Path to Parkinson Disease Prevention
Conclusion and Outlook

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Abstract
Tremendous progress in our understanding of the pathophysiology and clinical manifestations of the prodromal phase of Parkinson disease (PD) offers a unique opportunity to start therapeutic interventions as early as possible to slow or even stop the progression to clinically manifest motor PD. A Parkinson’s Prevention Conference, “Planning for Prevention of Parkinson’s: A trial design symposium and workshop” was convened to discuss all issues that need to be addressed before the launch of the first PD prevention study. In this review, we summarize the major opportunities and challenges in designing prevention trials in PD, organized by the following critical trial design questions: Who (should be enrolled)? What (to test)? How (to measure prevention)? and the pivotal question, When during the prodromal disease (should we start these trials)? We outline the implications of these questions and their meaning for a responsible, sustainable, and fruitful further planning for prevention trials. Despite the great progress that has been made, it needs to be acknowledged that several queries remain to be carefully considered and addressed because prevention trials are being planned and become a reality.
The past 3 decades have revolutionized our understanding of the early years of Parkinson disease (PD). The hypothesis that a long prodromal phase precedes the clinical diagnosis of PD was proposed in Neurology® as far back as 1991.1 Thirty years later, evidence supporting both the existence of prodromal nonmotor markers, reflecting underlying peripheral nervous system and CNS pathology, and of subtle motor signs of early nigrostriatal system involvement is well established. In parallel with advancements in better understanding of the disease biology and development of biologically targeted therapeutics, it is imperative to consider starting therapy in the prodromal phase to slow or even stop the progression to clinically manifest motor PD. Therapeutic trials targeting the prodromal population are being implemented in other neurodegenerative diseases, specifically Alzheimer disease, and can provide insights to the complexity and path forward.2 Reflecting insights shared throughout this Neurology supplement, Planning for the Prevention of Parkinson Disease: Perspectives on Trial Design, we believe that the field has accumulated sufficient critical knowledge to start addressing the quintessential questions of designing interventional studies in individuals at risk for developing PD. As mentioned in the Introduction,3 we provide a framework for addressing the critical next steps in designing trials to prevent PD by addressing the following questions: Who (should be enrolled)? What (to test)? and How (to measure prevention)? complemented ultimately by When during the disease (should we start these trials)?

Who (Should Be Enrolled)?

A prerequisite for any successful trial is its application in a well-suited population. The question of Who inherently entails:

1. Who is most likely to be in the prodromal phase?
2. Who is most likely to progress during the prodromal phase? Progression may be determined either by changes in progression (motor or nonmotor) markers during the prodromal phase or by conversion to manifest clinically defined PD. Identification of meaningful endpoints of progression (How?) over a manageable time period will be important in considering Whom to target.
3. Who is most likely to respond to the intervention? Targeted therapies may be efficacious in selected populations, for example, for pathogenic genetic variant carriers, whereas other interventions may have a broader benefit, being studied in all at-risk individuals (What?).
4. Who is willing to know about their individual risk? Who is willing to participate in a prevention study? Individual risk can almost never be accurately predicted. Ethical considerations including the fundamental “right to know” and the “right not to know” their individual risk are imperative.4,5 Individual choice to participate in a trial may also be influenced by the safety, burden, and anticipated efficacy of the intervention (What?) and the study design (How?).

Genetically defined at-risk populations, as summarized by Niotis et al.,6 provide illustrative examples. The penetrance of many PD pathogenic genetic variants is being estimated with increasing precision. Genetic testing for PD pathogenic genetic variants is now more widely available, with companies such as 23andMe offering direct-to-consumer testing for common variants in the GBA and LRRK2 genes and programs such as Parkinson’s Progression Markers Initiative and Rostock International Parkinson’s Disease Study testing nonmanifest individuals with certain risk factors. In recent years, we have learnt about these pathogenic genetic variants’ roles in PD, and with this knowledge, targeted genetic studies in individuals with manifest PD and genetic variants have commenced.

