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

Puschmann, Andreas; Brighina, Laura; Markopoulou, Katerina; Aasly, Jan; Chung, Sun Ju; Frigerio, Roberta; Hadjigeorgiou, Georgios; Kõks, Sulev; Krüger, Rejko; Siuda, Joanna; Wider, Christian; Zesiewicz, Theresa A; Maraganore, Demetrius M

Published in:
Parkinsonism & Related Disorders

DOI:
10.1016/j.parkreldis.2015.04.029

2015

Link to publication

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Clinically meaningful parameters of progression and long-term outcome of Parkinson disease: An international consensus statement.

Andreas Puschmann, MD, PhD a, Laura Brighina, MD, PhD b, Katerina Markopoulou, MD, PhD c, Jan Aasly, MD d, Sun Ju Chung, MD, PhD e, Roberta Frigerio, MD c, Georgios Hadjigeorgiou, MD f, Sulev Kõks, MD, PhD g, Rejko Krüger, MD, PhD h, Joanna Siuda, MD, PhD i, Christian Wider, MD i, Theresa A. Zesiewicz, MD k, Demetrius M. Maraganore, MD c

a Department of Neurology, Skåne University Hospital, and Lund University, Department of Clinical Sciences, Lund, Neurology, Sweden
b Department of Neurology, San Gerardo Hospital, Milan Center for Neuroscience, Monza, Italy
c Department of Neurology, NorthShore University Health System, Evanston, Illinois, USA
d St. Olav’s Hospital, Department of Neurology, Trondheim, Norway
e Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
f Faculty of Medicine, University of Thessalia, Larissa, Greece
g Department of Pathophysiology, University of Tartu, Tartu, Estonia.
h Clinical and Experimental Neuroscience, Luxembourg Center for Systems Biomedicine (LCSB), University of Luxembourg, Luxembourg and Centre Hospitalier de Luxembourg, Luxembourg.
1 Department of Neurology, Medical University of Silesia, School of Medicine in Katowice, Poland

2 Department of Clinical Neuroscience, Centre Hospitalier Universitaire Vaudois (CHUV-UNIL), Lausanne, Switzerland.

3 Department of Neurology, University of South Florida, Tampa, FL, USA.

# These authors have contributed equally to this work.

*Corresponding author: Dr. Demetrius M. Maraganore, Ruth Cain Ruggles Chairman, Department of Neurology, NorthShore University HealthSystem, 2650 Ridge Avenue, Evanston, IL 60201, USA; dmaraganore@northshore.org

Key words (MeSH): Parkinson Disease, Disease Progression, Risk Factors, Outcome Assessment (Health Care), Patient-Centered Outcomes Research

Short title: Outcome and progression of PD

Word count abstract: 249

Word count main text: 3,775
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 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.

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].

4. Factors influencing clinical progression and long-term outcomes

Factors associated with the risk to develop PD have been identified in many case-control and population-based studies that have been repeatedly replicated. Aging, male gender [20, 21] and a history of mild and moderate head injury [22] increase the risk to develop PD. Smoking and coffee consumption have been consistently shown to be lower in persons who develop PD, with a clear dose-response relationship [23], and recent data show that PD patients quit smoking more easily than controls [24]. A meta-analysis of 80 studies confirmed that exposure to pesticides, herbicides, and solvents increases PD risk [25]. Physical activity and certain dietary or diet-associated factors may lower PD risk [26, 27], whereas night shift work may increase it [28].

Well-established genetic causes or risk factors for PD include rare pathogenic mutations [1], strong genetic risk factors such as GBA mutations [29], and weaker genetic risk factors identified in over 20 independent loci [30]. Furthermore, a complex interplay between environmental and genetic factors is thought to be involved in the etiology of sporadic PD. For instance, head injury by itself increases PD risk twofold, whereas both head injury and exposure to paraquat increase PD risk threefold [31]. Individuals exposed to head injury and
harboring the long REP1 allele genotypes associated with increased alpha-synuclein expression levels may have earlier disease onset or accelerated course [32]. It is tempting to assume that factors that underlie the pathological process leading to the appearance of PD symptoms, will remain active once symptoms have become manifest and contribute to progressive worsening of initial symptoms as well as in the appearance of additional symptoms. However, recent data indicate that clinical progression and long-term outcomes are driven, at least in part, by factors other than disease development.

