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Outcome Assessment in Parkinson Disease Prevention Trials

Utility of Clinical and Digital Measures

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Abstract

Background and Objectives

The prodromal phase of Parkinson disease (PD) is accompanied by subtle clinical signs that are not sufficient for diagnosis but could potentially be measured in the context of clinical trials of therapies intended to delay or prevent more definitive clinical features. The objective of this study was to review the available literature on the presence and time course of subtle motor features in prodromal PD in the context of planning for possible clinical trials.

Methods

We reviewed the available literature based on expert opinion. We considered a range of outcomes including measurement of clinical features, patient-reported outcomes, digital markers, and clinical diagnosis.

Results

We considered these features and measures in the context of patient stratification, intermediate outcomes, and clinically relevant end points, including phenoconversion.

Discussion

Substantial progress has been made in understanding how motor features evolve in the period immediately before a PD diagnosis. Digital measures hold substantial progress for measurement precision and may be additionally relevant because they can be used in naturalistic environments outside the clinic. Future studies should focus on advancing digital sensor technology and analysis and developing methods to implement available methods, particularly determination of a clinical diagnosis of PD, in a clinical trial context.

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Glossary

ADL = activities of daily living; **DAT** = dopamine transporter; **FDA** = Food and Drug Administration; **GBA** = glucocerebrosidase A; **IADL** = instrumental ADL; **iRBD** = idiopathic RBD; **LRRK2** = leucine-rich repeat kinase 2; **MDS** = Movement Disorder Society; **MSA** = multiple system atrophy; **PD** = Parkinson disease; **PRO** = patient-reported outcome; **RBD** = REM sleep behavior disorder; **TUG** = Timed Up and Go; **UPDRS** = Unified Parkinson Disease Rating Scale.

The International Parkinson and Movement Disorder Society (MDS) Task Force on the definition of Parkinson disease (PD) has proposed that early disease should be divided into 3 stages: preclinical PD (neurodegenerative processes have commenced, but there are no evident symptoms or signs); prodromal PD (symptoms and signs are present but are insufficient to define disease); and clinical PD (i.e., diagnosis of PD based on the presence of classical motor signs).[1] Within this framework, it may be possible to detect the emergence of subtle clinical features in the second phase or track changes in these features between the second and third phase as outcome measures for clinical trials. A treatment effect either on emergence or progression of clinical signs measured in the prodromal context indicates delay or prevention of classically defined PD.

A major driver for development of measures of subtle clinical dysfunction in prodromal PD is the hypothesis that this stage of disease may be a window of opportunity for experimental therapeutics. Theoretically, treatments may be more effective in the earliest stages of disease when pathology is less well established. Second, there are logistical reasons for conducting clinical trials in prodromal patients. The use of dopaminergic medications, particularly, has a marked effect on the clinical manifestations of PD, thus limiting the observability of putative neuroprotective therapies. Relatedly, the pool of available participants who are able to stay off treatment for an extended period is limited. Finally, the US Food and Drug Administration (FDA) has signaled their willingness to consider treatments that target the prodromal phase of neurodegenerative disorders.[2] Although this guidance was crafted specifically for Alzheimer disease, it is not unreasonable to envision its application to other disorders, such as PD.

For these reasons, there is a need to develop sensitive and robust approaches to clinical assessment in prodromal PD. These approaches could be used at several points in clinical trials: (1) for patient stratification, (2) as intermediate clinical outcomes (recognizing there is a gap between early symptoms and a well-defined clinical syndrome), and (3) to operationalize the clinical diagnosis of PD (i.e., phenoconversion) for clinical trials. Addressing these gaps would enable trials that test whether it is possible to delay or prevent the onset of clinical disease. In this review, we will cover the current state of the field for measuring motor performance in the prodromal phase of PD and approaches to assessment of incident motor and cognitive abnormalities up to and including clinical phenoconversion.

