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Parkinson's Disease Screening Initiative:
Suggestions for the development of a simple screening tool

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Abstract

Parkinson's Disease Screening Initiative:
Suggestions for the development of a simple screening tool

By Fabiola de Louis

Background: Parkinson's Disease (PD) is a neurodegenerative disorder that is known to have genetic and environmental components, and the focus of much work in the public health community. With a noted decline of diagnosis in the primary care setting, as well as the vast number of exposures associated with the development of the disease, suggestions for a screening tool were developed in hopes of identifying at risk and marginalized populations that could benefit from services and interventions offered from a specialty provider.
Methods: 14 different questionnaires and 6 different vital signs were evaluated to gauge differences between PD patients and healthy controls, conducted as part of a case-control study. The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale and clinical variable of orthostatic hypotension were determined to be the best contributors towards the base model for this tool. Questions were dichotomized and selected based off of multiple parameters, including significance, generalizability and potential to be present in PD populations before motor symptoms develop. The final suggested 10 questions were then evaluated utilizing a logistic regression and Receiver Operator Curve analysis.
Results: 9 questions and 1 clinical variable were selected as suggestions for the development of a possible PD screening tool. The suggested tool had an AUC of 0.9298 (95% CI: 0.8749 to 0.9848) with a final sensitivity of 0.93, specificity of 0.82 and a YJ of 0.74 utilizing a set point of 3 or above as a "positive" indication to seek additional follow-up.
Conclusions: This survey should be considered a first step in helping to properly identify symptoms associated in PD in populations without immediate access to a specialist and to prompt them to seek follow-up with a specialty provider for further treatment, diagnosis, and possibly symptomatic management.

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Table of Contents

1. Introduction

Parkinson's Disease (PD) is a chronic and progressive neurodegenerative disorder that is known to have genetic and environmental components [2]. It is estimated that 160 per 100,000 people over the age of 65 are diagnosed with PD each year, giving it the second highest incidence among neurodegenerative diseases [3]. There is also a noted decline of PD diagnosis in the primary care setting, which is assumed to derive from improper diagnosis, rather than a true difference in incidence [4]. Most of the diseases' hallmark symptoms are motor, and can only be clinically identified retroactively, after the death of dopamine-producing cells. Current medical protocol is essentially dopamine replacement, which works better and more effectively for patients who are diagnosed early. The possibility of identifying PD in the prodromal phase, or before symptoms develop, would open the door to neuroprotective interventions which could be implemented before the onset of motor symptoms [2]. Recently, there has been a greater push to identify at risk populations, with the ultimate goal of targeting them for prevention strategies and interventions [5]. These could be as simple as early education and lifestyle adjustments (like increased physical activity), or more pharmaceutical focused with direct drug treatments. Regardless, early identification and treatment leads to better patient outcomes and ultimately, improved quality of life. This project was a cross sectional and exploratory data analysis with a two aims: the first, to describe the data and instrumentation used with hopes of assessing differences between PD patients and controls, and the second, to develop suggestions for a screening tool that can help identify persons who are at risk for developing Parkinson's Disease in underserved primary care populations.

1.2 Literature Review

While many surveys and questionnaires exist in order to assess the severity and progression of PD itself, to this authors knowledge, there is not one screening tool published. Andrew Siderowf, *et al*. identified some common pre-motor markers that could be used for early detection of the disease, including depression, anxiety, sleep disturbances, constipation, and olfactory anomalies, but noted the difficulty in establishing the suitable breadth of testing as their main limitation [6]. The future of early detection is moving in the direction of biomarker assays, however, in the meantime, there are large at-risk and marginalized populations who could benefit from a simple, low technology solution to bridge this gap.

1.3 Research Objectives

The overall goal of this project was to develop suggestions for a shortened, 10 question screening tool that could be used in a primary care physician's office or community clinic to screen for PD. It was important that this could be used in a low income setting and with minimal resources. The overview and rationale is depicted pictorially in Figure 1. A secondary exploratory question included assessing the relationship between education level and delay in seeking specialty follow-up, specifically to see if education was associated with the length of time between reported symptomatic development and disease diagnosis. This work is, in part, supported by the Michael J. Fox Foundation Study, grant number MJF-10854.

2. Methods

2.1 Study Design

This is a longitudinal case-control cohort study that began in February 2011 and slated to continue for the next several years, conducted through Emory University School of Medicine and The Emory Clinic. After providing informed consent, study participants underwent a 2-hour study visit that included obtaining all relevant demographic information, filling out the questionnaire battery, collecting vital signs, drawing blood and undergoing a research MRI in a BITC scanner. This MRI is specifically looking for anomalies in the Locus Coeruleus, a small part of the brain that is implicated in dopamine production [7]. Blood products underwent an assay for biomarker identification. This study was approved by the Institutional Review Board of Emory University.

2.2 Data Collection and Analysis

All questionnaires were self-reported by the patients themselves and administered on the same day as they study visit, where they were subsequently coded into an electronic database using IBM SPSS. Results were analyzed using SAS for Windows. Periodic auditing was done by random chart pulling in order to assess data integrity. Basic descriptive statistics, including mean, standard deviation (SD) and, when appropriate, proportional characteristics were calculated and reported. All variables underwent an individual appraisal in order to check for implausible values and overall data reliability. Each variable was then evaluated based on its type (categorical vs. continuous) before being analyzed and assessed appropriately. Graphical distributions were utilized to determine whether data was parametric or skewed. After, the applicable test was run and disclosed. These included the Two Sample Independent T-Test (T-Test, Pooled or Satterthwaite), Wilcoxon Rank Sum or Mann Whitney Test (WMW approx. or

WMW exact), Chi Square Independence Test (Chi-Square), Fisher's Exact Test (Fisher's, two sided) and Cochran-Mantel-Haenszel Test (CMH).

2.3 Study Population

Participants were volunteers that were recruited indiscriminant of sex or race on a rolling basis over the course of the study, largely from the metro Atlanta area, varying in age from 37 to 82, with an overall mean of 66. In order to qualify as a case, a physician confirmed diagnosis of PD was required. Controls had to be healthy, with no severe neurological deficits or parkinsonian symptoms like tremor. Initially, cases and controls were not aged matched, however, this was added to the study protocol in the second cohort, where they were caliper matched within two years.

Specifically, our PD population ranges from 40 to 81 years of age with a mean disease duration of 5.45 years. Of the total 67 PD patients, 57 (85%) are symptomatically treated with medication to manage their symptoms, with an overall average of 435.48 levodopa equivalency. Of those, 54 (80.6%) were examined in the "on" state, with 32 (47.8%) experiencing wearing off of their medication regularly. The average Hoen and Yahr stage was less than 1 (0.94) and 21 (31.3%) reported experiencing dyskinesia's. Motor examination of symptom severity was assessed, on average, approximately 7.13 hours after the participants last dose of medication.

3. Results

3.1. Descriptive Statistics and Clinical Characteristics

A total of 186 study visits were completed as of January 2017, with 91 Parkinson's Disease patients, 11 with Alzheimer's Disease (AD), 7 with Multiple System

Atrophy (MSA) and 77 controls. That number includes 150 first visits, 31 second visits and 5 third visits.

While our entire study database includes controls and patients with Parkinson's disease (PD), Alzheimer's disease (AD) and Multiple System Atrophy (MSA), only controls and those with PD were kept for data analysis. For evaluation of whole cohort data, only the first study visit was utilized. This means that even though a single participant may have completed three separate visits, only one was included as their contribution, leaving us with 132 study visits to analyze from a total of 168. For whole cohort examination, and for assessing major differences based on disease status, a grand total of 67 PD cases and 65 controls were used.

Study visits 1-95, or cohort A as we will hereby refer to them as, were the initially recruited study participants. After removal of the repeat visits 84 are left, composed of 48 cases and 36 controls.

Because our study protocol and questionnaire battery were fluid, both were updated as needed to reflect the depth of information that we sought to capture at that time. There was one major change at study visit 96, where several new questionnaires were added to the battery. Due to this, study visits 96 through 187 will be referred to as cohort B. These cohorts will be assessed both together and separately, depending on the amount of information that is shared between them.

At the beginning of cohort B, all contributors were given the option to re-enroll in the study. This resulted in 12 repeat visits, which were retained separately exclusively for analysis only in this set. It is important to note that each person is only represented one

time. This resulted in 84 total visits, comprised of 43 cases and 41 controls. Figure 2 depicts a visual representation of overall recruitment and cohort creation.

When evaluating the demographics of the entire cohort, as illustrated in Table 1, there is a significant difference in age overall. This is likely due to the recruitment pattern, as in cohort A, patients and controls were not age matched. This changed in cohort B, when all participants were caliper aged matched within roughly two years. Overall, controls were about four years older than cases. There are slightly more females than males, which is not statistically significant however notable since white males are generally found to have the highest incidence and prevalence rates of PD when these types of analysis are conducted [8, 9]. That being said, the vast majority of volunteers for this study identified as being Caucasian. There were more African American controls than cases, which likely accounts for the p-value obtained. Of note, there were two Hispanic cases compared to none in the control group. The education levels of the participants ranged, varying from no high school diploma to doctoral degrees. Controls exhibited a slightly higher mean years of education, which is reflected in their fewer overall individuals with high school degrees or below. When examining family histories, most participants did not have a direct family member with PD or Jewish grandparents. It should be noted that the question "Do you have an immediate family member with PD?" was not added to the study battery until the second cohort of participants (April 2016), which accounts for the seventy-five missing entries. The number of Jewish grandparents was asked in order to loosely screen for possible genetic phenotypes and mutations that are found commonly in Ashkenazi Jews, predisposing them to higher rates of PD overall [10].

In evaluating the data of cohort A by itself (displayed in Table 2), there is a significant difference in age, with controls approximately ten years older than cases due to the absence of age matching volunteers. There are slightly more females than males, however there is a relatively equal split in gender with cases as opposed to a nearly two to one ratio of females to males in the control group. The race breakdown is more homogenous in this group, with one hundred percent of cases identifying as Caucasian, compared to eight controls identifying as African American, adding in some slight variability. Regardless of disease status, there were no Hispanic, Asian or "others" represented in this study population. Education level remained highly variable, with controls exhibiting two more years in school than their counterparts. Most did not have any kind of Jewish ancestry. Because family history of PD was not asked about, it was omitted entirely from this data table.

Analyzing cohort B by itself, displayed in Table 3, reveals no significant difference in age or sex between cases and controls, with the mean age and standard deviations being nearly equal (64.35 vs. 64.83 and 8.75 vs. 8.94 respectively) and only a small difference in the gender structure of controls, with six more female than male contributors. There is increased variability in race when compared to the previous cohort, with Caucasian, African American, Hispanic and "Other" all represented. In a juxtaposition to cohort A, PD patients had increased diversity compared to their controls. Education levels were inadvertently matched quite evenly, with reported years of education also being synonymous across disease status. The question about having a blood related family member with Parkinson's was not assessed until approximately half way through this cohort, accounting for the twenty missing responses (equivalent to 24%

missing data.) However, of the conveyed answers, an increased amount of cases did in fact have a familial connection. Following in the trends of the overall data and data from cohort A, there is no significant difference in Jewish heritage.