4.1. Motor outcomes and survival

In longitudinal studies, factors associated with faster rates of motor progression, or with mortality, include older age at onset, akinetic-rigid subtype of PD, cognitive impairment and comorbidities [33-37]. There is only a very limited number of longitudinal studies that have investigated the influence of genetic variation on PD progression [38] and some unexpected or controversial results have been obtained. For instance, SNCA promoter REP1 genotypes known to increase levels of alpha-synuclein expression and to increase the risk of developing PD were associated with a) poorer motor outcome in a first study examining 363 cases [39], b) better motor and cognitive outcomes after the onset of PD symptoms in a second study examining 1,098 cases [8], and c) had no influence on survival in a third study on 6,154 cases from the GEO-PD consortium [9]. Polymorphisms in the SNCA and MAPT genes interact to influence the rate of progression of PD in its early stages [40]. However, studies investigating the effects of gene-gene and gene-environment interactions on PD progression using patient-centered outcome measures and over an adequate follow-up period are still missing. Higher cumulative doses of levodopa [41, 42] and longer duration of levodopa treatment [43] have been reported to increase the risk for motor complications and dyskinesias, but other studies have questioned these associations [44, 45], and the dyskinesias are often too mild to
pose a clinical problem for the patient [46]. Genetic factors – in particular, variations in genes related to dopamine metabolism and neuroplasticity – have been suggested to play a role in dyskinesia development, most likely by interacting among themselves [47] or with environmental factors [48]. Early onset of PD may increase the risk for dystonias [49]. It is important to note that none of the factors influencing risk for complications of therapy are associated with risk for developing PD. This suggests that factors that predispose to PD differ from those associated with worse motor outcomes.

4.2. Non-motor outcomes

Cognitive impairment is common in PD and is associated with increased morbidity and mortality [50]. Risk factors for cognitive impairment were investigated in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) cohort, an untreated early PD cohort with a relatively long-term follow-up (up to 7.6 years). This study identified older age, male gender, poorer performance on neuropsychological tests, hallucinations, worse motor function, the postural instability and gait disorder subtype, signs of early autonomic dysfunction and symmetry of motor symptoms as risk factors for PD dementia (PDD) [51]. It remains uncertain if the results from the DATATOP study population can be extrapolated to PD patients worldwide. Some of the rare monogenic PD forms are associated with a very high risk for cognitive impairment and frank dementia [1]. Genetic factors have also been implicated in progression to PDD, but studies investigating this association have yielded conflicting results and have been limited by small sample size or cross-sectional designs [52]. In particular, two risk genes for PD, MAPT and GBA, have been associated with cognitive impairment [36, 53, 54]. The tau gene variability constitutes a robust disease risk factor for PD, and the MAPT haplotype H1 (versus H2) not only predisposes to PD but has also been associated with cognitive decline in PD [53], possibly by altering the cortical expression of 4-
versus 3-repeat tau isoforms [55]. Subsequent studies, however, have obtained conflicting results, with some groups showing a positive correlation between PDD and the H1 allele [56, 57], while others providing negative results [58, 59]. Accordingly, two recent longitudinal studies regarding the association between tau CSF levels and subsequent cognitive decline in PD patients showed conflicting results [60, 61]. Studies evaluating a possible association of APOE risk alleles with PD or with cognitive decline in PD have shown conflicting results [62-65]; APOE ε4 was found not to be associated with progression of PD to cognitive decline or dementia previously [62, 64], but a recent, larger study reported such an association [65].