Stratification: Selecting Patients for Trials

Detailed studies of at-risk populations show that the prodromal period of PD is not entirely devoid of clinical features. These features may potentially be used to identify individuals at increased risk for manifest PD. Emerging data indicate that the progression of motor signs of parkinsonism often follows a pattern starting at least 7 years before PD diagnosis beginning with voice/facial expression changes, limb bradykinesia, and then rigidity and gait changes. Some subtle motor changes such as slowed finger tapping may appear as early as 15 years before diagnosis.[3,4] For patient-reported outcomes (PROs), tasks that rely on not only motor function but also nonmotor features such as cognition become significantly different from controls first, at 7 years before diagnosis, and basic activities of daily living (ADLs) that may rely more on motor function change subsequently.

In idiopathic REM sleep behavior disorder (iRBD), motor symptoms (Unified Parkinson Disease Rating Scale [UPDRS] part II) and motor signs (UPDRS part III) had the highest accuracy for distinguishing those who were diagnosed with a neurodegenerative disorder vs controls, with a UPDRS part III cutoff of 54 (excluding action tremor) distinguishing cases from controls with 92.6% sensitivity and 95.6% specificity. However, it is critical to note that sensitivity of PROs and rater-administered scales decreased substantially farther away from the time of diagnosis, dropping to 50% 4 years before. Quantitative measures such as the alternate tapping test had the highest area under the curve for predicting conversion and were more sensitive at 6 years before compared with rater or PROs, but sensitivity at 6 years was still relatively low at 77.3%.[5] In identifying optimal outcomes for motor conversion, additional data are needed to understand how long before conversion occurs must intervention occur to provide meaningful disease modification. These results suggest that it is possible to deploy clinical assessments to identify individuals at high risk for up to a decade before diagnosis. Thus, subtle motor and nonmotor signs can be part of a risk stratification model that could be used to enroll appropriate participants in clinical trials.

Parkinsonian Signs and Rating Scales in the Prodromal Period

It is clear that in the research setting, where lengthy trials are not feasible for both cost and scientific reasons, surrogate

outcome measures with sufficient lead time—that is, outcome measures that reflect pathologically confirmed PD years before it can be clinically established—are critically needed. Motor abnormalities are a key candidate for such markers. Individuals who are at risk for PD present clinically with motor and nonmotor symptoms of the prodromal state years before diagnosis.[5,6] In a case-control study of 8,166 individuals with PD and 46,755 individuals without PD presenting to primary case, symptoms of tremor, shoulder pain/stiffness, and rigidity were significantly more likely to occur in those who developed PD vs those who did not,[5] and presenting symptoms of tremor, balance problems, and rigidity (among others) independently predicted PD diagnosis.[7]

In considering motor abnormalities as outcome measures in PD prevention trials, they may be broadly categorized into signs (which may be clinical or subclinical), symptoms, and functional consequences. In turn, each of these may be measured using various modalities including expert ratings, patient report, or digitally. As mentioned, motor signs as assessed by a trained rater constitute a core criterion for PD diagnosis and are a main component of validated rating scales for parkinsonism. Several longitudinal cohort studies provide key insights into longitudinal changes in parkinsonian motor signs in the prodromal stages of PD and inform their utility as outcome measures for PD prevention trials (Table 1).

Darweesh et al.[3] conducted a nested case-control study within the Rotterdam prospective, population-based cohort study of 7,983 adults aged 55 years and older. A total of 6,456 patients at risk of PD free of it or dementia at baseline were followed for up to 22 years. Motor features of parkinsonism were assessed by trained research nurses over at least 3 visits (patient-reported assessments in this study are described separately in the section below). 109 individuals were diagnosed with PD (mean age at diagnosis, 78 years and SD, 7 years), and each case was matched to 10 controls based on age and sex (n = 1,199). Different motor features of parkinsonism emerged at different times before diagnosis, with features of bradykinesia/hypokinesia appearing first, followed by tremor, rigidity, and gait/balance signs and symptoms.

