### Title
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### Journal
Movement Disorders, 30(12)

### ISSN
0885-3185



### Authors
Berg, D
Postuma, RB
Adler, CH
et al.



### Publication Date
2015-01-01

### DOI
10.1002/mds.26431

Peer reviewed

REVIEW

CME

# MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,[1]* Ronald B. Postuma, MD, MSc,[2]* Charles H. Adler, MD, PhD,[3] Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5] Bruno Dubois, MD, PhD,[6] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[7] Glenda Halliday, PhD,[8] Lawrence Joseph, PhD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Inga Liepelt-Scarfone, PhD,[1] Irene Litvan, MD,[11] Kenneth Marek, MD,[12] José Obeso, MD, PhD,[13] Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15] Werner Poewe, MD,[16] Matthew Stern, MD,[17] and Günther Deuschl, MD[18]

[1]*Department of Neurodegeneration, Hertie-Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases, Tuebingen, Germany*
[2]*Department of Neurology, Montreal General Hospital, Montreal, Quebec, Canada*
[3]*The Parkinson's Disease and Movement Disorders Center, Department of Neurology, Mayo Clinic, Scottsdale, Arizona, USA*
[4]*Department of Neurology, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands*
[5]*Xuanwu Hospital of Capitol of Medical University, Beijing, China*
[6]*Hopital De La Salpetriere, Paris, France*
[7]*Rush University Medical Center, Chicago, Illinois, USA*
[8]*Neuroscience Research Australia & University of NSW, Randwick, Australia*
[9]*Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada*
[10]*Division of Neurology, Toronto Western Hospital, Toronto, Ontario, Canada*
[11]*Department of Neurosciences, University of California San Diego, La Jolla, California, USA*
[12]*Institute for Neurodegenerative Disorders, New Haven, Connecticut, USA*
[13]*University of Navarra-FIMA, Pamplona, Spain*
[14]*Department of Neurology, Philipps University of Marburg, Marburg, Germany*
[15]*Department of Neurology, The Mount Sinai Hospital, New York, New York, USA*
[16]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*
[17]*Penn Neurological Institute, Philadelphia, Pennsylvania, USA*
[18]*Department of Neurology, Christian-Albrechts University, Kiel, Germany*

**ABSTRACT:** This article describes research criteria and probability methodology for the diagnosis of prodromal PD. Prodromal disease refers to the stage wherein early symptoms or signs of PD neurodegeneration are present, but classic clinical diagnosis based on fully evolved motor parkinsonism is not yet possible. Given the lack of clear neuroprotective/disease-modifying therapy for prodromal PD, these criteria were developed for research purposes only. The criteria are based upon the likelihood of prodromal disease being present with probable prodromal PD defined as $\geq$80% certainty. Certainty estimates rely upon calculation of an individual's risk of having prodromal PD, using a Bayesian naïve classifier. In this methodology, a previous probability of prodromal disease is delineated based upon age. Then, the probability of prodromal PD is calculated by adding diagnostic information, expressed as likelihood ratios. This diagnostic information combines estimates of background risk (from environmental risk factors and genetic findings) and results of diagnostic marker testing. In order to be included, diagnostic markers had to have prospective evidence documenting ability to predict clinical PD. They include motor and nonmotor clinical symptoms, clinical signs, and ancillary diagnostic tests. These criteria represent a first step in the formal delineation of early stages of PD and will require constant updating as more information becomes available. 

**Key Words:** Parkinson's disease; diagnosis; prodromal

*Correspondence to: Dr. Ronald B. Postuma, Department of Neurology, L7-305 Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada H3G1A4; ron.postuma@mcgill.ca; or Dr. Daniela Berg, Hertie Institute of Clinical Brain Research, Hoppe, Seyler-Straße 3, 72076 Tubingen, Germany; Daniela.berg@uni-tueb

Drs. Berg and Postuma contributed equally.