Even if the APOE ε4 allele does not significantly alter the risk of developing PD [63, 66, 67], accumulating evidence confirms that APOE ε4 is an important predictor of cognitive function in PD across multiple cognitive domains [59] including the memory domain [65, 68].

The results of prospective epidemiological studies consistently indicate that among healthy people the risk of PD declines with increasing uricemia [27, 69, 70]. Genetic polymorphisms that correlate with serum urate levels have been associated with risk of PD [71], although this association was not identified in large GWAS. Urate has also been linked to clinical progression of PD, as investigated by the PRECEPT [72] and DATATOP [73] trials, where higher serum urate levels at baseline predicted slower rates of clinical disability or dopamine transporter imaging progression over 2 years follow-up. While low urate levels have been associated with an increased risk of dementia and worse cognitive function later in life [74], it remains controversial whether they have a significant impact on the risk of dementia in PD [75-77].

The potential involvement of environmental toxicants in the progression to PDD has only been addressed in a single study, which found that higher cumulative exposure to lead is associated with worse cognition in persons with PD, independent of age, sex, race education and smoking history [78].
Several risks factors for impulse control disorders (ICD) in PD have emerged from epidemiological studies and become well corroborated: dopamine agonist use and dose; male gender; younger age; current cigarette smoking; depression; anxiety; obsessive-compulsive, novelty seeking and impulsivity traits; personal or family history of alcohol addiction and gambling behavior, and a history of ICDs prior to PD onset [79, 80]. Only a few studies have examined genetic susceptibility to ICD in PD patients, and they have focused mainly on the polymorphisms of genes involved in the dopaminergic, serotonergic or glutamatergic systems [81]. However, these studies have been conducted in relatively small sample sizes and control group selection. It is important to compare groups who are matched for disease duration and stage, as well as receiving comparable doses of dopaminergic drugs; environmental and genetic risk factors for PD are other potential confounding factors that have to be controlled for in the analysis.

5. Research tools to capture clinically meaningful progression and outcomes

A large number of validated instruments and rating scales are available for the evaluation of PD symptoms and stages. Some instruments are completed by the examiner, whereas others by the patient. The rating scales have varying length and duration of administration. Commonly used assessment instruments capable of capturing clinically meaningful markers of progression and long-term outcomes were evaluated, and a panel of instruments that can be completed in the context of routine office visits in a standardized manner across different healthcare settings and countries was selected.

5.1. Assessment of motor function/progression

An important consideration in the choice of instrument for assessment of motor symptoms is the degree to which a particular instrument is susceptible to treatment effects. The widely
used Unified Parkinson Disease Rating Scale (UPDRS) part III score [82] is susceptible to treatment effects, especially in patients experiencing motor fluctuations. For an accurate assessment of an individual’s motor status at different time points when motor fluctuations are present, the UPDRS requires determinations in the OFF and ON states. This is not feasible during a routine office visit as the duration of the ON and OFF intervals may vary greatly. Given the long duration effect of levodopa, an evaluation even after 12 hours of levodopa abstinence is not enough to accurately reflect the OFF state and longer intervals off of levodopa are not considered safe.

The Hoehn and Yahr (H&Y) scale [83] is less susceptible to treatment effects than the UPDRS (part III), and therefore may reflect more accurately the patient’s functional status in the context of longitudinal clinical research. However, with only 8 stages, the H&Y scale is less sensitive to mild clinical progression than the UPDRS, and H&Y may improve in occasional patients who respond very well to treatment, for example after deep brain stimulation. Furthermore, patients may remain at a particular H&Y stage for variable lengths of time [84]. This non-linearity makes more detailed comparisons difficult, especially in studies of relatively short duration, and is why the H&Y scale is not usually used in therapeutic trials with short follow-up time periods. However, this instrument reflects endpoints and outcomes very accurately, as the progression from one stage to the next is clearly delineated and is not susceptible to evaluator bias or temporary medication-induced changes in motor function. In longitudinal studies, survival free of death or H&Y stage 4 or 5 may more meaningfully reflect clinical outcomes than the UPDRS part III. Support for this type of outcomes comes also from a recent study where the “dead or dependent” status was shown to be a reliable outcome measure.