In the prospective cohort study reported by Fereshtehnejad et al.,[4] 152 individuals with idiopathic RBD were compared with 102 age-matched/sex-matched controls and 69 with moderate-to-advanced PD. Clinical signs ascertained with UPDRS rating scale over an average of 5 follow-up visits, with follow-up duration ranging from 2 to 12 years. 55 patients developed parkinsonism or dementia on an average of 4.6 ± 2.5 years from baseline; clinical diagnosis was PD in 25 (45.4%) patients and multiple system atrophy (MSA) in 4 (7.3%). Motor examination findings changed slowly until 1–2 years before clinical conversion. The first statistically significant difference from controls occurred 5 years before clinical conversion. At clinical conversion, UPDRS motor subscore (part III) values approximated 35% of scores for moderately advanced treated patients with PD. As for the trajectory of individual motor features, changes in speech and voice occurred 1st, crossing healthy control values at 6–7 years before conversion, with statistically significant difference at year −4. Hypomimia, limb bradykinesia, and decreased arm swing emerged next at year −5. Rigidity appeared at 3–4 years before conversion. A cutoff on the UPDRS motor subscore of ≥4 had a specificity of 95% as early as 6 years before clinical conversion, but sensitivity was 16.7% at that time point, reaching 60.5% sensitivity at −2 years and 92.6% only at the time of clinical diagnosis.

In the Parkinson's Progression Markers Initiative, Chahine et al.[8] followed up 38 individuals with iRBD enriched for abnormal dopamine transporter (DAT) binding for a median of 4.7 years and compared them with a group of 205 individuals with early PD and 92 healthy controls of similar age and sex.[9] Individuals in the iRBD cohort received a research diagnosis of neurodegenerative parkinsonian disorder after a median of 4-year follow-up (final diagnosis 9 PD, 3 dementia with Lewy bodies, and 2 MSA). Among those who received a research diagnosis of neurodegenerative parkinsonian disorder, MDS-UPRDS motor subscore (part III) increased and approached that of the PD group within 2 years of diagnosis. In those who remained free of diagnosis, MDS-UPDRS motor subscore values remained similar to the HC group.

Data are limited regarding progression of motor features in other populations at risk or prodromal for PD but are beginning to emerge. In the Parkinson At Risk Syndrome study, Siderowf et al.[10] studied 185 individuals with hyposmia, of whom 21 had DAT deficit on SPECT (≤65% of age-expected uptake) and 30 had indeterminate DAT SPECT. The mean duration of follow-up was 6.3 years, and 112 participants had serial DAT scan. 26 patients received a clinician diagnosis of PD. Among those receiving a diagnosis of PD, UPDRS motor subscore at the clinical conversion visit was 16.8 (SD 10.1). Among those without DAT deficit at baseline, 19 developed DAT deficit on follow-up. Changes in DAT binding preceded changes in parkinsonian signs and clinical PD diagnosis. Neither total UPDRS nor change in UPDRS score predicted abnormal DAT binding in those with normal binding at baseline.

Prospective longitudinal studies of asymptomatic carriers of genetic mutations associated with increased risk of PD, such as mutations in glucocerebrosidase A (*GBA*)[11,12] or leucine-rich repeat kinase 2 (*LRRK2*)[13] genes, indicate small but measurable changes in motor function compared with controls in these at-risk populations as well.

Patient-Reported Outcomes

Another aspect of motor parkinsonism relates to patient-reported symptoms and/or function (Table 2). In the Darweesh et al.[3] Rotterdam study, functioning in basic ADL was assessed using the patient-reported disability index of the Stanford Health Assessment, and functioning in instrumental ADL (IADL) was assessed using the patient-reported IADL

Table 1 Longitudinal Studies Assessing Risk of Progression or Conversion Associated With Performance on Rater-Derived Motor Outcomes