Measuring prodromal markers in pathogenic genetic variant carriers may identify those in whom the neurodegenerative process has begun or is progressing. Individuals already in the prodromal phase may be most appropriate for and interested in prevention trials targeting mechanisms specific to their PD variant. Additional prodromal markers can further enrich participants with the highest likelihood to develop disease in a shorter time period. For example, in GBA pathogenic genetic variant carriers stratified by the presence of REM sleep behavior disorder (RBD), the prodromal period is rather short compared with other forms of PD.9

Shortcomings of genetically defined cohorts, however, are the long asymptomatic period before phenoconversion, the incomplete penetrance with many of the more common pathogenic genetic variants (i.e., with the majority of GBA and LRRK2 variation carriers never developing PD), and the potential limited generalizability of subpopulation-targeted therapies to idiopathic PD, although this currently remains unknown. There is currently a solid body of data demonstrating that the presence of prodromal clinical markers, that is, constipation, hyposmia, and idiopathic RBD (iRBD), is associated with an increased likelihood for future PD development,10,11 although the specificity of these markers varies.

Polysomnography-proven iRBD is currently considered the strongest prodromal marker for PD and other a-synucleinopathies. Large multicenter studies have shown that more than 80% of patients with iRBD will develop PD, dementia with Lewy bodies (DLBs), or rarely multiple system atrophy, and studies with the longest follow-up periods suggest that nearly all will eventually develop a neurodegenerative disease.12-14 Based on a phenoconversion rate in the largest RBD cohorts to PD or DLB of 6%–7% per year,15 designing a preventive trial with sufficient power is a reality in RBD. The addition of other PD prodromal markers to iRBD may allow a further reduction in the sample size required and increase the phenoconversion rate, as summarized by Ronald Postuma.16
However, challenges remain with prodromal at-risk populations. RBD, like genetic cohorts, is uncommon in the general population, with about 1% of people having polysomnography-proven iRBD.\textsuperscript{17,18} In addition, many people with RBD are not counseled and thus not aware of their risk for PD or other a-synucleinopathies, thus reducing the pool of individuals who can potentially qualify for interventional studies. In addition, progression markers in the prodromal phase of iRBD (How?) still need to be identified or substantiated to allow shorter trial periods. It also needs to be acknowledged that treatment options (What?) may intervene with the pathologic process but, at least so far, not with the cause (as in genetic forms) because the cause of neurodegeneration in RBD remains unknown. Moreover, the early appearance of RBD seems to be associated with the specific subtype of PD, which may mirror the a-synuclein aggregation and propagation of PD pathology in the sense of a “body-first” type, which may be distinct from and therefore not readily generalizable to its “brain-first” counterpart.\textsuperscript{19} An even broader spectrum of PD would be represented by taking into account a composite of prodromal features as presented by Molsberry et al.\textsuperscript{20} This approach benefits from the identification of numerous risk and prodromal markers that, when combined in a statistical model as suggested by the Movement Disorders Society task force, can estimate the probability of prodromal PD.\textsuperscript{10,12} It also offers the advantage of efficient screening strategies based on large heterogeneous populations using simple survey questions (e.g., on constipation or probable iRBD) and self-administered at-home tests (e.g., of olfaction). The low specificity of most of the risk and prodromal markers, however, will warrant use of an additional biomarker (e.g., dopamine transporter [DAT] imaging or a-synuclein aggregation assay once validated) to implicate a-synuclein pathology as the cause of the prodromal symptoms. Other challenges when implementing trials in this broader spectrum at-risk group include the current lack of progression markers in the prodromal phase (How?) and the limited ability to implement target-specific interventions (What?).