Vitals collected during study visits included blood pressure (BP, both systolic and diastolic) and heart rate while resting and lying flat on an exam table. The patient was then asked to stand for one minute, after which, all vitals were collected again using a mobile sphygmomanometer with heart rate monitor. In cohort A, as displayed in Table 4, there is no difference in the mean blood pressure, either systolic or diastolic, laying down. Cases had a much higher average resting heart rate while laying down as compared to controls. After standing for one minute, average systolic blood pressure was also significantly different, notably fifteen points higher in cases, while diastolic blood pressure remained relatively the same between both groups. Heart rate, after standing for the same time period, was also ten beats per minute higher in cases as compared to their disease-free counterparts. All variables were roughly normally distributed, so a parametric test was used for each analysis. Pooled p-values were reported.

Following in nearly identical trends as the first cohort, cohort B, outlined in Table 5, also exhibited no significant difference in average systolic or diastolic blood pressure. Heart rate, laying down, was on average ten points higher in cases. Systolic blood pressure taken one minute after standing was higher in controls, with no difference in the average diastolic blood pressure. Average heart rate was eleven beats per minute higher in cases. In this group, all variables with exception of systolic blood pressure, lying down and heart rate, lying down were normally distributed, utilizing pooled p-values. The two

aforementioned vital signs were non-parametric; therefore, Satterthwaite p-values were reported.

3.2. Summary of Question Battery

Our survey battery included 14 different questionnaires that will be outlined in the next portion of the paper. An extensive literature search was conducted to identify ranges, score cut-off and validation specifically in PD affected populations. The overall results are displayed in Table 6, including a denotation of whether they were utilized in cohort A, cohort B, or both.

Tables 7 and 8 display the mean, differentiated on case control status, p-value and method of obtaining relevant statistics for cohorts A and B, respectively. Tables 9 and 10 report findings from the same group of surveys, however utilizing cut-offs as defined in the cited literature (Appendix III).

3.3. UPDRS and MDS-UPDRS

While the entire literature review of assessments can be located in Appendix III, for analysis purposes, the focus will remain on two questionnaires: The Unified Parkinson's Disease Rating Scale (UPDRS) and its later update, The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS.)

The UPDRS is a commonly used numeric scale that is used to quantify the severity of motor and behavior symptoms, including their effect on the patients' day-to-day activities [11, 12]. It includes three subscales that are self-reported, in addition to one that is based on an assessment of motor symptoms rated by a clinician [13]. The end result is a summation of each rating, ranging in total from zero (no symptoms) to one

hundred and ninety nine (severe symptoms), which are, of note, not on an interval scale [13]. For this study, only the motor examination (Part III) was utilized during evaluation. As anticipated, there is a significant difference in the Motor UPDRS rating, with cases scoring on average sixteen points higher than controls in cohort A and eighteen points higher in cohort B.

The UPDRS was updated in 2008 to become the MDS-UPDRS in order to reflect greater understanding of the disease progression, reduce ambiguity and improve standardization [1]. Each portion assess a different aspect of PD, including the patient-reported and rated assessment of non-motor symptoms (Part I), motor symptoms (Part II) and motor complications (Part IV), with Part III's assessment of physical motor symptoms remaining at the discretion of the clinician administering it [1]. This scale is the golden standard for the measurement of severity of PD, and has been independently validated in the United States as well as across the globe [14-18]. For scoring purposes, it is recommended to treat the four parts (I, II, III and IV) separate for analysis [1]. Some scoring anchor points have been suggested by Martinez-Martin et al. to distinguish mild, moderate and severe parkinsonism as a further extension of the MDS-UPDRS[19]. It is reliable and valid for use in PD [20]. The full array of questions was only utilized in cohort B and analyzed with significant difference between controls and cases distinctly in each category. This is not surprising, given that it was a survey specifically designed to evaluate PD and its associated symptoms. The entire MDS-UPDRS can be viewed in Appendix V. Permission to use this scale was obtained as a part of the Michael J. Fox Foundation, grant number MJF-10854.

3.4. Orthostatic Hypotension

One of the most common non-motor symptoms in PD is orthostatic hypotension (OH), or the decrease in blood pressure from lying to standing [21]. Clinically, OH is measured as a ≥20 mmHg drop in systolic BP, ≥10 mmHg drop in diastolic blood pressure or increase in heart rate of ≥20 beats per minute from lying to standing [22]. This was initially measured 1 minute after standing, but later in the cohort, 3 and 5 minute intervals were also added to reflect updated changes in the literature's best practice [23]. When evaluating whole cohort data in Table 11, the overall change in systolic blood pressure from lying to standing ranged from -21 to 49. The difference in means of both groups were highly significant with a p-value of less than .0001. Since the variances between the two groups were unequal, the Satterwaithe value was reported. This trend also continued when evaluating the data categorically, with a p-value of 0.0004 obtained using a chi-square test.

The range of diastolic blood pressure change spanned from -43 to 28, with another significant difference between both groups. This was assessed utilizing a one-sided Mann Whitney Test. Categorically, this relationship remained intact with a p-value of 0.0466 utilizing a chi-square. Change in heart rate from lying to standing spread from a minimum of -10 to a maximum of 37, with essentially equal means between cases and controls. However, when utilizing the cut-off of an increase in 20 beats per minute, a significant difference arose between the two groups.

Utilizing the definitions as defined above for the change in systolic blood pressure, and additionally listed for brevity in Table 12, in our study population, the odds of having orthostatic hypotension among cases is 17.08 times the odds of having orthostatic hypotension among controls (CI: 2.17 - 134.40.) For diastolic blood pressure,

the odds of displaying orthostatic hypotension among cases is 3.64 times the odds of displaying orthostatic hypotension among controls (CI: 0.95 - 13.94.) Since our interval includes 1, we conclude that there is no association between this measurement and disease status. Lastly, for increase in heart rate, the odds of exhibiting orthostatic hypotension in cases is 5.38 times the odds of displaying orthostatic hypotension in controls (CI: 1.13 - 25.68.) Both systolic blood pressure and heart rate as indicators of orthostatic hypotension have a significant association with PD.

3.5. Criteria for Screening Use

Since the MDS-UPDRS was the most reliable and validated in PD populations, it was chosen as the model for the development of a suggestive screening tool. Traditionally when administering this survey, a trained rater asks the participant if they experience a particular problem or phenomenon associated with PD. If the patient denies a particular item, it is ranked 0, or normal. If a patient states that do in fact experience this, further prompting is elicited in order to solidify a numeric value which corresponds to severity, including 1, slight; 2, mild; 3, moderate; or 4, severe.

Each question was first dichotomized into a simpler yes or no answer choice before undergoing its own univariate analysis to determine the chi-square value, corresponding p-value, odd's ratio (if applicable) and corresponding 95% confidence limits. These are displayed in Table 13 located in the appendix. 4 questions from part I and 5 questions from part II were retained for the final suggestive tool. These were selected based on their statistical significance and generalizability to the population.

3.6. Finalization of the Suggested Screening Tool

After selecting the questions for the suggested screening tool (Table 14), a logistic regression was run, followed by a Receiver Operated Curve (ROC) analysis. The significance of the suggested PD Screening tool was <.0001. The Area Under the Curve (AUC) was 0.9298 (95% CI: 0.8749 to 0.9848) with the line well above the insignificant 50/50 chance. Within our sample population, the screening tool correctly identifies PD verses control patients in random pairs 92% of the time. The Chi-Square test was also significant ($p < 0.0001$), confirming that our tool is better at predicting disease status than chance.

In determining an optimal cut-off point, sensitivity, specificity and Youden's J (YJ) were evaluated after calculating base scores via the logit function. A score of 3 or higher on this screening tool was concluded to be the optimal number to warrant specialty provider follow-up, with a sensitivity of 0.93, specificity of 0.82 and a YJ of 0.74.

3.7. Association between delay in diagnosis and education level

As part of the rationale for designing a screening tool that could be used in low income settings, it was hypothesized that lower education levels would be associated with increased time between onset of symptoms and disease diagnosis. After recoding the data to reflect associates degree or lower verses bachelor's degree or higher, there was no significant difference appreciated between the groups' time to diagnosis ($p=0.4912$, Table 16.)

4. Discussion

Parkinson's Disease has been, and will continue to be, the focus of much work in the public health community, particularly as ties to new environmental exposures, like pesticides, are revealed and greater knowledge of the disease process is uncovered. Two

of the major limitations in research facing the scientific community today include an inability to diagnose the disease before motor symptoms develop and an incomplete understanding of the entire disease process. There exists a great need for new diagnostic techniques and procedures, especially those that fall alongside new findings in the pathological course.

In line with the traditional public health paradigm of preventing disease by inhibiting or lowering exposure, PD itself is known to be loosely associated with at least 75 risk factors [24]. Complicating this relationship is the known genetic component, that not only predisposes certain subgroups to developing this disease, but also plays a role in the susceptibility and direct effect of these risk factors and potential exposure variables alike [25].

In a short description of the pathogenesis, multiple factors, both known and unknown, promote and advance the death of specialized cells in the brain, known as neurons [26]. After these un-reversible changes occur to at least 60% of these cells in a particular part of the brain, known as the substantia nigra, the characteristic motor features of PD become apparent, which is the basis for the clinical diagnosis of the disease [27]. These cells specifically produce an important chemical used in the brain, also known as a neurotransmitter, called dopamine, which is involved in both the movement and reward circuities [28]. Once these cells are gone, there is no way to reverse the changes, and PD is essentially treated symptomatically utilizing dopamine replacement or related pharmaceutical agonists [29].

Of particular interest, there are two main phases of PD, including the motor phase where symptoms are clinically recognizable and the prodromal phase, or pre-clinical

presentation, where death of the neurons is occurring, but hallmark disease symptoms are not yet present (Table 4) [30]. Symptoms implicated in this stage of PD include balance problems, depression, anxiety, tremor, constipation and sleep disorders [31, 32]. These could be present in populations up to ten years before a diagnosis could reasonably be obtained, given current diagnostic standards [33].

Further complicating this narrative, there exist racial and socioeconomic (SES) gaps in PD, which could have a variety of explanations including obstacles to obtaining general or specialty treatment, trouble with obtaining a proper diagnosis and personal barriers, including lack of symptomatic awareness or views toward seeking healthcare [34].

Given the volume, complexity and interrelatedness of the aforementioned information surrounding PD, it was decided to develop suggestions for a questionnaire that could be used in a generalized primary care setting or community outreach event, in order to both draw attention to potential pre-motor features of the disease and identify at-risk populations in order to encourage them to seek specialty follow-up for evaluation of their symptoms. It should be noted that this project was a subset of a larger case-control study, with aims to define definitive MRI biomarkers that could be used to diagnose PD in its prodromal phase. Hand in hand, the simultaneous development of screening tools and early diagnosis methods would be the most effective way to get one step ahead of the disease progression. In short, early disease identification leads to better patient outcomes and improved quality of life.