Rater-ascertained					
Study	**Study design**	**Participants**	**Assessment**	**Latency to diagnosis[a]**	**Change over time**
Beavan et al., 2015[11]	Observational 2-y follow-up	30 individuals with homozygous GBA mutation, 28 with heterozygote GBA mutation, 26 controls	UPDRS III	Not reported	Cases showed 6.10 point increase over 2 y vs 0.92 among controls
Avenali et al., 2019[12]	Observational 6-y follow-up	31 individuals with homozygous GBA mutation, 16 with heterozygote GBA mutation, 16 controls	MDS-UPDRS III	Not reported	Homozygotes increased from 2.81 to 7.52, heterozygotes from 0.94 to 3.31, HCs from 0.44 to 2.06 over 6 y (p = 0.001 for GD vs HC and for HetGBA vs Hc; p = 0.209 for GD vs HetGBA)
Sierra et al., 2017[13]	Observational with 4 y of follow-up	29 carriers of LRRK2 mutation, nonmanifest; 3 individuals developed PD	UPDRS III	Not reported	2.5 point increase over 4 y in sample as a whole
Darweesh et al., 2017[3]	Population-based nested case-control study followed up for 22 y.	6,456 patients at risk of PD; 109 were diagnosed with PD during the follow-up.	Reduced arm swing	−8.6 y	Not reported
			Bradykinesia	−7.5 y	Not reported
			Tremor	−6.1 y	Not reported
			Postural imbalance	−3.8 y	Not reported
			Rigidity	−3.3 y	Not reported
			Posture abnormalities	−2.8 y	Not reported
			Falling	−1.7 y	Not reported
Fereshtehnejad et al., 2019[4]	Longitudinal observational cohort	152 iRBD, 102 controls, 69 PD. 55 converted to parkinsonism (22 PD, 4 MSA) or dementia	UPDRS III motor score	−5 y	2.05 points/year (95% CI 1.67 to 2.44)
			Facial expression	−5 y	Not reported
			Speech and voice	−4 y	Not reported
			Bradykinesia score	Not reported	+1.18 (95% CI 0.94 to 1.41)
			Tremor score	Not reported	0.11 (95% CI 0.02 to 0.19)
			Rigidity score	−3 to 4 y	0.32 points/year (95% CI 0.22 to 0.42)
			PIGD score	Not reported	0.31 (95% CI 0.22 to 0.39)
			Alternate tapping test	−6 y	−4.91 points/year (95% CI −6.59 to −3.22)
			Purdue pegboard	−4 y	−0.34 points/year (95% CI −0.45 to −0.22)
			Gait speed	−2 y	0.22 points/year (95% CI 0.13 to 0.31)

Abbreviations: GBA = glucocerebrosidase A; GD = Gaucher disease; HC = healthy control; iRBD = idiopathic REM sleep behavior disorder; LRRK2 = leucine-rich repeat kinase 2; MSA = multiple system atrophy; PD = Parkinson disease; PIGD = postural instability–gait difficulty; UPDRS III = Unified Parkinson Disease Rating Scale Part III (motor examination).
[a] Latency to diagnosis indicates the number of years before diagnosis that the mean scores for the group that was eventually diagnosed first showed significant differences compared with controls.

scale. Those who developed PD showed significant differences from controls in IADL score 7 years before diagnosis. Basic ADLs became significantly different from controls 5.4 years before, with problems eating being the earliest detected.

The cohort of iRBD and healthy controls followed up by Fereshtehnejad et al.[4] collected part II of the UPDRS as a patient-reported ADL scale of daily living. Among those who received a diagnosis of parkinsonism/dementia, scores began

Table 2 Longitudinal Studies Assessing Risk of Progression or Conversion Associated With Abnormal Performance on Patient-Reported Outcomes

Patient-reported outcomes					
Study	**Study design**	**Participants**	**Assessment**	**Latency to diagnosis[a]**	**Change over time**
Beavan et al., 2015[11]	Observational 2-y follow-up	30 individuals with homozygous GBA mutation, 28 with heterozygote GBA mutation, 26 controls	UPRDS II score		Cases showed 2.01 point increase over 2 y vs 0.58 among controls
Darweesh et al., 2017[3]	Population-based nested case-control study followed up for 22 y.	6,456 patients at risk of Parkinson's disease; 109 were diagnosed with PD during the follow-up.	IADL scale	−6.3 y	Not reported
			BADL	−3.3 y	Not reported
Fereshtehnejad et al., 2019[4]	Longitudinal observational cohort	152 iRBD, 102 controls, 69 PD. 55 converted to parkinsonism (22 PD, 4 MSA) or dementia	UPRDS II score	−3 y	Increase of 0.70 points/year among iRBD patients (95% CI 0.52–0.89)