The meeting participants agreed that the Movement Disorder Society-sponsored revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS) [85] has some improvements for
use in PD outcome studies over the UPDRS, such as evaluation of non-motor symptoms, but it has the disadvantage that a license must be obtained for its use that may restrict distribution and is somewhat cumbersome to administer in the routine office setting.

5.2. Assessment of cognitive function

The Mini Mental State Exam (MMSE) [86-89] has long been used as an office-based screening tool to assess cognitive outcomes in PD. However, the MMSE does not accurately assess the executive and visuospatial domains that are commonly impaired in PD patients. Therefore, the MMSE has been gradually replaced by the Montreal Cognitive Assessment (MoCA) [90] that specifically screens for executive and visuospatial dysfunction. A combination of the MoCA score and a clinical diagnosis of PDD or dementia with Lewy bodies (DLB), based on functionally significant impairment according to the DSM-V dementia definition, can be reliably and pragmatically used to define dementia. MoCA-scores below 26 in the absence of a clinical diagnosis of PDD or DLB indicate cognitive dysfunction or mild cognitive impairment. MoCA-scores below 26 and a clinical diagnosis of PDD or DLB indicate dementia.

5.3. Assessment of depression and anxiety

Among the non-motor manifestations of PD, depression and anxiety are fairly common. Different scales are available to screen for depression, some of which are administered by the examiner whereas others contain questionnaires that can be completed by the patient. Examples of commonly used scales are the Hamilton depression rating scale (Ham-D) [91], the Beck depression inventory (BDI) [92], the Geriatric Depression Scale (GDS) [93], Zung Self-Rating Depression scale (SDS) [94] and the UPDRS part I. These scales can be used to screen for the presence or absence of a particular feature or behavior but also for assessing
symptom severity. Their relative merits have previously been reviewed and evaluated [95]. Depression scales developed for psychiatric practice may record motor features, making them unsuitable for PD patients.

5.4. **Assessment of autonomic dysfunction**

Disturbances of the autonomic nervous system may be caused by the disease process itself or may be adverse effects of dopaminergic therapy. Autonomic dysfunction can have a profound impact on the patient’s disability and quality of life. Signs and symptoms of neurogenic bladder disturbance or erectile dysfunction can be assessed by direct questioning of the patient during a visit. Several rating scales that assess orthostatic hypotension are commonly used, including SCOPA-AUT [96], OHQ [97], and COMPASS [98], but these are relatively detailed and may take too long time to administer during routine office visits. The presence or absence of symptomatic orthostatic hypotension is assessed in UPDRS part IV. Blood pressure and pulse measurements supine or sitting and after 3 minutes standing can reliably identify a majority of patients with orthostatic hypotension.

5.5. **Assessment of quality of life**

Different motor and non-motor manifestations can impact on the quality of life (QOL) of PD patients. Available QOL instruments have been evaluated by the MDS task force [99]. The 39-item PD Questionnaire (PDQ-39) [100] is the most extensively used instrument; however, its length may make the administration of the test impractical in the office setting. Furthermore, the PDQ-39 is not sensitive to detect changes during the first five years after PD onset [13]. The Schwab and England Independence Scale (S&E) [101] is another well-established and easily administered scale. It assesses overall clinical progression and disabilities in performing activities of daily living, which impact the patient’s quality of life. It
may be used as a self-reported scale or reflecting the health care provider’s global impression. NeuroQOL is a widely used scale provided via the internet but is not disease-specific and requires computer access which may be limited in some office settings [102].