As a clinical diagnosis cannot be made at the time of presentation with risk or prodromal markers, important ethical considerations are raised when considering research in these at-risk individuals, and ongoing engagement with at-risk advocacy groups is critical. Clinicians and scientists strive to offer early, timely PD diagnosis and are often intrigued by the observation of a preceding prodromal phase, given the potential opportunity for disease modification at this stage. However, those who are affected by risk and prodromal markers, and thus are at risk of developing PD, may differ greatly in what they want to know.

In a recent study, patients with PD were asked to consider retrospectively, “Would you have liked to have known your risk for PD years before you got the diagnosis?” \textsuperscript{6} 85% of patients answered “yes,” when they themselves could have made a contribution (e.g., by lifestyle factors) to alter the course. \textsuperscript{6} 46% of the patients answered “yes,” even when no treatment option to postpone disease onset could be offered.\textsuperscript{6} These findings stress the importance of counseling these individuals on the potential benefits and limitations of receiving this potentially life-changing information and highlight the complexities of enrolling them in preventive trials. The altruistic, self-transcendent attitude of many individuals at risk also needs to be acknowledged, as evidenced in the recent VALOR-PD survey, in which 94% of individuals carrying the LRRK2 G2019S pathogenic genetic variant (mostly nonmanifesting and mostly new to research studies) responded that they would be willing to participate in an intervention trial to prevent PD.\textsuperscript{21} Thus, it should be kept in mind that many individuals are willing to participate in these studies, even if a personal benefit cannot be guaranteed. Moreover, keeping individuals at risk and their advocates (e.g., families, friends, and lay groups) informed and involved in all aspects of prevention trial planning is critical because they provide an essential perspective to the scientific community. Individuals in the prodromal phase deserve to have their wishes and rights for autonomy respected and their invaluable contributions to the research valued. In addition, insights gained from their experience with disease, which may be easily missed by researchers, should be incorporated into the study. They also deserve the investigators’ assurance that their safety is of highest priority, and that the lesser potential for an intervention’s benefit (for people who, while at increased risk, may never get PD) is adequately offset by the minimal risk of that intervention. Finally, as equal partners in this research enterprise, they deserve to be apprised of the results regardless of their impact.

What (to Test)?

The ideal agent to use in a clinical trial of persons at risk of developing PD might be considered to be an intervention already shown to be effective in slowing or stopping progression in established disease. However, more than 3 decades of work have failed to identify even 1 such agent.\textsuperscript{22} The reasons for the lack of success are multifactorial and largely based on still incomplete understanding of the disease biology and treating PD as one entity rather than subtyping based on the specific biological process, but one of them may be that intervening only after PD has been diagnosed may be too late to disrupt the disease process and substantially slow its clinical course.

Besides determining Who will be best suited for prevention clinical trials and the pivotal question: Is the intervention sufficiently safe?—which must be addressed regardless of the target population—a paramount consideration inherent in the What (to test) aspect is: What is the evidence to support efficacy? Crotty and Schwarzschild\textsuperscript{23} considered current and future therapies for the first PD prevention trials. In accordance with the considerations summarized in Who, populations at genetic risk of PD may be appropriate for a precision medicine approach. Unaffected persons with rare pathogenic genetic variant (e.g., in the SNCA gene) or with genetic variants strongly
associated with PD (e.g., in GBA or LRRK2 genes) are candidates for trials testing drugs specifically targeting the pathogenic mechanisms of these genes’ pathogenic genetic variant. Such interventions are definitely the ultimate goal. However, considering that all these interventions are investigational, they will require solid safety data as a prerequisite to be considered for the first PD prevention trials. That holds especially true for individuals who are far from phenoconversion (see also below, paragraph on ‘When’). A future consideration relates to the possibility that interventions targeting specific PD-associated gene mechanisms may ultimately benefit those with less specific risk profiles. This would be true if the pathophysiological mechanism is shared independently of the initiating cause. More specific biomarkers of target engagement and effect as well as improved outcome measures of progression will facilitate future trials (How?).