Abbreviations: BADL = basic activities of daily living; GBA = glucocerebrosidase A; IADL = instrumental activities of daily living; iRBD = idiopathic REM sleep behavior disorder; MSA = multiple system atrophy; PD = Parkinson disease; UPDRS = Unified Parkinson Disease Rating Scale.
[a] Latency to diagnosis indicates the number of years before diagnosis that the mean scores for the group that was eventually diagnosed first showed significant differences compared with controls.

to deviate from normal 9.3 years before clinical conversion, at a rate of 0.70 points per year and significantly faster than normal controls starting 3 years before conversion. Handwriting, turning in bed, walking speed, and speech/salivation changes were the earliest to appear, 7–11 years before conversion, whereas basic ADLs such as hygiene and eating difficulties occurred 1–3 years before conversion. A cutoff of ≥2 had a sensitivity of 63% and specificity of 92.6% for clinical 2 years before diagnosis; at 6 years prior, sensitivity was 44.4% and specificity was 92.6%.

Quantitative Motor Measures

In a retrospective cohort study, Yoo et al.[14] studied 1,196,614 community dwelling older adults who underwent Timed Up and Go (TUG) test at age 66 years. Using claims data, they identified 3,862 individuals who developed PD over a median of 3.5 years of follow-up. Participants with slow TUG test time at baseline had significantly increased hazards of developing PD compared with those with normal TUG time (adjusted hazard ratio: 1.28; 95% CI 1.20–1.37). Fereshtehnejad et al.[4] also evaluated several timed motor tasks in their cohort of patients with RBD. They found that scores on tasks including the TUG, alternative tap test, and Purdue peg board all differentiated cases from controls several years before diagnosis. Among these tests in this cohort, the Alternative Tap test became abnormal with the greatest latency before diagnosis.

Use of Digital Sensors

In the recent years, there is increasing interest in digital health technology for monitoring motor function relating to disease or disease progression in PD (Table 3). Technology in the forms of wearable sensors, smartwatches, or smartphones offers significant opportunities to collect quantitative data, objectively and frequently, with potentially greater sensitivity to change, than current clinical observation.[9,15,16] These technologies have become low cost, require less power (or battery), and are unobtrusive and accurate eliminating assessor bias while providing additional insight beyond that obtained during a clinical assessment.

The most common use of digital sensors in the field of PD is in the assessment of mobility and gait. Here, the advantage of quantifying movement using accelerometers and gyroscopes provides a wealth of information on the quality of movement and potential abnormalities.[17-19] A growing body of literature also shows the capability of digital technology to objectively quantify typical PD signs such as tremor, bradykinesia, and dyskinesia and the opportunities for real-world assessment, away from the clinic, which may reveal additional aspects into the patient's functioning in their daily lives that so far alluded clinicians. This type of evaluation is indeed promising because it can pave the way for objective assessment of disease progression.[20,21] Nonetheless, it is important to acknowledge the multiple challenges to the interpretation of unstructured mobility data.[22] Recent exciting work extends on the conventional mobility assessment to take full advantage of continuous data in the home, extracting from the devices information on behavior and ADLs. Iakovakis et al.[23] for example, evaluated subtle fine motor impairments from analyzing typing on a mobile touchscreen. This study showed high sensitivity and specificity (0.90/0.83) in discriminating patients with early PD from healthy controls. Kyritsis et al.[15] showed high discriminative value (77%) in analyzing in-meal eating behavior profiles of patients with PD and controls obtained from a wristwatch. Such studies show the potential of evaluating both motor and nonmotor aspects of the disease and are also essential to setting expectations from metrics in the prodromal phase.