In development for the suggestions of this screening tool, 14 different questionnaires and 6 different vital signs were evaluated, both as a whole and with

literature identified cut-off points utilized, in order to gauge differences between PD patients and healthy controls. In the end, The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale or MDS-UPDRS, and clinical variable of orthostatic hypotension, or the change in systolic blood pressure from lying to standing, were determined to be the best contributors towards a base model for this tool. The full MDS-UPDRS can be viewed in Appendix V.

This instrument is considered the golden standard for assessments of motor and non-motor symptoms in patients with PD. It has 4 parts, 3 of which are self-reported and 1 of which is a physical exam completed by a physician. It asks all questions in the time frame of the last week.

All 13 questions in Part I: Non-Motor Aspects of Experiences of Daily Living and the 13 questions in Part II: Motor Aspects of Daily Living, were transformed to dichotomized variables, and evaluated individually before determining the best 9 to include in the final screening tool. Question selection criteria was based on significance, p-values and generalizability to the general population, as well as ease of understanding. Some highly significant, but extremely specific questions were omitted due to their ties to the explicit progression of PD. Questions were also included based off of their possibility of being present in PD patients before motor symptoms develop, also known as the prodromal phase of the disease.

The final question selection included items 1.4 (Have you felt nervous, worried or tense? p=0.0244, 95% CI: 1.1289 - 6.8420, OR: 2.78), 1.11 (Have you had constipation troubles that cause you difficulty moving your bowels? p=0.0001, 95% CI: 2.4853 - 22.8922, OR: 7.54), 1.12 (Have you felt faint, dizzy or foggy when you stand up after

sitting or lying down? p=0.0448, 95% CI: 1.0072 - 7.2227, OR: 2.70), 1.13 (Have you usually felt fatigued? This feeling is not part of being sleepy or sad. p=0.0107, 95% CI: 1.3129 - 10.1079, OR: 1.1289 - 6.8420), 2.7 (Have people had trouble reading your handwriting? p<.0001, 95% CI: 5.6637 - 80.6693, OR: 21.38), 2.8 (Have you usually had trouble doing your hobbies or other things you like to do? p<.0001, 95% CI: 4.6885 - 66.0124, OR: 17.59), 2.10 (Have you usually had shaking or tremor? p<.0001, 95% CI: 19.5420 - 514.6458, OR: 100.29) 2.11 (Have you usually had trouble getting out of a bed, a car seat, or a deep chair? p<.0001, OR: 2.5169 - 17.5015, OR: 6.64), and 2.12 (Have you usually had problems with balance and walking? p<.0001, 95% CI: 5.1630 - 57.7451, OR: 17.27).

The phenomenon of orthostatic hypotension was also included as a part of this tool. After evaluating 3 different clinical ways to measure this, which included drops in systolic or diastolic blood pressure, and increase in heart rate, this feature was best represented as a change greater than or equal to a 20mmHg drop in blood pressure from lying to standing.

A Receiver Operator Curve (ROC) and subsequent analysis was run in order to determine the best cut-off point for this questionnaire. The AUC was significant (0.9298, 95% CI: 0.8749 to 0.9848) with a final sensitivity of 0.93, specificity of 0.82 and a YJ of 0.74 utilizing a set point of 3 or above as a “positive” result.

This survey should be considered a first step in helping to properly identify symptoms associated in PD in populations without immediate access to a specialist and to prompt them to seek follow-up with a specialty provider for further treatment, diagnosis, and possibly symptomatic management. It could also be used to simply draw awareness

to symptoms not specifically asked about during a primary care physician visit, like anxiety, constipation or excess fatigue. It is not meant to be used as a diagnostic tool in any way.

Immediate next steps would include incorporating this screening tool into our questionnaire battery in order to see in real time, how accurately it predicts disease status, with possible adjustment of the cut-off score after an appropriate period of assessment. This reassessment phase should be incorporated with a pilot study, in which it could be tested in a larger population setting, with possible question editing. After which, with physician input, validation could occur.

Long term, this questionnaire, and others like it, would have to undergo a cohort study, where those who screened "positive" were subsequently followed in order to assess the usefulness in predicting the development of PD. It could also be evaluated for use in a less formal setting, such as a smart-phone application or in conjunction with places that already offer free blood pressure screenings.

5. Limitations

One of the key limitations of this survey is that it is based off of a case-control study, and therefore, lacks temporality in the development of symptoms. Some of the questions that were picked for the final version, especially items that surround motor skills, like handwriting, physically being able to do hobbies, shaking or tremor, trouble with raising from a seated position, and noticeable problems with balance or walking, could be predominant in our PD population simply due to the natural progression of disease.

Another striking feature is our lack of diversity, especially in cohort B, which was the group that was administered the MDS-UPDRS. 84% identify as being Caucasian and nearly 87% stated that their education level was "some college" or above, which severely limited the assessment in differences based off of SES and race. Given this, the lack of association between education level and delay in disease diagnosis was not particularly surprising. The particular question about symptom onset was also added to our study battery during an update to our second cohort, resulting in low numbers overall and subsequently, a lower power to detect a difference if it did exist.

Additional limitation resides in the fact that nearly all of the data assessed was self-reported by participants, with restricted ability to cross-reference an electronic database or obtain physician's notes. As such is the nature of a volunteer study.

This study also likely suffers from recall bias. This could be interpreted in a twofold way as PD patients may be more likely to remember and report experiencing symptoms as compared to their healthy counterparts. Conversely, PD patients, especially those with advanced progression, may either have a hard time recalling, or exaggerate the manifestations of this complex disease.

With such a low cut-off score determined using our data, there is a possibility that the aging population, especially those that fall into the geriatric category, could overly qualify for a positive result, thus translating to a higher false positive rate than anticipated utilizing our case-control study. It also raises a larger question; at what point do we draw the line in symptomatic development to seek follow-up? And how do those lines vary across race, SES and gender? Analyzing these characteristics will assess, change and

improve how we identify at risk-populations, and thus advance how we are able to target them.

Ultimately, the usefulness of a questionnaire like this will also be determined by the patient themselves, as their own personal ability, access to resources and motivation will determine whether or not they actually seek follow-up or specialist care. A survey like this could also amplify the problems already associated with barriers to seeking additional assistance and obtaining the appropriate follow-up.

Disease screening is also somewhat limited without the development of diagnostic tools that can identify PD before motor features develop, putting us consistently one step behind.

6. Conclusion and Recommendations

As with any disease, early diagnosis leads to better treatment and better patient outcomes, no matter the etiology, cause or body system affected. With the overall aim to develop a screening tool to identify persons who are at risk for developing Parkinson's Disease in underserved primary care populations, this simple 10 question survey would be an easy addition to any primary care office or community health screening, particularly those which already incorporate a simple blood pressure reading. More importantly, this questionnaire touches on several features that may be present in PD populations at least 5 years before diagnosis, including tremor, balance anomalies, constipation, hypotension and anxiety, opening the possibility to diagnosis before advanced degeneration of dopamine producing neurons, especially in conjunction with new, technologically advanced diagnostic techniques, like MRI imaging and blood testing, that are sure to become increasingly refined within the next several years.

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Appendix I: Tables

Table 1: Characteristics of Entire Cohort

Characteristic	Overall	Case	Control	P-Value	Method
Age					
Mean (SD)	65.06 (8.82)	63.13 (9.03)	67.05 (8.21)	0.0001*	WMW
Missing, n	0	0	0		approx.
Sex, n (%)					
Male	59 (44.70)	35 (52.24)	24 (36.92)	0.0768	Chi-
Female	73 (55.30)	32 (47.76)	41 (63.08)		Square
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
Race, n (%)					
Caucasian	111 (84.09)	61 (91.04)	50 (76.92)	0.0003*	Fisher's
African American	16 (12.12)	2 (2.99)	14 (21.54)		
Hispanic	2 (1.52)	2 (2.99)	0 (0.00)		
Asian	0 (0.00)	0 (0.00)	0 (0.00)		
Other	0 (0.00)	0 (0.00)	0 (0.00)		
Missing	3 (2.27)	2 (2.99)	1 (1.54)		
Education, n (%)					
Less than HS	1 (0.76)	1 (1.49)	0 (0.00)	<.0001*	Fisher's
High School	10 (7.58)	8 (11.94)	2 (3.08)		
Some college	14 (10.61)	8 (11.94)	6 (9.23)		
Associate's	8 (6.06)	5 (7.46)	3 (4.62)		
Bachelor's	42 (31.82)	24 (35.82)	18 (27.69)		
Master's	38 (28.79)	16 (23.88)	22 (33.85)		
Doctoral	13 (9.85)	3 (4.48)	10 (15.38)		
Missing	6 (4.55)	2 (2.99)	4 (6.15)		
Education (years)					
Mean (SD)	16.61 (2.56)	16.01 (2.60)	17.22 (2.38)	0.0067*	T-Test,
Missing	4	2	2		Pooled
Family History, n (%)					
Yes	12 (9.09)	9 (13.43)	3 (4.62)	0.0046*	Fisher's
No	45 (34.09)	13 (19.40)	32 (49.23)		
Missing×	75 (56.82)	45 (67.16)	30 (46.15)		
Jewish History, n (%)					

Yes	12 (9.09)	7 (10.45)	5 (7.69)	0.5445	Chi-
No	118 (89.39)	58 (86.57)	60 (92.31)		Square
Missing	2 (1.52)	2 (2.99)	0 (0.00)		
Total, n (%)	132 (100.00)	67 (50.76)	65 (49.24)		

*****Denotes significance at an α level of 0.05

×Not added to study battery until April 2016

Table 2: Characteristics of Cohort A

Characteristic	**Overall**	**Case**	**Control**	**P-Value**	**Method**
Age					
Mean (SD)	65.65 (8.82)	61.44 (8.73)	71.15 (5.21)	<.0001*	T-test,
Missing, n	0	0	0		0.0007
Sex, n (%)					
Male	27 (45.00)	18 (52.94)	9 (34.62)	0.1574	Chi-
Female	33 (55.00)	16 (47.06)	17 (65.38)		Square
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
Race, n (%)					
Caucasian	51 (85.00)	33 (97.06)	18 (69.23)	0.0007*	Fisher's
African American	8 (13.33)	0 (0.00)	8 (30.77)		
Hispanic	0 (0.00)	0 (0.00)	0 (0.00)		
Asian	0 (0.00)	0 (0.00)	0 (0.00)		
Other	0 (0.00)	0 (0.00)	0 (0.00)		
Missing	1 (1.67)	1 (2.94)	0 (0.00)		
Education, n (%)					
Less than HS	1 (1.67)	1 (2.94)	0 (0.00)	<.0001*	Fisher's
High School	4 (6.67)	4 (11.76)	0 (0.00)		
Some college	7 (11.67)	5 (14.71)	2 (7.69)		
Associate's	2 (3.33)	2 (5.88)	0 (0.00)		
Bachelor's	19 (31.67)	11 (32.35)	8 (30.77)		
Master's	18 (30.00)	8 (23.53)	10 (38.46)		
Doctoral	8 (13.33)	2 (5.88)	6 (23.08)		
Missing	1 (1.67)	1 (2.94)	0 (0.00)		
Education (years)					
Mean (SD)	16.86 (2.70)	15.98 (2.74)	17.96 (2.24)	0.0043*	T-Test,
Missing, n	1	1	0		Pooled
Jewish History, n (%)					

