2 > 1).

Additionally, in the analytical sample, 1142 (45%) patients had discordance between MANAGE-PD rating and real-world clinician judgment. Among discordant pairs, 729 (64%) patients were rated at higher category by MANAGE-PD and 413 (36%) patients were rated at higher category by clinician judgment [Fig. 3]. Comparing these two discordant groups, patients rated as higher severity by MANAGE-PD were observed to have: (i) ~1.4x higher average daily of off-time (1.4 ± 1.8 h vs 0.9 ± 2 h, $p < 0.009$), (ii) significantly poorer PD-related quality of life (PDQ-39 index score 30.8 ± 18.6 vs 26.8 ± 17.4, $p = 0.025$), (iii) increased cognitive impairment (MMSE score 24.2 ± 4.6 vs 26.3 ± 3.8, $p < 0.0001$), (iv) ~2x higher hospitalization rate (13% vs

Table 1
Real-world validity in identifying patients with PD with inadequate symptom control.

Characteristics	Overall (n = 2546)	Patient classification based on the MANAGE-PD tool		
		Category 1[a] (n = 1180)	Category 2[a] (n = 707)	Category 3[a] (n = 659)
Time since PD diagnosis	4.8 (4.8)	2.6 (2.8)	4.6 (4)[g]	9.2 (5.6)
PD severity n (%)				
Early	1098 (43.1)	906 (76.8)	175 (24.8)[g]	17 (2.6)[d,e,f]
Intermediate	1057 (41.5)	265 (22.5)	421 (59.5)[g]	371 (56.3)[d,e,f]
Advanced	391 (15.4)	9 (0.8)	111 (15.7)[g]	271 (41.1)[d,e,f]
Duration of Off-time (hrs/day) [b]	1 (1.8)	0 (0.2)	1.3 (2.2)[g]	2.4 (2)[d,e,f]
Duration of dyskinesia (hrs/day) [b]	0.3 (1.2)	0 (0.3)	0.2 (0.9)[g]	1.1 (1.9)[d,e,f]
UPDRS Score [b]	30.3 (27)	20.9 (18.5)	36.3 (31.8)[g]	44 (29.4)[d,e,f]
MMSE Score [c]	25.2 (4.3)	27.3 (3.2)	24.1 (4.3)[g]	24.3 (4.6)[d,e]
PD-related Quality of Life (PDQ-39) [b]				
Summary Index	28 (18.8)	18.4 (14.7)	28.4 (16.8)[g]	40.2 (18.9)[d,e,f]
Mobility	39 (27.6)	22 (21)	42.5 (24.4)[g]	57.6 (25.3)[d,e,f]
Activities of Daily Living	33.4 (26.9)	20.2 (20.7)	35.3 (25)[g]	48.4 (27.6)[d,e,f]
Emotional Well-being	33.6 (23.7)	25.1 (20.3)	33.8 (22.6)[g]	44.1 (24.5)[d,e,f]
Stigma	28.5 (24.6)	21.6 (22.3)	27.5 (23.5)[g]	38.7 (25.3)[d,e,f]
Social Support	18.2 (21.3)	11.4 (15.2)	17.7 (21.4)[g]	27.9 (24.3)[d,e,f]
Cognition	29 (21.7)	19.9 (18.3)	29.2 (19.5)[g]	40.5 (22.4)[d,e,f]
Communication	20.6 (22.1)	12.6 (16.4)	19.9 (21.2)[g]	31.7 (24.7)[d,e,f]
Bodily Discomfort	23 (22)	16.1 (18.5)	22.8 (22.3)[g]	32.3 (22.6)[d,e,f]
General Quality of Life (EQ-5D) [c]				
Index	0.7 (0.3)	0.8 (0.2)	0.6 (0.2)[g]	0.5 (0.3)[d,e,f]
VAS	60.4 (19.1)	68 (16.9)	59.4 (18.3)[g]	51.7 (18.8)[d,e,f]
ZBI Caregiver Burden [b]				
Total Score	30.2 (18)	22.6 (16.5)	31.6 (16.1)[g]	36.3 (18.6)[d,e,f]
No burden 0–20, n (%)	140 (32.8)	64 (45.4)	42 (29.2)[g]	34 (23.9)[d,e,f]
Mild to Moderate 21–40, n (%)	156 (36.5)	50 (35.5)	61 (42.4)[g]	45 (31.7)[d,e,f]
Moderate to Severe 41–60, n (%)	107 (25.1)	25 (17.7)	36 (25.0)[g]	46 (32.4)[d,e,f]
Severe 61+, n (%)	24 (5.6)	2 (1.4)	5 (3.5)[g]	17 (12.0)[d,e,f]
Caregiver Utilization [b]				
Professional (hrs/week)	3.5 (17)	0.4 (4.5)	5.4 (21.8)[g]	6.8 (23.1)[d,e]
Non-professional (hrs/week)	17.5 (35.8)	7.1 (21.7)	20.2 (37.1)[g]	32.7 (46.6)[d,e,f]
Overall (hrs/week)	20.9 (39.3)	7.6 (22.3)	25.7 (41.8)[g]	39.5 (50)[d,e,f]
Overall Burden [b]				
Number of comorbidities	1.7 (1.7)	1.2 (1.3)	1.8 (1.8)[g]	2.3 (1.9)[d,e,f]
Hospitalized in last 12 months, n (%)	223 (9.6)	31 (2.9)	66 (10.2)[g]	126 (21.6)[d,e,f]