The impetus for using digital technology in the prodromal phase stems from the notion that motor changes likely

Table 3 Longitudinal Studies Assessing Risk of Progression or Conversion Associated With Abnormal Performance on Digital Measures

Digital					
Study	**Study design**	**Participants**	**Motor measure**	**Latency to diagnosis[a]**	**Change over time or risk relative vs controls**
Von Coelln et al., 2019[38]	Two community-based longitudinal cohort studies, annual testing follow-up of 2.5 y (SD = 1.28)	683 older adults; 139 individuals developed parkinsonism (20.4%)	Sit to stand range (from TUG)-collected with a sensor on the lower back	−2.5 y	HR 1.42 (1.10–1.84)
			Turning (yaw from TUG)-collected with a sensor on the lower back	−2.5 y	HR 0.58 (0.43–0.77)
Del Din et al., 2019[37]	Population-based nested case control study.	696 older adults Longitudinally assessed 4 times at 2-y intervals. Sixteen participants were diagnosed with PD, on average 4.5 y after first visit.	Step velocity-collected with a sensor on the lower back	−3.3 y	−0.0295 (0.0353) yearly change (SD)
			Step length-collected with a sensor on the lower back	−4.1 y	−0.0134 (0.0138) yearly change (SD)

Abbreviations: HR = hazard ratio; PD = Parkinson disease; TUG = Timed Up and Go.
[a] Latency to diagnosis indicates the number of years before diagnosis that the mean scores for the group that was eventually diagnosed first showed significant differences compared with controls.

develop overtime and exist several years before diagnosis.[24,25] Thus using quantitative, sensitive data capture methods may unmask indicators reflective of prominent disease which are present before the appearance of the cardinal motor signs required for diagnosis. Several cross-sectional studies have used digital technology to explore motor measures in at-risk cohorts.[26-28]

Cavallo et al.[29] found high accuracy and precision in differentiating between healthy controls and individuals with idiopathic hyposmia using a wearable inertial device worn on the hand during the performance of tasks from the MDS-UPDRS III. Differences between the groups were not observed in the clinically scored assessment. These findings highlight the sensitivity of digital technology in detecting subtle changes.

Several studies explored gait and mobility measures. Balance stability was explored in individuals with high risk for PD defined by the presence of hyperechogenicity in the mesencephalon on transcranial sonography and either 1 motor sign or 2 risk and prodromal markers of PD.[30] Using measures extracted from an accelerometer worn on the lower back, performance on the functional reach test showed high specificity (85%) and sensitivity (74%) in differentiating high risk for PD from controls suggesting subthreshold balance abnormalities in this cohort. Increased gait variability, reduced axial rotation, and increased arm swing asymmetry and variability were observed in nonmanifesting *G2019S-LRRK2* mutation carriers as compared with noncarriers.[28,31] Another study in this population detected higher intraindividual variability of gait-associated movements in individuals with PD and nonmanifesting mutation carriers but not in controls using bilateral ambulatory actigraphy.[32] Subtle gait abnormalities were also observed in individuals with mild parkinsonian signs as compared with controls.[13] Interestingly, these differences in gait and stability were observed under challenging conditions (e.g., balance tasks or dual tasking) and were not detected under usual walking conditions. Considering that the onset of PD appears after depletion of 70%–80% of striatal dopamine, the lack of clinically observed gait and mobility deficits under undisturbed walking conditions (i.e., comfortable walking conditions) suggests satisfactory compensatory mechanisms in the motor system, offsetting the slowly progressing nigrostriatal dopamine depletion, both within and outside the basal ganglia.[33] It has been suggested that dual task walking might be a valuable tool for unmasking the use of these compensatory strategies.[33,34]