Yes	2 (3.33)	1 (2.94)	1 (3.85)	0.5015	Fisher's
No	57 (95.00)	32 (94.12)	25 (96.15)		
Missing	1 (1.67)	1 (2.94)	0 (0.00)		
Total, n (%)	60 (100.00)	34 (56.67)	26 (43.33)		

*Denotes significance at an α level of 0.05

Table 3: Characteristics of Cohort B

Characteristic	Overall	Case	Control	P-Value	Method
Age					
Mean (SD)	64.58 (8.79)	64.35 (8.75)	64.83 (8.94)	0.8041	T-Test,
Missing, n	0	0	0		Pooled
Sex, n (%)					
Male	36 (42.86)	21 (48.84)	15 (36.59)	0.2567	Chi-
Female	48 (57.14)	22 (51.16)	26 (63.41)		Square
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
Race, n (%)					
Caucasian	71 (84.52)	37 (86.05)	34 (82.93)	0.0141*	Fisher's
African American	8 (9.52)	2 (4.65)	6 (14.63)		
Hispanic	2 (2.38)	2 (4.65)	0 (0.00)		
Asian	0 (0.00)	0 (0.00)	0 (0.00)		
Other	1 (1.19)	1 (2.33)	0 (0.00)		
Missing	2 (2.38)	1 (2.33)	1 (2.44)		
Education, n (%)					
Less than HS	0 (0.00)	0 (0.00)	0 (0.00)	0.0003*	Fisher's
High School	6 (7.14)	4 (9.30)	2 (4.88)		
Some college	7 (8.33)	3 (6.98)	4 (9.76)		
Associate's	10 (11.90)	7 (16.28)	3 (7.32)		
Bachelor's	29 (34.52)	17 (39.53)	12 (29.27)		
Master's	21 (25.00)	9 (20.53)	12 (29.27)		
Doctoral	6 (7.14)	2 (4.65)	4 (9.76)		
Missing	5 (5.95)	1 (2.33)	4 (9.76)		
Education (years)					
Mean (SD)	16.41 (2.44)	16.15 (2.55)	16.69 (2.31)	0.3247	T-Test,
Missing, n	3	1	2		Pooled
Family History, n (%)					
Yes	14 (16.67)	11 (25.58)	3 (7.32)	0.0018*	Chi-

No	50 (59.52)	16 (37.21)	34 (82.93)		Square
Missing×	20 (23.81)	16 (37.21)	4 (9.76)		
Jewish History, n (%)					
Yes	10 (11.90)	6 (13.95)	4 (9.76)	0.2184	Fisher's
No	73 (86.90)	36 (83.72)	37 (90.24)		
Missing	1 (1.19)	1 (2.33)	0 (0.00)		
Total, n (%)	84 (100.00)	43 (51.19)	41 (48.81)		

*Denotes significance at an α level of 0.05
×Not added to study battery until April 2016

Table 4: Clinical Characteristics of Cohort A

Characteristic	Overall	Case	Control	P-Value
Systolic BP, lying down				
Mean, SD	137.28 (18.50)	134.38 (17.31)	140.85 (19.61)	0.1876
Missing, n	2	2	0	
Diastolic BP, lying down				
Mean, SD	78.33 (8.48)	78.31 (8.08)	78.35 (9.11)	0.9882
Missing, n	2	2	0	
Heart rate, lying down				
Mean, SD	70.00 (10.58)	72.81 (11.78)	66.54 (7.79)	0.0234*
Missing, n	2	2	0	
Systolic BP, standing up				
Mean, SD	127.00 (20.13)	120.50 (18.31)	135.00 (19.67)	0.0053*
Missing, n	2	2	0	
Diastolic BP, standing up				
Mean, SD	77.81 (10.75)	76.38 (11.05)	79.58 (10.30)	0.2629
Missing, n	2	2	0	
Heart rate, standing up				
Mean, SD	78.41 (12.84)	82.66 (12.46)	73.19 (11.48)	0.0043*
Missing, n	2	2	0	
Total, n (%)	60 (100)	34 (56.67)	26 (43.33)	

*Denotes significance at an α level of 0.05

Table 5: Clinical Characteristics of Cohort B

Characteristic	Overall	Case	Control	P-Value
Systolic BP, lying down				
Mean, SD	130.61 (17.30)	128.84 (14.37)	132.46 (19.92)	0.3439
Missing (n)	0	0	0	
Diastolic BP, lying down				
Mean, SD	77.27 (8.49)	78.12 (9.44)	76.39 (7.38)	0.3548
Missing (n)	0	0	0	
Heart rate, lying down				
Mean, SD	69.14 (11.49)	73.64 (12.44)	64.16 (7.86)	0.0001*
Missing (n)	4	1	3	
Systolic BP, standing up				
Mean, SD	124.46 (19.02)	119.31 (16.27)	130.16 (20.39)	0.0100*
Missing (n)	4	1	3	
Diastolic BP, standing up				
Mean, SD	78.78 (10.68)	78.40 (11.36)	79.18 (10.02)	0.7468
Missing (n)	4	1	3	
Heart rate, standing up				
Mean, SD	78.83 (12.61)	84.10 (12.02)	72.66 (10.41)	<.0001*
Missing (n)	8	2	6	
Total, n (%)	84 (100.00)	43 (51.19)	41 (48.81)	

*Denotes significance at an α level of 0.05

Table 6: Question Battery Summary

Questionnaire Title	Abbreviation	Range	Cohort A	Cohort B	Validation×
Motor UPDRS	UPDRS	0-108	X	X	Yes
Montreal Cognitive Assessment	MoCA	0-30	X	X	Yes
The Movement Disorder Society-	MDS-UPDRS	0-264		X	Yes

Sponsored Revision of the Unified Parkinson's Disease Rating Scale					
Part I:Non-Motor Experiences of Daily Living		0-52		X	
Part II: Motor Experiences of Daily Living		0-52		X	
Part III: Motor Examination		0-136		X	
Part IV: Motor Complications		0-24		X	
REM Sleep Behavior Disorder Screening Questionnaire	RBDSQ	0-12	X	X	Yes
Non-Motor Symptoms Questionnaire	NMSQuest	0-30	X	X	Yes
Beck Depression Inventory-II	BDI-II	0-63	X	X	No
Beck Anxiety Inventory	BAI	0-63	X	X	No
Epworth Sleepiness Scale	ESS	0-24	X	X	Yes
Patient Sleep Questionnaire	PSQ	*	X	X	No
Apathy Scale	AS	*	X	X	Yes
Fatigue Severity Scale	FSS	9-63	X	X	Yes
Freezing of Gait Questionnaire	FOG-Q	0-24	X	X	Yes
Physical Activity Scale	PAS2	N/A	X	X	No
State-Trait Anxiety Inventory	STAI	40-160		X	Yes

Scale for Outcomes in PD for autonomic symptoms	SCOPA AUT	*	X	Yes
Geriatric Depression Scale	GDS-15	0-15	X	Yes

*Indicates that a definitive scoring guide could not be located
ˣSurvey was or not validated in an exclusively PD affected population

Table 7: Question Battery Summary of Cohort A

Survey	Case	Control	P-Value	Method
Motor UPDRS				
Mean (SD)	18.75 (9.89)	2.65 (2.67)	<.0001*	WMW exact
Missing, n	2	0		1 tailed
MoCA				
Mean (SD)	26.06 (3.33)	27.65 (1.92)	0.0447*	WMW exact
Missing, n	1	0		1 tailed
RBDSQ				
Mean (SD)	4.85 (2.78)	2.50 (2.16)	0.0003*	WMW exact
Missing, n	0	0		1 tailed
NMSQuest				
Mean (SD)	10.36 (4.87)	3.62 (3.13)	<.0001*	WMW exact
Missing, n	1	0		1 tailed
BDI-II				
Mean (SD)	8.70 (5.75)	4.46 (4.06)	0.0020*	WMW approx.
Missing, n	1	0		1 tailed
BAI				
Mean (SD)	9.31 (7.21)	3.04 (3.08)	0.0001*	WMW approx.
Missing, n	0	1		1 tailed
ESS				
Mean (SD)	10.18 (5.11)	6.08 (3.54)	0.0009*	T-Test
Missing, n	0	0		Pooled
AS				
Mean (SD)	17.55 (3.36)	18.52 (3.49)	0.3055	T-Test
Missing, n	3	3		Pooled
FSS				
Mean (SD)	26.94 (12.01)	20.42 (8.02)	0.0127*	WMW approx.
Missing, n	1	0		1 tailed

FOG-Q				
Mean (SD)	6.06 (4.76)	0.58 (1.33)	<.0001*	WMW approx.
Missing, n	0	0		1 tailed
Total, n	34	26		

*Denotes significance at an α level of 0.05

Table 8: Question Battery Summary of Cohort B

Survey	Case	Control	P-Value	Method
Motor UPDRS				
Mean (SD)	19.95 (6.50)	2.49 (3.07)	<.0001*	WMW exact
Missing, n	2	0		1 tailed
MDS-UPDRS				
Part I: Mean (SD)	9.00 (5.18)	5.22 (2.87)	0.0002*	WMW approx.
Missing, n	0	0		1 tailed
Part II: Mean (SD)	9.72 (7.15)	0.98 (1.82)	<.0001*	WMW approx.
Missing, n	0	0		1 tailed
Part III: Mean (SD)	24.37 (7.81)	3.12 (3.78)	<.0001*	WMW approx.
Missing, n	0	0		1 tailed
Part IV: Mean (SD)	4.65 (4.57)	0.53 (0.53)	<.0001*	WMW approx.
Missing, n	3	9		1 tailed
MoCA				
Mean (SD)	27.67 (2.31)	27.54 (2.17)	0.3871	WMW exact
Missing, n	0	0		1 tailed
RBDSQ				
Mean (SD)	3.95 (2.58)	2.46 (2.09)	0.0022*	WMW exact
Missing, n	0	0		1 tailed
NMSQuest				
Mean (SD)	7.35 (4.28)	3.49 (2.98)	<.0001*	WMW approx.
Missing, n	0	0		1 tailed
BDI-II				
Mean (SD)	6.70 (6.17)	4.10 (4.57)	0.0078*	WMW approx.
Missing, n	0	0		1 tailed
BAI				
Mean (SD)	7.02 (6.69)	2.63 (3.69)	<.0001*	WMW approx.
Missing, n	0	0		1 tailed