**Relevant conflicts of interest/financial disclosures:** Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

**Received:** 3 April 2015; **Revised:** 11 August 2015; **Accepted:** 12 August 2015

**Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.26431**

Parkinson's disease (PD), as with all neurodegenerative diseases, does not start suddenly. This implies that the disease progresses through early phases, during which neurodegeneration has commenced but has not yet progressed to the point at which PD can be definitively diagnosed. The early phase of PD has both motor and nonmotor aspects, and in many cases, certain nonmotor abnormalities are the first to emerge.

The International Parkinson and Movement Disorder Society (MDS) Task Force on the definition of PD was created to clarify challenges to our current definition of PD. An introductory statement of this task force was recently published,[1] in which we proposed that early PD should be divided into three stages: preclinical PD[2] (neurodegenerative processes have commenced, but there are no evident symptoms or signs); prodromal PD (symptoms and signs are present, but are yet insufficient to define disease); and clinical PD (i.e., diagnosis of PD based on presence of classical motor signs).

Diagnostic criteria for clinical PD have been developed (the MDS-PD criteria) and appear in this issue of *Movement* Disorders.[3] This article presents the MDS criteria for *prodromal* PD. These are intended as a research tool; in the absence of a clear neuroprotective/disease-modifying therapy against PD, given the potential ethical issues of disclosure of disease risk in a nonmedical context, and especially given the uncertainty inherent to this early-development field, we do not yet recommend using these prodromal criteria outside of a research setting. Because new data are constantly being generated from the fields of neurobiology, genetics, neuroimaging, and other arenas, these criteria will require continuous reupdating.

## Key Definition Features of Prodromal PD

Several key definition aspects of prodromal PD deserve particular emphasis[1]:

1. Whereas the diagnostic criteria for clinical PD remain centered on a motor syndrome, prodromal PD can be defined also based upon nonmotor markers ("marker" here refers to any disease indicator, whether a symptom, sign, or biomarker). The prodromal terminology makes no assumptions about the order in which motor versus nonmotor markers develop.
2. The speed of progression from prodromal to full clinical stages varies among patients and cannot be reliably predicted on the individual level. Therefore, the criteria center upon *whether* symptomatic neurodegeneration is present, and not *when* this will progress to full clinical PD. Note that in many situations (e.g., clinical trials that require conversion within a limited time window), further stratification may be required, using markers that signal faster progression or advanced prodromal stage.
3. The criteria incorporate estimates of risk, based upon age, sex, and documented PD risk factors. However, prodromal PD criteria cannot be met with only risk markers; some markers of ongoing neurodegeneration (i.e., prodromal markers) must also be present.
4. The selection of criteria is primarily data driven. Criteria required prospective studies documenting their predictive value for clinical PD.
5. As outlined in our definition statement,[1] dementia with Lewy bodies (DLB) is not considered an exclusion criterion for PD. Therefore, if patients with prodromal PD markers develop DLB, we do not consider such cases as "false positives"; many of these subjects will eventually also meet criteria for PD. Some studies included in our analysis (particularly rapid eye movement [REM] sleep behavior disorder [RBD] studies) assessed DLB and PD as a combined outcome. Because most DLB patients in these studies also meet the MDS-PD criteria,[4] we used the combined conversion rates to calculate likelihood ratios. For studies of prodromal DLB that did not clearly assess coexisting PD (e.g., studies of nonamnestic mild cognitive impairment [MCI][5]), we could not identify how many DLB patients would meet MDS-PD criteria, so we could not include these studies in our calculations.
6. Given that there are currently no means to identify prodromal PD with 100% certainty, diagnostic criteria for prodromal PD must be based upon probability. We specified probable prodromal PD as a high likelihood (i.e. $\geq$80%) that prodromal PD is present. This category might be used to select candidates for future disease modification trials. However, in a specific research setting, investigators may elect to select patients with different probability cutoffs. For example, for a long, randomized trial of a very well-tolerated agent, investigators may elect to include all those who have a >50% calculated probability of prodromal PD.
7. Although the task force is aware that a primary use of these criteria will be for enrolling patients in neuroprotective trials, we do not wish to define any details about trial procedures, means of stratification, assessment of conversion rates to classical PD or dementia, and so on. The criteria simply attempt to define the probability that an individual patient has prodromal PD; the ultimate use of the criteria depends upon context.