Smartphone devices are equipped with accelerometers, gyroscopes, global positioning technology, and sensing capabilities which provides them with unique properties that can be used for the assessment of both task performances and passive monitoring. A recent study showed that assessment of the performance of 7 active tasks using the smartphone (voice, balance, gait, finger tapping, reaction time, rest tremor, and postural tremor) was able to accurately distinguish between individuals with PD, healthy controls, and individuals with iRBD with a mean sensitivity and specificity of 91.9% (3.5%) and 90.0% (3.7%), respectively.[26] Voice was the most discriminatory factor between iRBD and controls accounting for approximately 50% of the most salient features. This finding is also consistent with earlier studies using smartphone speech analysis.[35,36] Additional discriminatory features included postural and rest tremor and gait-related metrics.[26]

Findings from these cross-sectional studies are important and show the potential of these technologies; however, they do not reflect prodromal progression. Only 2 observational longitudinal studies were found that used digital technology

to identify motor features in the prodromal phase or predict incidence PD. Del Din et al.[37] evaluated the gait of 696 healthy adults recruited in the Tubingen Evaluation of Risk Factors for Early Detection of Neurodegeneration study using a single wearable sensor worn on the lower back. Assessments were performed longitudinally 4 times at 2-year intervals. Sixteen participants were diagnosed with PD on average 4.5 years after the first visit. Higher step time variability and asymmetry of all gait characteristics during the initial visit were associated with a shorter time to PD diagnosis. The analysis indicated that step length and velocity deviate from that of non-PD convertors approximately 4 years after diagnosis. Interestingly, unlike previous work,[27,28] differences in gait measures were observed in the undisturbed comfortable walking condition and not in the dual task condition. The participants in this cohort were older than those in the cross-sectional studies. It is possible that the challenging motor test (i.e., dual task) identifies motor abnormalities even earlier, when compensation is optimal, while changes in unobstructed gait become visible closer to diagnosis. However, this hypothesis needs to be further assessed in future longitudinal studies.

In another study,[38] the motor performance of 683 ambulatory, community-dwelling older adults was annually assessed using a single sensor worn on the lower back. All participants were without parkinsonism at baseline assessment. During follow-up of 2.5 years (SD = 1.28), 139 individuals developed parkinsonism (20.4%). Six of 12 mobility scores were individually associated with incident parkinsonism, including speed and regularity, sway, transitions, and turning. The sensor-derived mobility metrics improved the prediction of incident parkinsonism in a model which included terms for chronic health conditions and clinical assessment. These findings suggest that sensor-derived mobility metrics can complement conventional clinical assessments and offer the potential for identifying older adults at risk for parkinsonism.

Although evidence is accumulating in favor of the use of digital technology in the prodromal phase of PD, to date there are very few examples where these devices have been used beyond exploratory or feasibility study settings. Generally, studies using digital technology are cross-sectional, with only a few examples assessing the ability to detect change in longitudinal studies (in either the prodromal phase or overt PD). This is partially due to a lack of proper validation of this technology and standard benchmarks.[20,39] This aspect is somewhat circular as only when digital outcomes demonstrate robust validity, their use in large cohort studies will become widespread.

Recently, the MDS Task Force on technology published concrete steps to facilitate inclusion of digital technology into clinical practice.[40] To foster adoption, there needs to be sufficient evidence to show that metrics derived from digital technology are indeed superior to traditional assessment methods. This could be measured in many ways such as cost, discriminative and predictive value, or identification of progression outcomes. Such added value will also help to promote acceptance by regulatory bodies (e.g., European Medicines Agency and FDA). This absence further impedes clinical adoption and the inclusion of digital technology as primary outcomes in clinical trials. It is important to develop digital data standardization and data sharing platforms to enable cross-study comparisons and incorporate also behavioral and nonmotor features toward the development of more complete disease characterization and the understanding of heterogeneity in progression. An increasing number of groups are working with digital sensors including 2 large Innovative Medicines Initiative projects (e.g., Mobilise-D and IDEA-FAST) which aim to address some of the limitations in the field.[41] With the rapid penetrance of technology to every aspect of life, it seems likely that their presence is for the long term.

