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Editor's Comment: Puschmann and colleagues provide a consensus statement derived from the discussions of participants at an international conference organized by the Genetic Consortium on Epidemiology of Parkinson's Disease (GEO-PD). They propose a panel of rating scales that could be used longitudinally and during routine office visits for the assessment of motor and non-motor manifestations of Parkinson's disease (PD), with the hope that use of these instruments will allow better phenotypic characterization of this illness and that they can be used internationally. They also aim for better characterization of long-term outcomes that will permit more precise prognostication and eventually lead to optimization of treatment strategies that will encompass the promises of personalized/individualized medicine.

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Point of view

Clinically meaningful parameters of progression and long-term outcome of Parkinson disease: An international consensus statement

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ABSTRACT

Parkinson disease (PD) is associated with a clinical course of variable duration, severity, and a combination of motor and non-motor features. Recent PD research has focused primarily on etiology rather than clinical progression and long-term outcomes. For the PD patient, caregivers, and clinicians, information on expected clinical progression and long-term outcomes is of great importance. Today, it remains largely unknown what factors influence long-term clinical progression and outcomes in PD; recent data indicate that the factors that increase the risk to develop PD differ, at least partly, from those that accelerate clinical progression and lead to worse outcomes. Prospective studies will be required to identify factors that influence progression and outcome. We suggest that data for such studies is collected during routine office visits in order to guarantee high external validity of such research. We report here the results of a consensus meeting of international movement disorder experts from the Genetic Epidemiology of Parkinson's Disease (GEO-PD) consortium, who convened to define which long-term outcomes are of interest to patients, caregivers and clinicians, and what is presently known about environmental or genetic factors influencing clinical progression or long-term outcomes in PD. We propose a panel of rating scales that collects a significant amount of phenotypic information, can be performed in the routine office visit and allows international standardization. Research into the

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progression and long-term outcomes of PD aims at providing individual prognostic information early, adapting treatment choices, and taking specific measures to provide care optimized to the individual patient's needs.

1. Background

In the last two decades, research in Parkinson disease (PD) focused primarily on etiology, pathogenesis, and therapeutic intervention. Tremendous progress has been made in understanding the role of genetic and environmental factors in its etiology [1,2]. Clinical, radiological and biochemical markers that represent early manifestations of the underlying neurodegenerative process and that identify individuals at high risk of developing PD have been reported [3–5].

By contrast, there have been fewer studies about clinical progression or long-term outcomes. PD is associated with a variable clinical course, severity and combination of motor and non-motor features [6,7]. At this juncture, it is largely unknown which factors influence PD progression or long-term outcomes. Recent reports suggest that the factors and biological processes that underlie disease pathogenesis may differ from those that determine its course [8,9]. Some of the factors contributing to disease progression may be modifiable. For the patient who has been diagnosed with PD, for caregivers and clinicians, information on expected clinical progression and long-term outcomes are of greater importance than the quest for etiology.

We convened a meeting of international movement disorder clinician experts from the Genetic Epidemiology of Parkinson's Disease (GEO-PD) consortium to define the following; a) which long-term outcomes are of interest to patients, caregivers and treating clinicians, b) which milestones and research tools accurately capture these outcomes and can be administered in the routine clinical setting at the point of care across diverse clinical practice settings worldwide, and c) what is presently known about environmental or genetic factors that may influence clinical progression or long-term outcomes.

2. Methods

The meeting was organized by DMM and RF and held at the Department of Neurology, NorthShore University HealthSystem, Evanston, Illinois, USA June 16–18, 2014. This position paper summarizes the consensus reached during the meeting, reflecting participants' clinical experiences, as well as an informal review of the published literature. Based on all participants' contributions, KM drafted the section on research tools, LB the section on factors influencing disease risk and outcome. AP drafted the remaining sections and coordinated rounds of manuscript editing among meeting participants.

3. Clinically meaningful markers of disease progression and long-term outcomes

Clinicians have long voiced concerns that the disease severity biomarkers commonly used in PD research studies, especially in therapeutic trials, do not adequately reflect the disease features that matter most to the patient, caregiver or treating physician [10–12]. There is a bias towards assessing motor features and their response to treatment, whereas other clinical features such as dementia or non-motor features do not receive adequate attention but are important to the patient, especially when motor symptoms are well-controlled. Furthermore, valid and reliable means to measure clinical progression in PD are lacking [12–14].

Patients who have been diagnosed with Parkinsonism frequently ask their physician about the likely impact the disorder will have on their quality of life, whether they will develop dementia or whether the disease will result in premature death or nursing home placement. The authors identified the following milestones in PD progression that are likely important from the patient perspective: being able to continue living at home, being able to drive a car, work until retirement, retaining cognitive function, remaining ambulatory, or not dying prematurely [15,16].

The overwhelming majority of PD patients with long disease duration live with a family member as a regular caregiver [17]. From the caregiver's perspective, the following issues are of importance in addition to the ones mentioned above: At what point in the disease course will the patient require a caregiver? To what degree will the patient be dependent on the caregiver? What are the overall financial implications of the disease? Although caregiver strain can be assessed by a specific inventory [18], the necessity of a caregiver can be recorded as a simple milestone. Caregiver burden can be approximated during a patient interview and measured in hours per day or graded according to lifestyle changes for the caregiver. Costs of medications can be calculated rather easily, but overall financial implications may be very complex and difficult to measure and dependent on the healthcare system in each country (see Fig. 1).

Clinicians share responsibility for the treatment with their patients and in most countries have legal obligations with regard to patient safety [19]. From a clinician's perspective, meaningful outcomes in addition to the ones named above, are: treatment compliance, response and efficacy, freedom from adverse effects, access to treatment, patient safety at home and when driving. Compliance and response to treatment are not outcomes per se but may modify outcomes. Good response to dopaminergic therapy may predict a good overall outcome that will be reflected in outcome measures. The current consensus among clinicians is that PD patients who fail to respond to dopaminergic therapy when treatment is initiated are likely to have worse outcomes. Patients who continue to receive dopaminergic therapy may develop bothersome complications of therapy, such as falls due to orthostatism, hallucinations, behavioral changes, sleep disorders, or motor fluctuations. Clinical experience has shown that patients who respond well initially to dopaminergic therapy will continue to benefit for a number of years, and only a subset of them will develop serious complications.

At present, it remains unknown why a subset of PD patients develop postural instability and frequent falls or dementia early in the disease course. It is also unknown whether the early development of dyskinesias is a good prognostic sign, as these patients often respond favorably to surgical therapy. It would be desirable to identify the group who will have a favorable clinical course even after many years, and to be able to provide accurate information and counseling when the diagnosis is revealed. Knowing an individual patient's risk to develop treatment adverse effects or complications would allow optimizing individual treatment plans [19].