## Methodology of Criteria Design

The primary methodology for sequentially adding diagnostic information is termed the naïve Bayesian classifier. This methodology takes a baseline pretest (i.e., "prior") probability of disease, then adds the results of a new diagnostic test to arrive at a new (post-test) probability of disease. Results of additional diagnostic tests can then be sequentially added, to further refine disease probability. This analysis requires two types of data:

1. The prior: This is the baseline probability of disease, given no diagnostic testing information. In this case, it is the estimated age-adjusted prevalence of prodromal PD.
2. Likelihood ratios: Likelihood ratios (LRs) describe the strength of a diagnostic test. One can define positive LRs, which indicate how much a positive test result increases disease probability (expressed as $LR^+ > 1$), and negative LRs, which indicate how much a negative test decreases the probability ($LR^- < 1$). $LR^+$ can be calculated as sensitivity / 1-specificity, and $LR^-$ as 1-sensitivity / specificity, or they can inputted directly from 2:2 tables into Bayesian calculators (e.g., http://araw.mede.uic.edu/cgi-bin/testcalc.pl).

## Calculations Used to Generate Criteria

### A. Estimating the Prior Probability (i.e., Prevalence of Prodromal PD)

The true prevalence of prodromal PD is unknown. In estimating the prior probability, the Task Force considered four complementary sources of information:

1. The prevalence of PD. Point prevalence of PD is approximately 0.25% at age 60, 0.5% at age 65, 0.5–1.0% at age 70, 1.0–1.5% at age 75, 2.0–2.5% at age 80, and 3.0–4.0% at age 85.[6,7] If one posits that prodromal PD has approximately a 10-year average duration, this would estimate a prodromal prevalence of 0.5% at age 55, 1.0–1.5% at 65, and 3.5% at 75.
2. Incidence of PD. The incidence of PD is approximately 50 in 100,000 at age 65, 150 in 100,000 at age 75, and 400 in 100,000 at 85.[6] Assuming a 10-year prodromal period, this would translate to a prodromal prevalence of 0.5% at age 55, 1.5% at age 65, and 4% at age 75.
3. Cumulative lifetime risk of PD. According to cumulative life risk tables, the chance of a 60-year-old developing PD by age 80 approximates 2.5%.[8] Therefore, with an average 10-year prodromal period, the estimated prevalence is 1.25% (i.e., half of 2.5%). With a 20-year prodromal period, prevalence is 2.5%
4. Prospective studies: In prospective, population-based studies that directly assessed PD as a primary outcome, the incidence was higher than any other estimation procedure. For example, in the Honolulu Asia Aging study, 37 of 1,865 (2.0%) developed PD over 8 years[9] (average age at diagnosis = 83), and the PRIPS study had 21 of 1,282 (1.6%) over 5 years (average age = 76).[10] This rate may more closely reflect the disease risk in disease-modification trials, which will also follow patients systematically. Assuming equal risk distribution over a 10-year prodromal period, these two studies would estimate prodromal prevalence as approximately 2.5% at age 73 and 3.2% at age 66.

These estimates are clearly age dependent. They will likely also increase with changes in definition of PD, particularly the removal of dementia as an exclusion criterion for PD.[1] Based on current knowledge, we combined estimates from these different sources together, adding subjective weighting and smoothing, to create an age-specific estimate of prodromal PD prevalence.

**We Estimate the Prior Probability According to 5-Year Age Intervals:**

0.4% from ages 50 to 54;
0.75% from ages 55 to 59;
1.25% from ages 60 to 64;
2.0% from ages 65 to 69;
2.5% from ages 70 to 74;
3.5% from ages 75 to 79; and
4.0% age 80 and over.

### B. Estimating LRs of Markers

The second critical piece of information is the LR of each marker.

#### *1. LRs of Risk Markers*

Identifying risk and protective factors can help stratify risk. Conceptually, risk markers help refine the prior probability, rather than diagnosing the stage of prodromal PD. For simplicity of calculations, these can be combined with prodromal markers; however, risk factors cannot diagnose disease alone. Prodromal markers with combined minimum LR of at least +4 (i.e., approximating one strong or two combined moderate-strength markers) must also be present, to indicate that the neurodegenerative process has likely started. We included only those risk factors that have broad consensus as true risk factors for PD, and which were sufficiently powerful to contribute meaningfully to probability estimation. For inclusion, we required consistent evidence from at least two prospective cohort studies or meta-analyses. Estimation of the strength of each risk factor is anchored in meta-analyses wherever possible.