ESS				
Mean (SD)	8.40 (4.27)	5.71 (3.12)	0.0015*	T-Test
Missing, n	1	0		Pooled
AS				
Mean (SD)	17.78 (2.83)	17.85 (2.90)	0.9021	T-Test
Missing, n	3	0		Pooled
FSS				
Mean (SD)	25.63 (11.94)	20.07 (9.05)	0.0162*	WMW approx.
Missing (n)	0	0		1 tailed
FOG-Q				
Mean (SD)	3.74 (4.82)	0.15 (0.53)	<.0001*	WMW approx.
Missing, n	0	0		1 tailed
STAI				
Mean (SD)	92.62 (7.91)	93.52 (6.56)	0.3004	WMW approx.
Missing, n	0	0		1 tailed
GDS-15				
Mean (SD)	1.85 (2.16)	1.27 (1.53)	0.1590	WMW approx.
Missing, n	9	8		1 tailed
Total, n	43	41		

*Denotes significance at an α level of 0.05

Table 9: Score breakdown of battery, based on reported cut-offs, Cohort A

Survey	Overall	Case	Control	P-Value	Method
MoCA, n (%)					
PD-MCI	14 (23.33)	12 (35.29)	2 (7.69)	0.0102*	Chi-
Normal	45 (75.00)	21 (61.76)	24 (92.31)		Square
Missing	1 (1.67)	1 (2.94)	0 (0.00)		
PD-D	1 (1.67)	1 (2.94)	0 (0.00)	0.5593	Fisher's
No dementia	58 (96.67)	32 (94.12)	26 (100.00)		
Missing	1 (1.67)	1 (2.94)	0 (0.00)		
RBDSQ, n (%)					
"Positive"	22 (36.67)	16 (47.06)	6 (23.08)	0.0561	Chi-
"Negative"	38 (63.33)	18 (52.94)	20 (76.92)		Square
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
BDI-II, n(%)					

Minimal	54 (90.00)	29 (85.29)	25 (96.15)	0.2925	CMH
Mild	2 (3.33)	1 (2.94)	1 (3.85)		
Moderate	3 (5.00)	3 (8.82)	0 (0.00)		
Severe	0 (0.00)	0 (0.00)	0 (0.00)		
Missing	1 (1.67)	1 (2.94)	0 (0.00)		
Depression	5 (8.33)	4 (11.76)	1 (3.85)	0.2125	Fisher's
No Depression	54 (90.00)	29 (85.29)	25 (96.15)		
Missing	1 (1.67)	1 (2.94)	0 (0.00)		
BAI, n (%)					
Minimal	40 (66.67)	18 (52.94)	22 (84.62)	0.0282*	CMH
Mild	12 (20.00)	9 (26.47)	3 (11.54)		
Moderate	6 (10.00)	6 (17.65)	0 (0.00)		
Depression	1 (1.67)	1 (2.94)	0 (0.00)		
Missing	1 (1.67)	0	1 (3.85)		
ESS, n (%)					
Tiredness	21 (35.00)	17 (50.00)	4 (15.38)	0.0044*	Fisher's
Normal	39 (65.00)	17 (50.00)	22 (84.62)		
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
AS, n (%)					
Apathetic	47 (78.33)	27 (79.41)	20 (76.92)	0.3146	Fisher's
Normal	7 (11.67)	4 (11.76)	3 (11.54)		
Missing	6 (10.00)	3 (8.82)	3 (11.54)		
FOG-Q, n (%)					
FOG	20 (33.33)	19 (55.88)	1 (3.85)	<.0001*	Fisher's
Normal	40 (66.67)	15 (44.12)	25 (96.15)		
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
Total, n (%)	60 (100)	34 (56.67)	26 (43.33)		

*Denotes significance at an α level of 0.05

ˣ Unable to calculate p-value due to non-missing level 0

Table 10: Score breakdown of battery, based on reported cut-offs, Cohort B

Survey	Overall	Case	Control	P-Value	Method
MoCA, n (%)					
PD-MCI	13 (15.48)	5 (11.63)	8 (19.51)	0.3179	Chi-
Normal	71 (84.52)	38 (88.37)	33 (80.49)		Square
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
PD-D	1 (1.19)	1 (2.33)	0 (0.00)	0.5119	Fisher's
No dementia	83 (98.81)	42 (97.67)	41 (100.00)		

Missing	0 (0.00)	0	0		
RBDSQ, n (%)					
"Positive"	22 (26.19)	16 (37.21)	6 (14.63)	0.0187*	Chi-Square
"Negative"	62 (73.81)	27 (62.79)	35 (85.37)		
Missing	0 (0.00)	0	0		
BDI-II, n (%)					
Minimal	76 (90.48)	39 (90.70)	37 (90.24)	0.0930	CMH
Mild	5 (5.95)	1 (2.33)	4 (9.76)		
Moderate	3 (3.57)	3 (6.98)	0 (0.00)		
Severe	0 (0.00)	0 (0.00)	0 (0.00)		
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
Depression	8 (9.52)	4 (9.30)	4 (9.76)	0.2867	Fisher's
No Depression	76 (90.48)	39 (90.70)	37 (90.24)		
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
BAI, n (%)					
Minimal	65 (77.38)	29 (67.44)	36 (87.80)	0.0281*	CMH
Mild	14 (16.67)	10 (23.26)	4 (9.76)		
Moderate	4 (4.76)	3 (6.98)	1 (2.44)		
Depression	1 (1.19)	1 (2.33)	0 (0.00)		
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
ESS, n (%)					
Tiredness	19 (22.62)	17 (39.53)	2 (4.88)	<.0001*	Fisher's
Normal	64 (76.19)	25 (58.14)	39 (95.12)		
Missing	1 (1.19)	1 (2.33)	0 (0.00)		
AS, n (%)					
Apathetic	76 (90.48)	37 (86.05)	39 (95.12)	0.3162	Fisher's
Normal	5 (5.95)	3 (6.98)	2 (4.88)		
Missing	3 (3.57)	3 (6.98)	0		
FOG-Q, n (%)					
FOG	14 (16.67)	14 (32.56)	0 (0.00)	<.0001*	Chi-Square
Normal	70 (83.33)	29 (67.44)	41 (100.00)		
Missing	0 (0.00)	0 (0.00)	0 (0.00)		
STAI, n (%)					
Anxiety	78 (92.86)	39 (90.70)	39 (95.12)	0.2490	Fisher's
No Anxiety	6 (7.14)	4 (9.30)	2 (4.88)		
Missing	0 (0.00)	0 (0.00)	0 (0.00)		

GDS-15, n (%)					
Depression	0 (0.00)	0 (0.00)	0 (0.00)	0.1585	Fisher's
Possible depression	5 (5.95)	4 (9.30)	1 (1.19)		
No depression	62 (73.81)	30 (69.77)	32 (78.05)		
Missing	17 (20.24)	9 (20.93)	8 (19.51)		
Total, n (%)	84 (100.00)	43 (51.19)	41 (48.81)		

*Denotes significance at an α level of 0.05

Table 11: Clinical Indicators of Orthostatic Hypotension

Measurement	Overall	Case	Control	P-Value	Method
Systolic BP					
Mean (SD)	7.42 (11.97)	11.69 (13.24)	3.02 (8.57)	<.0001 *	T-Test
Missing, n	6	3	3		
Diastolic BP					
Mean, SD	-0.95 (8.49)	0.88 (9.90)	-2.84 (6.27)	0.0042*	WMW
Missing, n	6	3	3		Approx.
Heart Rate					
Mean, SD	-8.88 (7.61)	-9.68 (8.83)	-8.02 (6.01)	0.1841	WMW
Missing, n	10	4	6		Approx.
Systolic BP (n,%)					
Orthostatic	15 (11.36)	14 (20.90)	1 (1.54)	0.0004*	Chi-
Normal	111 (84.09)	50 (74.63)	61 (93.85)		Square
Missing	6 (4.55)	3 (4.48)	3 (4.62)		
Diastolic BP (n,%)					
Orthostatic	13 (9.85)	10 (14.93)	3 (4.62)	0.0466*	Chi-
Normal	113 (85.61)	54 (80.60)	59 (90.77)		Square
Missing	6 (4.55)	3 (4.48)	3 (4.62)		
Heart Rate (n,%)					
Orthostatic	12 (9.09)	10 (14.93)	2 (3.08)	0.0179*	Chi-
Normal	110 (83.33)	53 (79.10)	57 (87.69)		Square
Missing	10 (7.58)	4 (5.97)	6 (9.23)		
Total, n (%)	132 (100.00)	67 (50.76)	65 (49.24)		

*Denotes significance at an α level of 0.05

Table 12: Odds Ratios of Orthostatic Hypotension

Clinical Measure	Odds Ratio	95% Confidence Limits
Systolic Blood Pressure	17.08	2.17 - 134.40
Diastolic Blood Pressure	3.64	0.95 - 13.94
Heart Rate	5.38	1.13 - 25.68

Table 13: Individual Question Assay [1]

Question	Chi-Square	P-Value	Odd's Ratio	95% Confidence Interval
1.1	1.1056	0.2931	1.66	0.6037 - 4.5489
1.2	8.4308	0.0037	N/A×	N/A×
1.3	0.0336	0.8546	1.11	0.3627 - 1.6117
1.4	5.0655	0.0244	2.78	1.1289 - 6.8420
1.5	2.0034	0.1570	2.45	0.6900 - 8.6883
1.6	2.6718	0.1021	5.26	0.5876 - 47.1432
1.7	2.0043	0.1569	2.20	0.7276 - 6.6519
1.8	2.4418	0.1181	2.11	0.8203 - 5.4375
1.9	0.2170	0.6413	0.81	0.3436 - 1.9312
1.10	3.0105	0.0827	2.16	0.9003 - 5.1642
1.11	14.6117	0.0001	7.54	2.4853 - 22.8922
1.12	4.0252	0.0448	2.70	1.0072 - 7.2227
1.13	6.5227	0.0107	3.64	1.3129 - 10.1079
2.1	27.2973	<.0001	27.08	5.7786 - 126.9362
2.2	9.9263	0.0016	6.05	1.8232 - 20.0628
2.3	6.8427	0.0089	10.59	1.2761 - 87.8568
2.4	18.8454	<.0001	N/A×	N/A×
2.5	33.9377	<.0001	N/A×	N/A×
2.6	10.8234	0.0010	N/A×	N/A×
2.7	28.1313	<.0001	21.38	5.6637 - 80.6693
2.8	24.3948	<.0001	17.59	4.6885 - 66.0124
2.9	19.2967	<.0001	10.00	3.2808 - 30.4799
2.10	52.6642	<.0001	100.29	19.5420 - 514.6458
2.11	15.8671	<.0001	6.64	2.5169 - 17.5015
2.12	27.2755	<.0001	17.27	5.1630 - 57.7451
2.13	14.6649	0.0001	N/A×	N/A×

*Denotes significance at an α level of 0.05

× Due to a zero cell, the OR was unable to be calculated

Table 14: Questions Selected from the MDS-UPDRS [1]

1.4 Anxious Mood	Over the past week, have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people?

1.11 Constipation Problems	Over the past week have you had constipation troubles that cause you difficulty moving your bowels?
1.12 Light Headedness on Standing	Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down?
1.13 Fatigue	Over the past week, have you usually felt fatigued? This feeling is not part of being sleepy or sad
2.7 Handwriting	Over the past week, have people usually had trouble reading your handwriting?
2.8 Doing Hobbies and Other Activities	Over the past week, have you usually had trouble doing your hobbies or other things that you like to do?
2.10 Tremor	Over the past week, have you usually had shaking or tremor?
2.11 Getting out of bed, a car, or a deep chair	Over the past week, have you usually had trouble getting out of a bed, a car seat, or a deep chair?
2.12 Walking and Balance	Over the past week, have you usually had problems with balance and walking?