Conversely, as detailed by Molsberry et al., candidate neuroprotectants inversely associated with idiopathic PD may also be considered for their preventive potential in specific at-risk populations. As examples, 2 common medicinal and dietary exposures with established safety profiles—the non-steroidal anti-inflammatory drug ibuprofen and the adenosine receptor antagonist caffeine—have recently been linked to PD resistance among LRRK2 pathogenic genetic variant carriers. Unexpectedly, these associations with a reduced likelihood of LRRK2 PD appeared to be even stronger than in idiopathic PD idiopathic PD, suggesting their candidacy as relatively safe therapeutic agents for potential use in prevention studies for genetically at-risk participants.

Janssen Daalen and colleagues review lifestyle factors. High-intensity aerobic exercise is posited to be an ideal intervention for the first clinical trial to prevent PD. As summarized in this special issue, exercise has plausible though nonspecific mechanistic effects. Epidemiologic studies suggest that exercise may reduce the risk of developing PD. Studies in people with PD provide preliminary evidence of clinical benefit, although whether this benefit represents disease modification is not known. Exercise has other accepted health benefits, and when prescribed correctly, with medical monitoring, the safety profile is good. As with other lifestyle interventions, compliance provides a challenge. Use of technology may improve trial design and enhance compliance. Combining exercise with other lifestyle modifications may be optimal but has to be formally tested.

In our conference’s workshop, a modest majority (62%) of participants felt that there was sufficient evidence currently to select an intervention to test in a first trial targeting people thought to have prodromal PD. Low-risk interventions such as exercise may provide overall health benefits even if the specific effects on PD are not clear cut. Of the therapeutic options outlined above, workshop participants gave exercise the highest ranking as a first intervention for a PD prevention trial. Participants identified the incomplete understanding of the biologic effects of exercise on PD pathophysiology as a limitation, although laboratory and clinical evidence supporting a beneficial effect of exercise in slowing progression in people with PD is increasing. Other concerns included challenges in motivating compliance, blinding, and measuring its effect, given the lack of established biomarkers for measuring PD prevention (How?).

While exercise is at the top of the “readiness list” of interventions for the prodromal population in terms of feasibility and safety that, in all likelihood, exercise will be complementary to the ultimate therapeutic choices that target disease biology. Such are moving from the future goals into the reality with the Michael J. Fox Foundation for Parkinson’s Research (MJFF) recent announcement of planning to launch PD prevention platform trials testing most promising therapeutics in the prodromal population. Obviously, the choice of interventions will have to be carefully selected, with safety being an essential criterion. Such platform will require close collaboration between all stakeholders including industry, academia, and advocacy organizations with direct input from the PD community. Although challenging, experience from the other field supports feasibility and timeliness of such approach.

**How (to Measure Prevention)?**

Although a number of observational studies comprehensively summarized by Mirelman et al. have provided substantial data on the risk of phenoconversion in prodromal cohorts to clinically defined PD, definition of endpoints for clinical trials still remains challenging. Possible endpoints for trials in the prodromal phase follow different concepts, each with inherent limitations.

1) Phenoconversion, that is, a clinical diagnosis of PD: Although this endpoint seems most relevant, operationalization of this subjective clinical outcome is difficult, and standardization of phenoconversion as an outcome measure remains a major challenge. Even in the most clearly defined prodromal cohorts—those with iRBD and hyposmia—the annual rate of phenoconversion (6%–10%) introduces practical challenges. Determining the efficacy of an intervention in a sensible timeframe (e.g., 2–3 years) may not be possible without a prohibitively large study population or further enrichment (e.g., for prediagnostic motor and/or DAT deficits).