Calculation of each LR is based upon the relative risk as well as the prevalence of the risk factor (LRs are calculated independent of the disease prevalence). A prior probability (i.e., estimated prodromal PD prevalence) of 2% is used for calculations. An example is provided for caffeine, assuming relative risk (RR) = 1.5 for nonuse of caffeine, with 25% of the population having this risk factor.[11,12] In a population of 10,000, 200 will have prodromal PD. Furthermore, 2,500 will be nonusers of caffeine. If RR = 1.5, then 67 of 2,500 (2.68%) of nonusers would get PD compared to 133 of 7,500 (1.77%) of caffeine users. A 2:2 table can be generated:

| | Test + | Test − | |
|---|---|---|---|
| PD + | 67 | 133 | 200 |
| PD − | 2,433 | 7,367 | 9,800 |
| | 2,500 | 7,500 | 10,000 |

LR of + test ($LR^+$) = 1.35
LR of – test ($LR^-$) = 0.88[11]

Using a prior (i.e., prodromal PD prevalence) of 1% or 4% produces almost exactly the same $LR^+$ (1.36, 1.34). Note that when the prevalence of a risk factor is less than 10%, the $LR^-$ is very close to 1 (i.e., absence of the risk factor does not add much information). Therefore, for risk factors with population prevalence <10%, only $LR^+$ calculations are pertinent ($LR^-$ need not be applied and are indicated as not applicable [N/A]).

### *2. LRs of Markers*

LRs are estimated in three ways, depending upon the type of evidence:

(a) Prospective studies with control groups: This approach is the most reliable and is available for most prodromal markers. These studies included control groups, allowing generation of a 2:2 table, and a simple calculation of LR directly from the tables ($LR^+$ = sensitivity / 1-specificity, $LR^-$ = 1-sensitivity / specificity). An example is provided below:

Transcranial ultrasound: In a prospective study[10] of 1,175 individuals, 17 developed PD; 14 of these had SN hyperechogenicity at baseline. Of the 1,158 without PD, 203 had positive ultrasound at baseline. Therefore, the resulting table is:

| | Test + | Test − | |
|---|---|---|---|
| PD + | 14 | 3 | 17 |
| PD − | 203 | 955 | 1,158 |
| | 217 | 958 | 1,175 |

Sensitivity = 82.4%; specificity = 82.5%
LR+ 4.7 (95% CI = 3.7–6.1),
$LR^-$ 0.21 (95% CI = 0.08–0.60)

(b) Prospective studies without control groups: In certain cases, prospective follow-up of an at-risk group is reported, but without control data. In this case, we estimate LR using 2% prior probability of PD, with published prevalence estimates of the prodromal marker in the general population and the PD population. For example:

Polysomnogram-proven RBD: Prospective studies show that more than 75% will develop disease (combining five long-term cohort studies[13-17]). MSA patients (8% of convertors, or 9 "Test +" patients) are eliminated from calculations (note that most patients diagnosed as DLB would also meet MDS-PD criteria for PD over their lifetime[4]). Prevalence of RBD in general population=1.15%[18]; population comparison uses lifetime PD risk, assuming risk = 2%:

| | Test + | Test − | |
|---|---|---|---|
| PD + | 77 | 123 | 200 |
| PD − | 29 | 9,771 | 9,800 |
| | 106 | 9,894 | 10,000 |

Sensitivity = 38.5%; specificity = 99.7%
$LR^+$ 130 (confidence interval not calculable)
$LR^-$ 0.62

## Selection of Markers

A literature review (Medline search, supplemented by review of reference lists of articles and expert consultation) was conducted to identify prospective studies of prodromal markers of PD. The results of this review and resultant LRs are provided in Table 1 and detailed calculations in the Supporting Methods section. Note again that for uncommon markers, $LR^-$ are generally so close to 1 that they need not be added to the calculations (delineated N/A). Two prodromal markers, color vision ($LR^+$ 1.9 before adjustment, $LR^-$ N/A)[19] and the PD-related pattern of glucose utilization ($LR^+$ 3.0 before adjustment, $LR^-$ 0.5)[20] have thus far been tested only in idiopathic RBD patients; because of generalizability concerns, they were not included in these criteria.