Table 15: Reported Cut Offs

Cutoff	**Sensitivity**	**Specificity**	**Youden's J**
3.0001	0.92857	0.81579	0.74430
5.002	0.71429	0.94737	0.66165
4.0001	0.73810	0.89474	0.63283
6.0002	0.61905	0.97368	0.59273
2.0000	0.97619	0.60526	0.58145
7.0003	0.38095	0.97368	0.35464
8.0003	0.21429	1.00000	0.21429
1.0000	1.00000	0.15789	0.15789
9.0004	0.14286	1.00000	0.14286

Table 16: Association Between Education and Time to Diagnosis

Time to Diagnosis	Low Education	High Education	P-Value
Mean (SD)	2.1 (0.21)	2.15 (0.04)	0.4912
Total, n	13	26	

Appendix II: Figures

Figure 1: Overview and Rationale Diagram

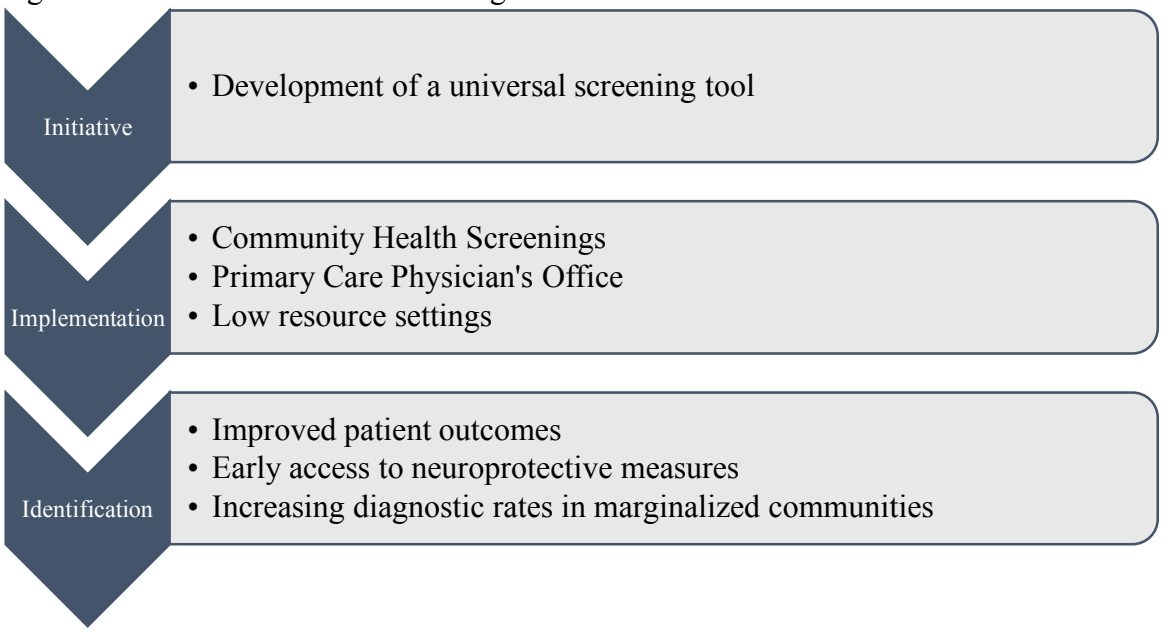


Figure 2: Study Participants and Cohort Creation

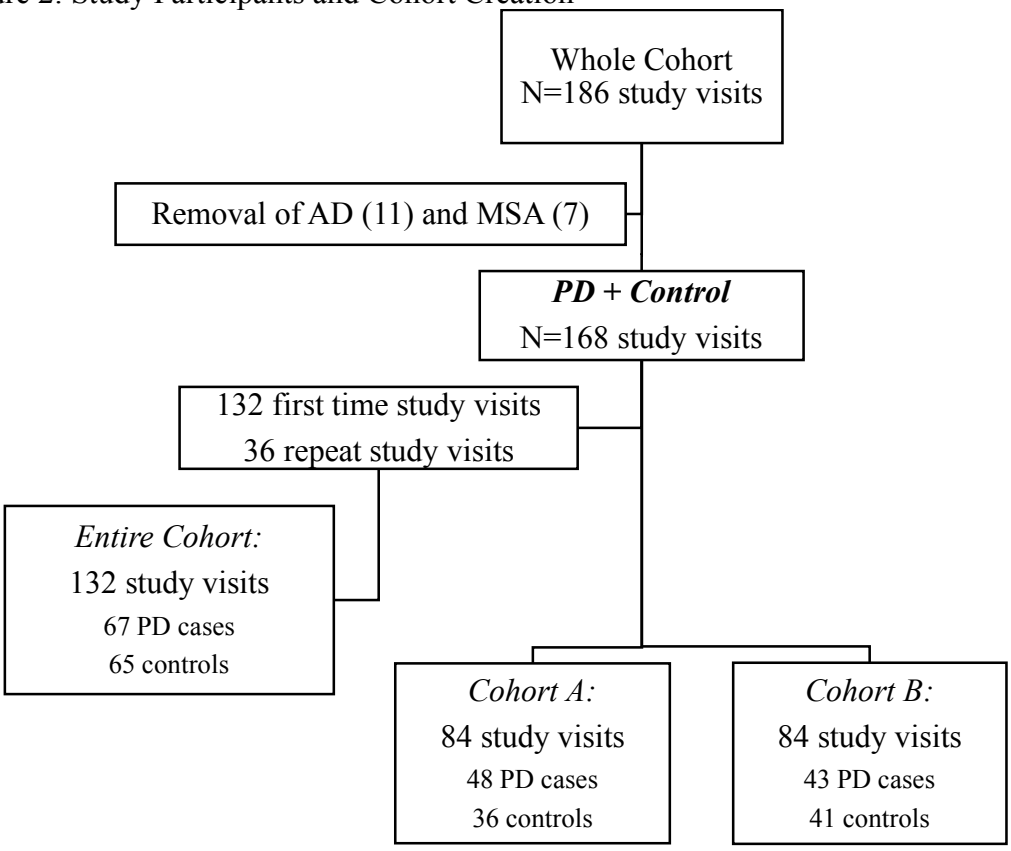


Figure 3: ROC Curve for Suggestive PD Screening Tool

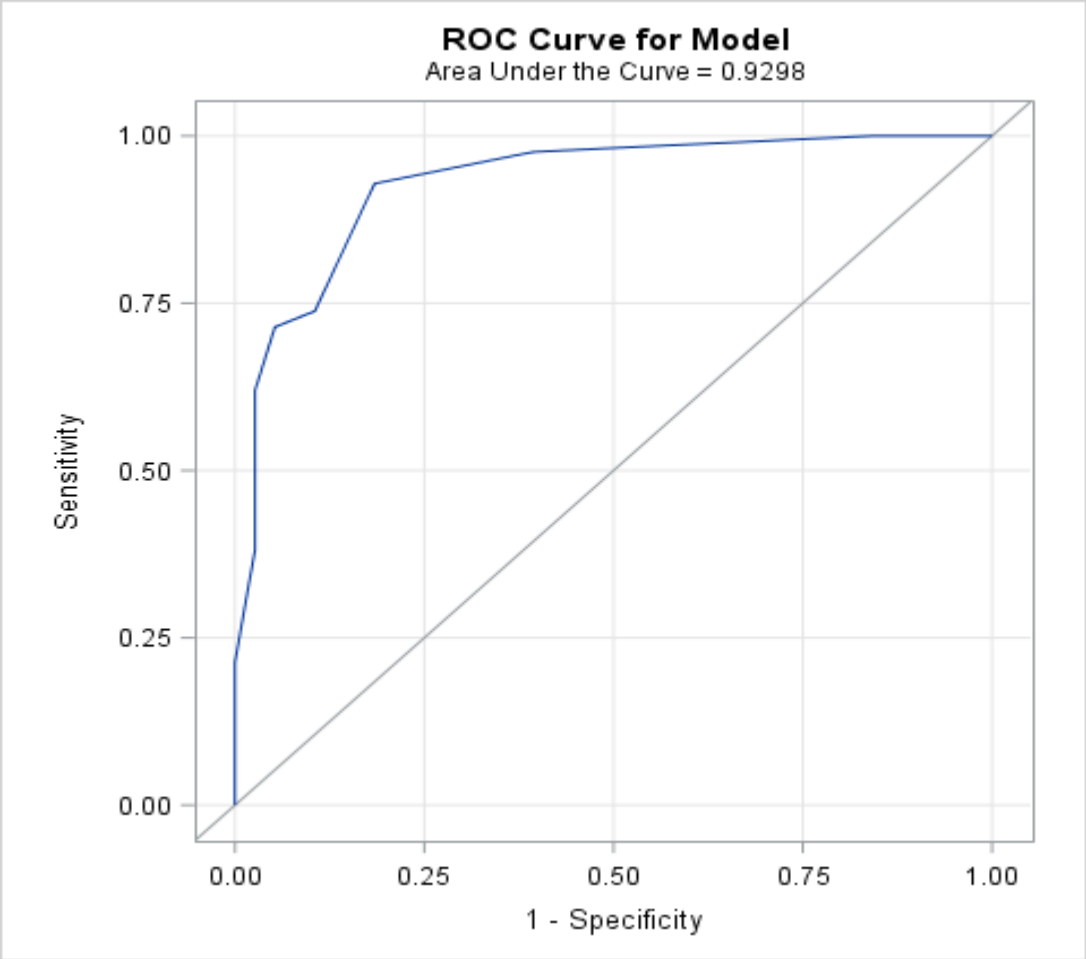
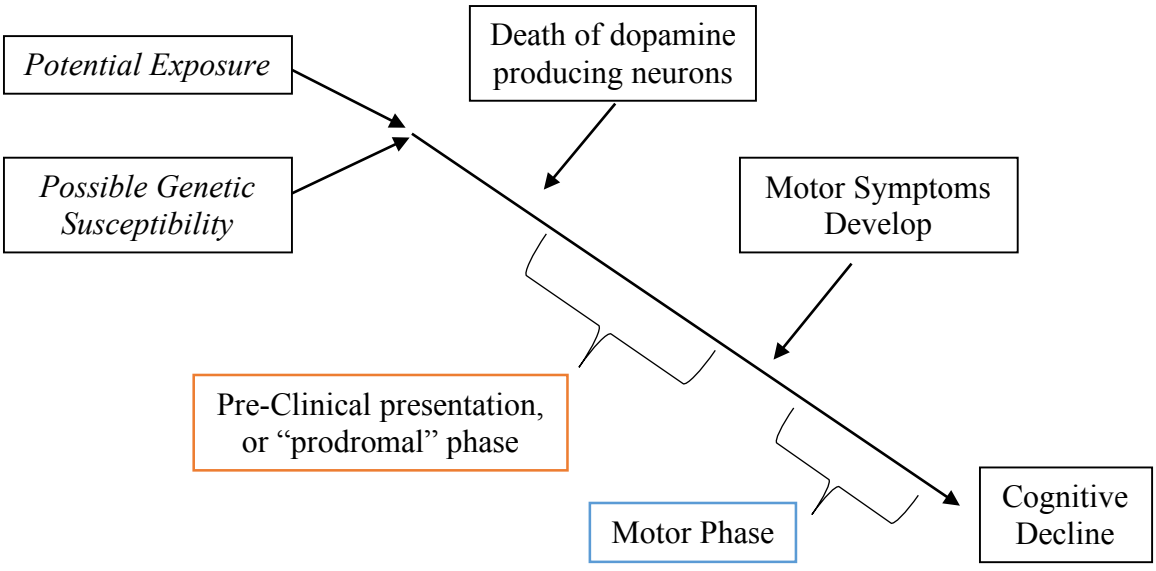