Abbreviation: PD: Parkinson's Disease; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; PDQ, Parkinson's Disease Questionnaire; EQ-5D, EuroQol 5 Dimension; VAS, Visual analog scale; ZBI, Zarit Burden Interview.

Notes: Estimates represent Mean (SD) unless indicated otherwise.

[a] MANAGE-PD Category 1: adequately controlled on oral therapy; Category 2: inadequately controlled on oral therapy and consider oral optimization only; Category 3: inadequately controlled on oral therapy and consider evaluation for DAT along with oral optimization.

[b] outcomes where higher scores/numbers equal worse health.

[c] outcomes where higher scores/numbers equal better health.

[d] significant difference based on p-value<0.0001 comparing category 3 vs. category 2 vs. category 1.

[e] significant difference based on p-value<0.0001 comparing category 3 vs. category 1.

[f] significant difference based on p-value<0.05 comparing category 3 vs. category 2.

[g] significant difference based on p-value<0.05 comparing category 2 vs. category 1.

7%, $p < 0.004$), (v) ~1.5x higher average weekly caregiver use (31.5 ± 45.6 h vs 18.5 ± 38.2 h, $p < 0.001$), and (vi) significantly higher caregiver burden (ZBI score 32.2 ± 17.5 vs 24.6 ± 18.2, $p < 0.002$).

4. Discussion

The MANAGE-PD tool demonstrated robust validity in identifying patients with PD with suboptimal symptom control based on hypothetical vignettes and real-world patients. The tool also showed promising clinical utility in complementing physician decision-making when managing patients with PD in real-world practice. Patients identified as having higher severity by the MANAGE-PD tool demonstrated incrementally higher clinical, economic, and humanistic burden. Our findings support the value of MANAGE-PD in complementing physician decision-making and facilitating identification of patients who might benefit from treatment optimization and/or consideration for advanced treatment options.

Although effective disease management is key at all stages of PD, the need for greater individual customization becomes increasingly important as the disease advances [6]. However, without a simple screening test or gold standard index to determine the severity of PD, staging of the disease tends to rely on a subjective clinical evaluation and medical history [11]. Lack of routine standardized assessments in current clinical practice results in delayed treatment optimization of patients, which may exacerbate the burden experienced by patients with PD and their caregivers [9]. Timely evaluation of PD symptoms using a standardized and validated tool may aid in harmonizing comprehensive and individualized assessments, encouraging timely treatment optimization, and facilitating referrals as appropriate to PD specialists. Such validated and standardized tools can reduce the time during which patients remain suboptimally controlled and may help alleviate their burden in a timelier manner.