2) Measurement of the pathologic process:

a) Measurement in tissues and biofluids: Measurement of α-synuclein biomarkers has been a focus in recent years because the aggregation of misfolded α-synuclein is a common pathologic feature in most PD cases. Synuclein seeding assays offer tremendous promise for the early identification of synuclein pathology in central biofluids (CSF) and peripheral tissues (skin, submandibular gland, and nasal mucosa). However, at present, these assays are largely qualitative, and their longitudinal sensitivity to change remains to be tested. As such, they may be more helpful in determining Who? (enrichment with
b) Imaging of the pathologic process: Unfortunately, as yet no imaging marker can detect misfolded α-synuclein. Preliminary evidence suggests that the visualization of neurodegeneration in the peripheral nervous system may be effective for “body-first” prodromal syndromes. For example, for a neurodegenerative process starting in the gut, a readout that includes imaging markers of the colon, heart, and lower brainstem could be envisioned to describe anatomic progression of the neurodegenerative process. Slowing or stopping progression to the striatum could be seen as an endpoint. However, the radioactive nuclear medicine techniques needed for these assessments cannot easily be applied in larger cohorts. Moreover, the expected time course of the progression of neurodegeneration from the gut to the striatum, and the variability among individuals, is not known.

c) DAT imaging: As discussed in detail by Seibyl and Kuo and further elaborated in the statistical discussion by Macklin and colleagues, there are sufficient data on both the longitudinal change in DAT imaging and the feasibility of collecting high-quality data in a multicenter setting in prodromal populations to allow sample size estimation. A DAT-based outcome measure allows a smaller sample size compared with the clinical measures of progression currently used (e.g., Movement Disorders Society-Unified Parkinson Disease Rating Scale) and, thus, provides an attractive option for early phase studies. In fact, DAT imaging currently constitutes the best option to measure changes in DAT functioning quantitatively. Consequently, reduced DAT binding, measured in a DAT-based imaging study, reflects the amount of neurodegeneration of the nigrostriatal system and thus may serve as a progression marker in the prodromal phase. However, degeneration of the nigrostriatal system occurs rather late with respect to conversion to motor PD in at least some subtypes (e.g., those in whom the neurodegenerative process starts in the gut) and may not be sensitive to the earliest stages of the neurodegenerative process. Thus, for the measurement of the pathologic process, a combined approach, using DAT imaging along with clinical measures of progression and, if available, quantitative markers of change in α-synuclein aggregates, may be most suitable for testing therapeutic interventions, particularly in phase 3 studies.

3) Clinical progression markers in the prodromal phase: The large number of nonmotor and early motor markers that may occur in the prodromal phase seems to provide a promising option for application as endpoints for clinical studies, once their progression in the prodromal phase is understood. However, so far, no unambiguous clinical progression marker in this phase is known. Many nonmotor markers are stable or vary in their expression in the prodromal (as well as clinical) phase (e.g., hyposmia, constipation, and depression) and may even vanish over time, illustrating that not even the accumulation of nonmotor markers constitutes a perfectly suitable progression marker. Abnormalities in quantitative motor assessments, particularly change over time, appear to be the most promising. However, abnormalities in motor function only become apparent when the nigrostriatal system is affected, which is rather late in the prodromal phase. Progression markers identifying change before nigrostriatal pathology has advanced would allow earlier—and perhaps more effective—intervention.

When During the Early Disease Process (Should We Start These Trials)?

The 3 fundamental questions—Who? What? and How?—cannot be answered effectively without also addressing a fourth question—When (should we start these trials)? Considering the complex interplay of factors determining optimal participant selection, choice of specific intervention, and selection of outcome measures, it soon becomes clear that a single overarching principle of trial design for the whole prodromal phase may not be appropriate. Rather, When the intervention is planned will differ and depend on:

1) The individual situation, that is, what are the prodromal features in an individual, and what stage in the prodromal phase does this represent (the latter may differ by cause or subtype)?
2) The projected course and the estimated time to phenoconversion, that is, can meaningful progression markers in this person for this specific phase be determined?
3) The interventions available, their safety, and the likelihood to be effective in this at-risk individual.