Figure 4: Disease Progression and phases of Parkinson's Disease



Appendix III: Review and Analysis of Additional Questionnaires Utilized in Study Battery

The Montreal Cognitive Assessment (MoCA) is the preferred screening tool to quickly assess for mild cognitive impairment (PD-MCI) and dementia (PD-D) in PD populations [35]. Out of thirty total summed points, a score of less than twenty-six is an indication for MCI, while a score of less than twenty-one suggests PD-D [36]. There is a one-point difference in the average scores of cohort A, but no significant difference appreciable between the groups in cohort B. When screening for MCI, there is a considerable distinction amongst PD patients and controls in cohort A that is not replicated in cohort B. This is likely a result of the means being somewhat comparable in the latter group. Neither had a distinguishable difference in PD-D, though the three cases who met the cut-off score for possible dementia all had a diagnosis of PD.

The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) is another investigatory instrument that can be utilized to screen for rapid eye movement (REM) anomalies, even before a formal PD diagnosis is obtained [37, 38]. However, since it is self-reported with five "yes" answers out of thirteen potential total points indicating a possible neurological irregularity, this questionnaire, in particular, can be biased due to the patient's own knowledge, with varying reported validations in PD populations [39, 40]. Nonetheless, it is generally accepted as validated in PD [39]. When comparing the mean scores, the data fell in line with the literature with significant differences reflected in both groups. No formal training was administered prior to administration of this survey however, most participants had a significant other or caretaker with them who may have been able to assist with answering some of the questions. Cohort A had a nearly significant p-value (0.0561) while cohort B did demonstrate a contrast between PD and controls who scored a "positive" result. Both groups incidentally had an equal number of cases and controls with REM symptoms that would warrant following up with a sleep specialist.

The Non-Motor Symptoms Questionnaire (NMSQuest) is a thirty question self-reported and validated survey that is intended to screen for, and identify, common non-motor features of PD, some of which that can interfere with daily activities and substantially play a role in overall quality of life, and which are often not addressed directly during a routine doctor's visit [41-43]. The questions also assess symptoms that could be present in the prodromal phase of the disease, signaling to providers that further specialist care could be necessary [44]. As anticipated, there is a significant difference between the mean score of both cohorts. It is important to note that this scale is not meant to be quantified to correlate with disease severity or progression, but simply to draw attention to a set of possible pre-identified symptoms often associated with the pathology of PD, including Lewy bodies and dopamine cell loss [44-46]. For this reason, no cut off score was utilized to distinguish between those with non-motor symptoms and those without.

The Beck Depression Inventory-II (BDI-II) is a twenty-one question survey that when summed, gives a quantifiable value that can be used to classify the intensity of specifically psychological depressive symptoms, separating them from the other non-motor symptoms that are often associated with PD [47, 48]. This scale ranges from zero to sixty-three, with the scoring guide noting four cut-offs including minimal depression (zero through thirteen), mild depression (fourteen through nineteen), moderate depression

(twenty through twenty eight) and severe depression (twenty-nine through sixty-three) [49]. Average score in both cohorts was significantly different. When utilizing the BDI-II's specific scoring guide there was no distinguishable differences between cases and controls, with most participants falling into the minimal depression category regardless of case control status. There are PD cases that fall into the class for moderate depression in both cohorts, with no cases qualifying for this level. No participants met the criteria for severe depression on this scale. When used and validated exclusively in PD populations, multiple optimal cut-off scores arise to specifically differentiate between major depressive disorder (MDD) and no depression in the original BDI, all pivoting around a score of fourteen, specifically thirteen/fourteen [50] verses fourteen/fifteen [51]. There appears to be no direct validation of the BDI-II assessed singularly in PD-affected populations, though the cut-off of great than or equal to fourteen seems to be the accepted value [52]. Using that number, there is no discernable difference between depression and no depression across disease categories. Three more cases than controls qualified for depression in cohort A, with equal numbers in cohort B. In a more recent study comparing nine commonly used depressive scales, Williams, Hirsch et al. had no cut-off score recommendations for the BDI-II or GDS-30, however, suggested that the GDS-30 may have superior features as an effective screening tool [53].

The Beck Anxiety Inventory (BAI) attempts to enumerate anxiety on a scale of zero through sixty-three, utilizing twenty-one questions, each with four answer choices that are subsequently assigned a numeric value correlated with severity (zero, not at all; one, mild; two, moderate; three, severe), summed in totality, and scored into four final categories, including minimal anxiety (zero though seven), mild anxiety (eight through fifteen), moderate anxiety (sixteen though twenty-five) and severe depression (twenty-six through sixty-three) [54]. This scale has not been validated in PD populations, however it is noted to be useful for screening and differentiation between anxiety and depression [55]. Significant differences arise in cohort A, with cases averaging six points higher than their disease free counterparts, and also in cohort B, with cases averaging four points higher. Adopting the scoring guides advised breakdown, there is a categorical difference between cases and controls in cohort A, as though most were in the minimal anxiety range, there were six more cases that qualified for both mild and moderate anxiety. No contributors met the summation score for depression. In cohort B, there a non-significant distinction between the two groups with six more cases qualifying for mild anxiety, two more for moderate anxiety and one that met the criteria for depression. It has been advised that this scale is not suggested for use in PD populations, with other screening tools, specifically the Parkinson's Anxiety Scale (PAS) and Geriatric Anxiety Scale (GAI) demonstrating an increased practicality and greater interpretability of results [56].

The Patient Sleep Questionnaire with the Epworth Sleepiness Scale (PSQ w/ ESS) is a combined tool used to assess quality, quantity and notable events that occur while sleeping. It is composed of thirteen questions with varying answer formats, including self-rating on a scale, fill in the blank reporting and selection of the severity from a list of answer choices (including never, a few times, sometimes, quite often, usually and don't know.) The first question is specifically the ESS, which is an eight-question assessment that is used to measure sleepiness during the day, with a score greater than ten signifying substantial tiredness, which has been identified as a possible symptom of PD that could be present in the prodromal phase [57]. Since no definitive scoring guide could be

located for the PSQ in its entirety, only the ESS was used. There were significant differences in the average score of both groups, with cohort B's PD score one point greater than the differenced seen in cohort A, four verses three when compared to controls respectively. This trend continued when utilizing the ESS's key to discern symptoms, with fifty percent of cases exhibiting excessive sleepiness as opposed to sixteen percent of controls in cohort A and forty percent verses five percent in cohort B.

The Apathy Scale (AS) is a set of fourteen questions that aims to assess the presence of apathy directly and situationally with self-rated scores ranging from "not at all" to "a lot."[58] The last question (fifteen) will be omitted from analysis, as it asks the participant to rate their apathy on a scale, which is represented as a blank line with the poles labeled "not at all apathetic" and "completely apathetic" leaving subjectivity in teasing a practical number [58]. This scale appears to have been self-validated in PD when it was originally published [58]. The means of both groups in both cohorts are relatively equal, with controls averaging slightly higher than cases each time. Utilizing a score greater than or equal to fourteen as a positive indication of apathy[58], slightly more cases than controls qualified in cohort A (seventy-nine percent verses seventy-seven percent), while cohort B displayed the opposite trend of eighty-six percent cases as opposed to ninety-five percent of controls. It is important to note the distinction between depression and apathy in PD, which are both very real, but evident independently[59], however, the cut-off score of fourteen seems like a low threshold for a positive screening result as compared to the other tools used and analyzed in this study.

The Fatigue Questionnaire (FQ) is a brief two question survey designed to rate the onset, quantity and impact of fatigue on a person's day to day activities. The first question involves a simple rating on strictly the amount of this symptom, while the second is actually the Fatigue Severity Scale (FSS). The FSS is composed of eight separate questions, each rated one through seven on the factors that surround fatigue and its effects. Fatigue is a known factor that influences life satisfaction in PD patients, especially as the disease progresses in severity, hence why this information was collected [60]. For the purpose of analysis, we have omitted the first question, as it must be extrapolated subjectively by the rater. There was a significant difference between the raw means in both cohorts, measuring seven points and six points respectively. While the FSS by itself has been validated exclusively in PD populations [61] this specific survey as a whole appears to not be validated in PD. There are multiple additional validated scales including the Modified Fatigue Impact Scale (MFIS)[62] and Parkinson's Fatigue Scale (PFS) [63].

The Freezing of Gait Questionnaire (FOG-Q) is a simple six question assessment developed specifically to evaluate the magnitude of non-fall affiliated FOG, which is the delay in walking after initiating the thought to do so [64, 65]. Each question has five distinct answer choices from zero to five, respectively associated with a description of severity[64]. Question three tends to be the best representation of occurrence [66, 67], while questions 4-6 are better used to describe FOG whilst it is occurring [68]. Not surprisingly, the difference between patients and controls was highly significant in both groups, as this symptom is an extremely disease specific. When using question three by itself as a proxy for the entire survey, the same trend holds. Fifty-six percent of patients in cohort A reported experiencing this, as compared to sixty-eight percent of cohort B. Of note, one control, who inadvertently belonged to the original group, stated that they also

experienced this phenomenon. This scale was originally validated in PD populations when it was first created in 2000, and subsequently re-validated independently in 2009 [66].