A review of the different approaches that attempt to define advanced PD highlights the need for new strategies that are standardized, comprehensive, feasible to use in clinical practice, and help to identify patients with greater disease burden. Several previous attempts have been made to develop consistent and objective approaches to identify advancing or inadequately controlled patients with PD. Examples of such tools include measures of disease duration, rating scales (i.e., Hoehn and Yahr, UPRDS), the 5-2-1 criteria, medication-based proxies (i.e., ≥1000 mg levodopa equivalent daily dose), sensors to detect fluctuations, patient diaries, and biomarkers (i.e., cognitive biomarkers, alpha synuclein protein) [11,25–28]. While these measures are helpful to assess certain aspects of PD or can be used as quick screening or monitoring tools, their utility in informing treatment management is limited in everyday clinical practice [29]. For instance, the 5-2-1 criteria can be beneficial to quickly identify advancing PD patients with inadequate symptom control [11]. That being said, 5-2-1 evaluates 3 out of 10 domains included in MANAGE-PD and does not provide further recommendation regarding management of oral or device-aided

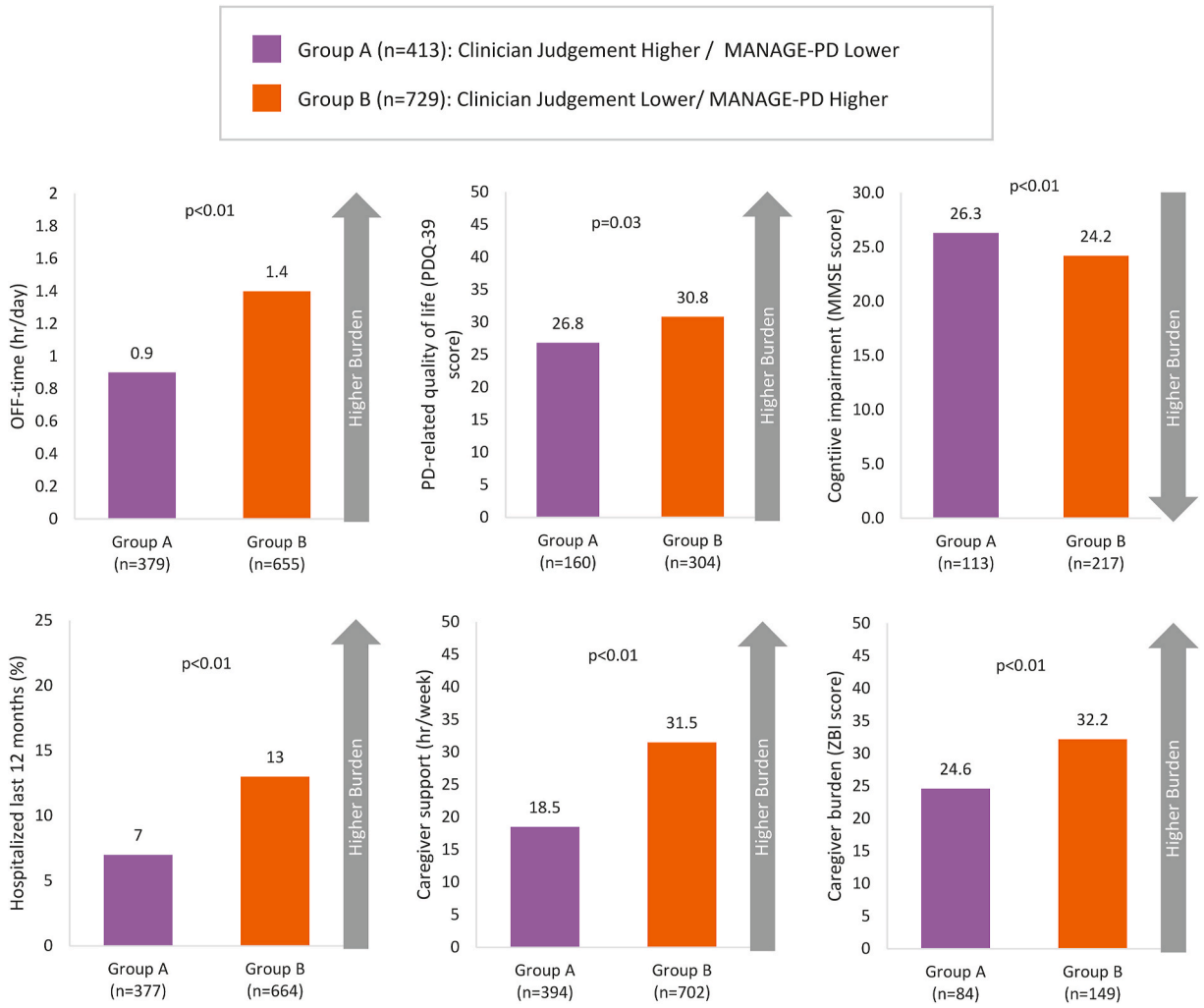

Fig. 3. Real-world clinical value in complementing clinician evaluation of PD symptom control. **Notes:** Hospitalization rate is based on percentage hospitalized in last 12 months, caregiver support includes weekly professional and non-professional caregiver use. **Abbreviations:** MANAGE-PD: Making Informed Decisions to Aid Timely Management of Parkinson's Disease; MMSE: Mini-mental state examination, PDQ-39: Parkinson's Disease Questionnaire; ZBI: Zarit Burden Index.

therapy.