5.6. A panel of rating scales to assess PD outcomes during a routine office visit

Our discussions among clinicians seeing PD patients in clinics on three continents revealed marked differences in clinical practice. For example, the amount of time spent with a patient during a routine office visit, access to translations of rating scales to different languages and the availability of additional health care personnel in connection with clinic visits. Taking these practice differences into account, we propose a panel of tests that longitudinally collect a significant amount of phenotypic information, can be obtained during routine office visits, and standardized across different institutions and countries. This panel consists of the following: The UPDRS (parts I-IV) at the time of the office visit, documenting the patient’s ON, partial ON or OFF state, despite its weaknesses described above, the H&Y scale, the MoCA-score, the 15-item version of the GDS, and the S&E scale. Blood pressure and pulse measurements with the patient supine or sitting and after standing for 3 minutes should be performed when possible. We consider this panel feasible to perform at regular intervals in large numbers of patients and over more than 10 years in purely office settings or in clinical research settings.

In addition to the rating scales, “routine” clinical information such as social situation, most prominent complaint(s), current medications including response and side effects, comorbidities, etc. are necessary. Information regarding additional meaningful outcomes for patients and caregivers such as the abilities to work, drive and communicate, the presence of dysphagia, necessity of a caregiver, institutionalization, and others, may be extrapolated from the UPDRS part II or collected during interviews of patients and/or caregivers. All these data
can be captured in commonly used electronic medical record systems. Specific statistical and mathematical methods will be employed to analyze data from clinical rating scales that are used to document longitudinal disease progression [103].

6. Perspective

Individuals who have developed symptoms of a progressive neurological disorder are understandably more concerned about how the disorder likely will impact their future, rather than what factors in their past may have caused their disease. Prospective, long-term collection of relevant clinical, environmental and genetic data, starting soon after diagnosis, will provide the necessary information to assess progression and long-term disease outcomes and help identify the contributing factors. Such studies are feasible with the proposed panel of clinical assessment instruments that are accurate and practical to use in the routine clinical practice setting. Performing research studies in routine settings will generate results with high external validity, and facilitate implementation in the clinical practice setting [104].
Acknowledgements

The Evanston meeting was supported by NorthShore University HealthSystem, Evanston IL (USA). The preparation of this article was supported by governmental funding for clinical research within the Swedish National Health Services (ALF-YF) and by funding from The Swedish Parkinson Foundation (Parkinsonfonden) to AP. The sponsors had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Potential conflict(s) of interest / relevant financial disclosures:

In the context of the discussions that resulted in this manuscript, an international longitudinal clinical and genetic study, the “LONG-PD study”, was launched. It will include patients presenting with Parkinsonism (except drug-induced Parkinsonism) as defined previously [105] and will continue to follow patients for up to 15 years. Patients in whom the diagnosis is modified to atypical PD at a subsequent time point after study entry will remain in the study as they may provide additional insight into PD progression. They will be analyzed separately from the “typical” PD patients. To date, 32 member sites of the GEO-PD consortium, representing 20 countries and five continents, have agreed to share DNAs for ~5,000 patients and baseline and follow up data for up to 15 years. The study is expected to provide important information that can help guide treatment and develop accurate prognostic indicators for clinical progression and response to treatment.
References


Figure legend

**Figure 1: Schematic representation of the clinical course of Parkinson disease**

This diagram summarizes the principal hypotheses behind studying clinical progression and long-term outcome in PD. Past research has intensively investigated the factors influencing disease development (left), which was partly driven by the hope that neuroprotective treatments would become available. On the contrary, the clinical trajectory of PD after disease manifestation (right) has remained understudied. PD is a very heterogeneous disorder and only subgroups of patients develop severe disease and disabling complications. There is a need to identify the factors that influence clinical progression or determine long-term outcome. This would make it possible to provide individualized prognostic information to patients soon after the diagnosis is established, and hopefully to improve outcome by addressing modifiable factors of disease progression.