Composite Measures to Detect and Measure Prodromal PD: MDS Prodromal Criteria

The prodromal phase of PD is characterized clinically by not only several mild and slowly progressive motor abnormalities but also several nonmotor features such as olfactory changes, neuropsychiatric signs and symptoms, and sleep abnormalities. Biomarker changes such as reduced DAT binding are also detectable in the prodromal phase. These features often, but not always, follow the pattern of pathology progression posited by Braak, whereby neuropathologic changes of PD begin in the lower brainstem and progress rostrally to the pons, midbrain, and then to the cortex.

Many of the abnormalities detectable clinically are nonspecific in isolation, but multimodal models such as the one proposed by the MDS[1,42] are able to detect individuals at risk or in the prodromal phases of PD.[43,44] These criteria may be useful for sample selection in PD prevention trials. It is also possible, however, that these multimodal prodromal detection models can also be used to inform outcome measures in PD prevention trials. That is, and especially in asymptomatic at-risk groups (such as carriers of LRRK2 or GBA mutations), reaching a threshold for prodromal state as defined by the MDS criteria could be an outcome measure. A limitation of the MDS prodromal criteria are their low accuracy for detecting individuals at risk for PD at the population level.[45-47] As additional data become available, these models will be refined and improved, and which motor measures are optimal for including in these models will become clearer as well.

Clinical Diagnosis as a Trial Outcome

Physician diagnosis serves as a practical global benchmark when considering outcome measures for PD prevention trials: A diagnosis of PD on clinical grounds is associated with

disability and increased mortality worldwide, reduced functional status and quality of life, and increased healthcare expenditures. The MDS diagnostic criteria for PD[42,48] provide a useful framework within which to operationalize physician diagnosis for clinical trial purposes; the highest level of certainty in diagnosis is designated as "clinically established," emphasizing that histopathologic findings postmortem are the only means of making definitive diagnosis of PD as of the present time. Central to the diagnosis of PD is the presence of the core motor features of parkinsonism. However, parkinsonism is common and nonspecific in older adults,[27] and the criteria also incorporate the presence (or absence) of other clinical features, medication response, and clinical evolution. Passage of time is a key component of PD diagnostic criteria as well and is one of the most important means of strengthening diagnostic accuracy for PD.[49] For that and other reasons, diagnostic accuracy for PD is lowest in the early stages of parkinsonism, especially in older populations.

In further considering to what degree are conventional clinically defined outcomes, such as physician diagnosis, are feasible outcome measures in PD prevention trials, it is also necessary to keep in mind that PD is a relatively rare disorder, when considered epidemiologically at the population level and that, as discussed, its features emerge gradually over time. In a secondary prevention trial that would aim to prevent clinically defined PD in individuals with iRBD, even in carefully selected samples at high risk for PD, a clinically defined disorder may emerge at the rate of only 6%–9% a year.[8,25] Thus, trials with very large sample sizes and of several years' duration would be needed to accrue a sufficient number of primary outcome events (i.e., cases of PD).

Conclusion: Enabling Clinical Trials

Although the prodromal phase of PD is defined by the absence of clinical features sufficient for a diagnosis, changes in subtle motor and nonmotor features, up to and including conversion to a clinical diagnosis of PD can be measured and could potentially be used as outcomes in clinical trials. Modeling exercises using data from cohorts with either iRBD or hyposmia[10,50] have shown that clinical phenoconversion occurs frequently enough in carefully selected groups to be a feasible outcome measure for a clinical trial, but of fairly long duration given reasonable recruitment constraints. Clinical features, timed tests, or progression on digital sensor measures could be intermediate clinical outcomes in shorter, smaller proof-of-concept trials. Preliminary studies show measurable change in these metrics, and advances in digital sensor technology and analysis holds the promise of more precise measurement of subtle motor signs before diagnosis. Further refinement of sample size estimates using a range of outcome measures and in carefully stratified populations is an important area for future study. This information will enable efficient testing of novel therapeutics in the prodromal period of PD with the objective of identifying therapeutic strategies to delay or prevent disease onset.

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Andrew Siderowf, PhD	Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
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Outcome Assessment in Parkinson Disease Prevention Trials: Utility of Clinical and Digital Measures

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