In particular, there is a need for decision aids that identify patients with PD who require treatment optimization or escalation to advanced treatments. MANAGE-PD furnishes a comprehensive and standardized assessment of frequency and severity of key motor, non-motor, and functional impact clinical indicators. The domains in MANAGE-PD are based on Delphi consensus-based clinical indicators of advancing PD that have demonstrated excellent accuracy and validity in real-world settings [13,16,17].

Implementing the MANAGE-PD tool in clinical practice may be useful in facilitating the following scenarios: 1) nurse specialists to decide whether the intervention of a PD specialist is required for medication adjustment, 2) GNs to decide whether a referral to a movement disorder clinic for complex medication adjustments or device aided therapies is warranted, 3) to help PD specialists with limited access to device-aided therapy in timely referral to a higher level movement disorder center, and/or 4) support the selection of potential candidates for clinical trials addressing fluctuating disease.

The development of MANAGE-PD was guided by an international panel of leading PD experts with extensive expertise in clinical practice guidelines, involvement in clinical trials, and experience in treating advancing patients with PD. In contrast with other tools, utility of MANAGE-PD is not limited to a specific treatment scenario, nor does the tool guide the selection of any specific PD treatment (i.e., tools to assess eligibility for Deep Brain Stimulation) [30]. Therefore, MANAGE-PD allows flexibility in evaluating patients with PD and providing global recommendations to help complement decision-making.

Several study limitations exist. While vignette-based experimental designs allow researchers to control the stimulus and reduce confounding sources, there are limitations to vignettes representation of the 'real world'. PD specialist and GNs were recruited through a non-random purposive sample and reported high percentage of experience with device-aided therapy. This may not reflect degree of expertise with device-aided therapy worldwide and may limit generalizability of the findings. PD specialist and GNs were instructed to consider the signs/limitations presented in the vignette to make their judgement; however, clinicians may have disregarded instructions in their scoring of the vignette. In the GN validation, only GNs from US and UK participated, which may limit generalizability of the findings given differences in practice guidelines across countries. The sampling of patients in the real-world study was not random, and this could have introduced bias. The quality of data partly depends on the accurate reporting of information, which may result in recall bias. Patient-, physician-, practice-, and country-level factors can impact performance and utilization of the tool. Patients with levodopa unresponsive symptoms (dementia, "On" freezing, postural instability, dysphagia, speech problems) may not benefit from medication adjustment, and specially not from device-aided therapies. A limitation of the tool is that it does not address

levodopa-unresponsive patients; clinician judgement is essential for the evaluation of treatment for these patients.

This study has several strengths. The two-pronged approach including hypothetical patient vignettes and real-world patients with PD reinforces the study robustness and replication of the findings in both settings. This study also leveraged expertise from a diverse panel of leading movement disorder specialists who informed the development of the vignettes and the tool. The study also included a diverse sample of GNs who practiced across 15 countries, which improves the generalizability of the findings. The real-world validation approach included a large global sample for patients with PD receiving care in real-world clinical setting across 7 countries. This further expands the generalizability and utility of the tool to patients receiving care in everyday clinical practice.

5. Conclusions

The MANAGE-PD tool demonstrated validity and clinical value in identifying patients with PD with inadequate symptom control while on oral medications. Our findings were robust, based on vignette-based and real-world patient-level approaches. Similar trends were observed across different physicians' specialties, clinical practice settings, and geographic locations. The vignettes-based approach demonstrated strong validity of the tool among PD specialists and GNs. Patient-based validation showed validity in a large global sample of PD patients. The tool also demonstrated clinical utility based on the improved accuracy in identifying patients with worse clinical, economic, and humanistic disease burden. Clinical use of MANAGE-PD may complement clinician decision-making and facilitate identification of patients who might benefit from treatment optimization and/or consideration for device-aided therapies. Future prospective research may evaluate the impact of MANAGE-PD in facilitating timely patient identification and treatment optimization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.10.009.

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