The Physical Activity Scale (PAS2) is a strictly fill in the blank form evaluating daily and weekly sedimentary and active hours using 9 different scenarios [69]. It is known and understood that physical activity decreases with increases in PD's symptoms, as motor systems progressively decline and mental instability intensifies [70]. This particular scale, while useful, has not been validated in PD populations. Without proper scoring guidelines, and the obvious confounding present in evaluating the relationships that could exist with exertion in a not only geriatric, but motor disease affected population, it was omitted from analysis.

The State-Trait Anxiety Inventory (STAI) is another scale used to measure and identify the occurrence of anxiety, utilizing forty questions answered by the patient, each rated in four distinct categories which are then subsequently summed to obtain a final score, ranging from twenty to eighty [71, 72]. In general, a larger the number translates to increased anxiety, with a score of greater than or equal to forty as the defined cut point for "significant" anxiety [72]. Other studies have suggested using gender specific cut-offs to specifically diagnosis anxiety in PD patients with men set at greater than or equal to forty-one verses women at greater than or equal to forty-two [52]. This was added to the study battery for only the second cohort, where there was no difference between the two groups. In fact, controls scored on average one-point higher than cases and when utilizing cut-offs, there was an equal number of thirty-nine people in each group with anxiety. Separately, it has been validated at least twice in PD specific populations [73], however, it seems to have a low threshold for a positive result. Both the BAI and the STAI are "suggested" scales to be used for evaluating anxiety in PD, with none of the five total evaluated reaching the highest endorsement of "recommended", further highlighting the need for improvement in this area [55].

The Scale for Outcomes in PD for autonomic symptoms (SCOPA AUT) is, as the name directly describes, a measurable, valid and reliable gauge for the exhibition of solely autonomic symptoms exclusively in patients that have been diagnosed with PD [74, 75]. It covers an extensive variety of symptomatic fields, which can be assessed in unison or altogether as a whole, including gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor and sexual dysfunction [74]. As expected, there is almost always a greater score in PD patients than controls, though increase in autonomic dysregulation tends to be commonly correlated with age, disease duration and disease stage [76, 77]. This survey was also only used in cohort B, and a definitive scoring guide was unable to be located. Due to this, it will also not be included in this author's analysis.

Lastly, the Geriatric Depression Scale (GDS-15) is a fifteen question binary answer (yes/no) form specifically designed for the geriatric population in order to screen for depression [78-80]. Each question is weighted equally, with a score of greater than five indicative of a "positive" result, meriting a further work-up and a score greater than or equal to ten considered a direct indicator of depression itself [80, 81]. This scale has been validated for use for patients with PD, however with varying cut-off scores including four/five [82], five [83] and five/six [84] have been identified [85]. There was no significant difference between the average scores in patients and controls, and utilizing the published criteria, only five participants met the threshold for "possible

depression. Of those, four had PD. No one met the score for definite depression using this scale.

Appendix IV: Suggested Screening Tool

For the participant:

Please circle yes or no indicating whether or not you have experienced the following in the *last week*.

1. Have you felt nervous, worried or tense? Yes/No
2. Have you had constipation troubles that cause you difficulty moving your bowels? Yes/No
3. Have you felt faint, dizzy or foggy when you stand up after sitting or lying down? Yes/No
4. Have you usually felt fatigued? This feeling is not part of being sleepy or sad. Yes/No
5. Have people had trouble reading your handwriting? Yes/No
6. Have you usually had trouble doing your hobbies or other things you like to do? Yes/No
7. Have you usually had shaking or tremor? Yes/No
8. Have you usually had trouble getting out of a bed, a car seat, or a deep chair? Yes/No
9. Have you usually had problems with balance and walking? Yes/No

For the clinician:

i. Systolic Blood Pressure Lying Down _____mmHg

ii. Systolic Blood Pressure Standing Up _____mmHg

iii. Difference (Lying – Standing) _____mmHg

10. Is the difference in blood pressure greater than 20 mmHg? Yes/ No

Scoring Guide:

All "yes" answers should be tallied and scored. A score of ≥ 3 warrants visiting a neurologist for a specialty evaluation of symptoms.

Appendix V: MDS-UPDRS [1]

MDS-UPDRS Permissions

Permission is required to use the MDS-developed Rating Scales (with the exception of personal/individual use). Reproduction, translation, modification, sale, or distribution of any portion of the MDS Rating Scales is strictly prohibited. MDS Rating Scales may not be incorporated into clinical trials, training or certification programs or materials, software programs, or otherwise except through use of the Permissions Request Form and payment of applicable fees.

Continue to p. 2 to view the MDS-UPDRS

MDS-UPDRS

The *Movement* Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt
Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
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July 1, 2008

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:
In administering Part IA, the examiner should use the following guidelines:

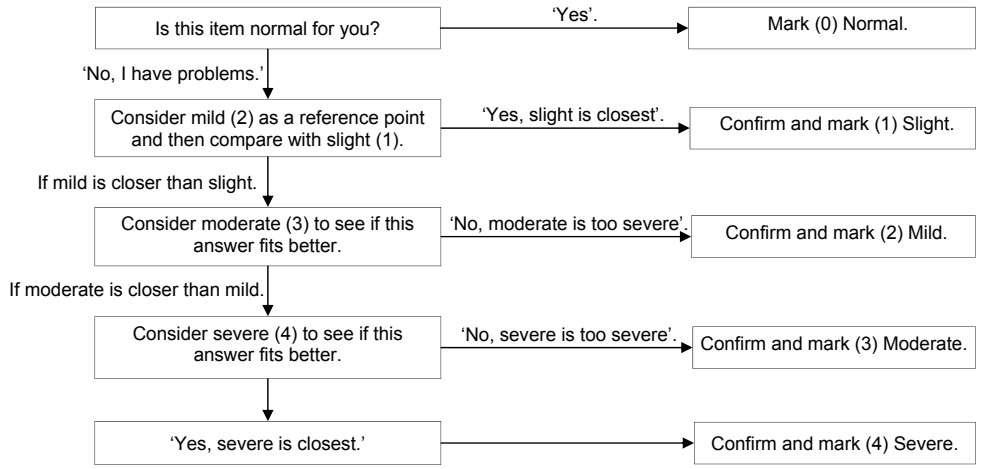
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

Suggested strategies for obtaining the most accurate answer:
After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine Normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



___ ___ ___ ___ ___ ___ ___ ___ Patient Name or Subject ID	___ ___ ___ Site ID	___ ___ - ___ ___ - ___ ___ ___ ___ (mm-dd-yyyy) Assessment Date	___ ___ ___ Investigator's Initials

MDS UPDRS

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part 1A: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT	**SCORE**
Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver. *Instructions to patients [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information]* 0: Normal: No cognitive impairment. 1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions. 2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions. 3: Moderate: Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions. 4: Severe: Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	☐

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patients insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patients [and caregiver]: Over the past week have you seen, heard, smelled or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information] 0: Normal: No hallucinations or psychotic behaviour. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐
1.3 DEPRESSED MOOD Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions. *Instruction to the patient (and caregiver): Over the past week have you felt low, sad, hopeless or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people?* If yes, examiner asks patient or caregiver to elaborate and probes for information] 0: Normal: No depressed mood. 1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3: Moderate: Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.	☐

	SCORE
1.4 ANXIOUS MOOD Instructions to examiner: Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patients [and caregiver]: Over the past week have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people*? [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No anxious feelings. 1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions. 3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	☐
1.5 APATHY Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression. *Instructions to patients (and caregiver): Over the past week, have you felt indifferent to doing activities or being with people?* If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No apathy. 1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions. 2: Mild: Apathy interferes with isolated activities and social interactions. 3: Moderate: Apathy interferes with most activities and social interactions. 4: Severe: Passive and withdrawn, complete loss of initiative.	☐

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME	SCORE
Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity). *Instructions to patients [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop?* [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patients. 0: Normal: No problems present. 1: Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver. 2: Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life. 3: Moderate: Problems are present and usually cause a lot of difficulties in the patient's personal and family life. 4: Severe: Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.	☐

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	**SCORE** ☐
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs but I can resist and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches tingling or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐
Part II: Motor Aspects of Experiences of Daily Living (M-EDL)	
2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not everyday. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA & DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knifes, spoons, chopsticks? 0: Normal: Not at all (No problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another persons to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor. 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐
This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.	

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

	SCORE
3.3 RIGIDITY Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0: Normal: No rigidity. 1: Slight: Rigidity only detected with activation maneuver. 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved. 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort. 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.	☐ Neck ☐ RUE ☐ LUE ☐ RLE ☐ LLE
3.4 FINGER TAPPING Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/ her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from arms of chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking , and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

	SCORE
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. Extremity ratings 0: Normal: No tremor. 1: Slight.: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 3 cm in maximal amplitude. 3: Moderate: 3 - 10 cm in maximal amplitude. 4: Severe: > 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 2 cm in maximal amplitude. 3: Moderate: > 2 cm but < 3 cm in maximal amplitude. 4: Severe: > 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

3.18 CONSTANCY OF REST TREMOR

SCORE

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0: Normal: No tremor.

1: Slight: Tremor at rest is present < 25% of the entire examination period.

2: Mild: Tremor at rest is present 26-50% of the entire examination period.

3: Moderate: Tremor at rest is present 51-75% of the entire examination period.

4: Severe: Tremor at rest is present > 75% of the entire examination period.

☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

☐

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and Dyskinesias. For "OFF dystonia", the total "Off" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching". It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture".

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects".

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A . DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]. Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculation).

0: Normal:	No dyskinesias.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours with Dyskinesia: _____
3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS | **SCORE**

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.	
1: Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.	☐
2: Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.	
3: Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.	
4: Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.	

B . MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ____ (Use this number for your calculations).

0: Normal:	No OFF time.	
1: Slight:	≤ 25% of waking day.	
2: Mild:	26 - 50% of waking day.	
3: Moderate:	51 - 75% of waking day.	
4: Severe:	> 75% of waking day.	

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions. 1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer. *Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable. (≤ 25%).	☐

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ___ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal: No dystonia OR NO OFF TIME.

1: Slight: < 25% of time in OFF state.

2: Mild: 26-50% of time in OFF state.

3: Moderate: 51-75% of time in OFF state.

4: Severe: > 75% of time in OFF state.

1. Total Hours Off: _____
2. Total Off Hours w/Dystonia: _____
3. % Off Dystonia = ((2/1)*100): _____

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

_____ Patient Name or Subject ID	___ ___ ___ Site ID	__ __ - __ __ - __ __ __ __ (mm-dd-yyyy) Assessment Date	___ ___ ___ Investigator's Initials

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping–Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest	
2.12	Walking and balance			Were dyskinesias presen	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on Levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

July 1, 2008