The interplay of the questions Who? What? How? and When? will determine our next steps. A schematic representation of the interplay of these 4 questions in determining the optimal prevention trial is provided in Figure 1. This model provides a starting point but will need to be amended with growing knowledge, including better diagnostic markers for the identification of at-risk and prodromal individuals, greater understanding of disease mechanisms, and consequent improved interventions and outcome measures.

When can be answered in the individual sense—at what stage in the disease process is the person being considered for the intervention? But, When can also be posed in a broader sense. When is it appropriate to test a specific intervention in a...
certain population? Relatively safe, low-cost interventions, such as physical activity (Janssen Daalen et al.28) may be appropriate even at the earliest prodromal stage. Participants in such a trial need not be aware of their level of personal risk. But, the scientific capacity and resources to monitor large numbers of persons over long periods of time would be necessary. And, whether participants in long-term, low-risk interventions would be eligible for future trials would require consideration. On the other hand, very new treatments with uncertain safety profiles may be most appropriate when the disease is more advanced, and progression to PD is predicted to be highly likely. Yet, if over time the new agent is found to be effective, and the safety profile is reasonable, trials at ever earlier prodromal time points may be appropriate, in the hope of delaying or even preventing PD.

The final determinant of when will rely on the voices of those at risk of PD, including those with prodromal PD. On an individual basis, when an individual chooses to learn about risk may influence the timing and the type of intervention. When in the progression process may also determine individual interest in an intervention. Also, ethical issues including the respect of autonomy of individuals entailing their right to know and equally their right not to know, involvement of those who are affected, and safety of the intervention need to be further elaborated. The most efficient and effective approach to preventing PD will involve a partnership of the scientific community, persons at risk of PD, persons with prodromal PD, people with PD, and other stakeholders spanning industry, philanthropy, and regulatory agencies. To that end, a clear consensus from a broad range of these assembled stakeholders was the value of their early

Figure 1 Conceptual Framework of Prodromal PD: What is Meant, How to Diagnose, and When to Treat Whom

(A) Gives a schematic overview of our current understanding of the neurodegenerative process in PD and illustrates that the prodromal phase can be divided into 3 stages. Notably, these are hypothetical frameworks only—the specific elements represented and the timeframes specified are not proven. These stages do not need to be evident in all individuals, may have different durations, and can even occur simultaneously (e.g., individuals with mild motor abnormalities may become hyposmic at the same time the motor changes become obvious). In (B), markers for the specific phases are suggested. (C) Provides examples of specific cohorts (who?) for clinical trials dependent on the stage and accompanying markers. Pharmacologic trials in all cohorts can only be justified when PD-specific pathology is proven—by demonstrating either α-synuclein pathology or involvement of the nigrostriatal system (early motor). Conversely, low-threshold interventions (e.g., exercise) may be applied at all stages even if pathology cannot be proven. The choice of intervention (what?) may differ, depending on the clinical subtype (who?) and the specificity of biomarkers, that is, endpoints for clinical studies (how?). PD = Parkinson disease; SN = substantia nigra.
convening as a precompetitive consortium. A PD prevention collaborative could efficiently coordinate broad strategies and resources in a manner akin to the established collective endeavors to design trials for Alzheimer disease prevention through the Collaboration for Alzheimer’s Prevention.53 Indeed, the MJFF has announced intent to launch a therapeutic program targeting the prodromal population.

Conclusion

Over the past 30 years, our knowledge of PD has significantly increased, with the recognition of a prodromal phase, risk, and clinical markers, along with genetic variations in PD. This special issue based on our recent conference, “Planning for Prevention of Parkinson’s: A trial design symposium and workshop,” summarizes and highlights the progress that has been made and which, as a result, has allowed the PD field to begin contemplating prevention trials. However, many questions remain, and further research is warranted. Before the implementation of a prevention trial, questions such as Who (to enroll)? What (to test)? and How (to measure prevention)? require addressment by all stakeholders in the PD community, while also considering the pivotal question When during the early disease (should we start these trials)?

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