## Risk Markers

1. Sex: men have approximately a 1.5-fold increased risk of PD.
   - LR = 1.2 for men, 0.8 for women
2. Regular occupational exposure to pesticides (or very frequent [>100 episodes] of nonoccupational exposure)—RR/odds ratio [OR] = 1.5–1.8,[21,22] prevalence approximately 5%.
   - $LR^+$ 1.5, $LR^-$ N/A
3. Occupational exposure to solvents: OR = 1.58[21] (prevalence <5%).
   - $LR^+$ 1.5, $LR^-$ N/A
4. Nonuse of caffeine, defined as <3 cups of coffee or <6 cups of tea per week. RR = 1.5, prevalence = 25%.
   - $LR^+$ 1.35, $LR^-$ 0.88[11]
5. Nonsmoking status: This has three possible categories—only one LR is applied.

**TABLE 1.** LRs of risk and prodromal markers

| | $LR^+$ | $LR^-$ |
|---|---|---|
| Risk markers | | |
| Male sex | 1.2 (male) | 0.8 (female) |
| Regular pesticide exposure | 1.5 | n/a |
| Occupational solvent exposure | 1.5 | n/a |
| Nonuse of caffeine | 1.35 | 0.88 |
| Smoking | | |
| Current | n/a | 0.45 |
| Never | 1.25 | n/a |
| Former | n/a | 0.8 |
| Sibling had PD with age onset <50 | 7.5 | n/a |
| or | | |
| Any other first-degree relative with PD | 2.5 | n/a |
| or | | |
| Known gene mutation | see Supporting Table II | n/a |
| SN hyperechogenicity | 4.7 | 0.45 |
| Prodromal markers | | |
| PSG-proven RBD | 130 | 0.62 |
| or | | |
| Positive RBD screen questionnaire with >80% specificity | 2.3 | 0.76 |
| Dopaminergic PET/SPECT clearly abnormal (e.g., <65% normal, 2 SDs below mean) | 40 | 0.65 |
| Possible subthreshold parkinsonism (UPDRS >3 excluding action tremor) | 10 | 0.70 |
| or | | |
| Abnormal quantitative motor testing | 3.5 | 0.60 |
| Olfactory loss | 4.0 | 0.43 |
| Constipation | 2.2 | 0.80 |
| Excessive daytime somnolence | 2.2 | 0.88 |
| Symptomatic hypotension | 2.1 | 0.87 |
| Severe erectile dysfunction | 2.0 | 0.90 |
| Urinary dysfunction | 1.9 | 0.90 |
| Depression (± anxiety) | 1.8 | 0.85 |

n/a, not applicable.

- current smoker RR = 0.4 (20% prevalence)[12,22]
- $LR^-$ 0.45
- never smoker (40% prevalence)
- $LR^+$ 1.25
- former smoker (minimum 1 pack-year) RR = 0.75 (40% prevalence)
- $LR^-$ 0.8

6. Genetics: For this analysis, one can use *either* a positive family history of PD or results from a known genetic mutation. Because these are not independent variables, both cannot be used for the same patient.
   a. Sibling of PD patient, who had PD onset at <50 years age (prevalence <5%)
      - LR+ 7.5, $LR^-$ N/A
      or
   b. Any other first degree relative with PD (sibling with >50 age of onset, parent)[23-25] (prevalence approximately 10%)
      - LR+ 2.5, $LR^-$ N/A
   c. Known genetic mutation: In the case that a genetic mutation or polymorphism associated with higher risk of PD has been identified, the LR for this mutation can be used directly. Supporting Table 1 lists the best current estimates of LR for given mutations; further revisions will need to take into account new advances in genetics of PD. Note that depending on pathogenic considerations, certain studies might exclude patients with certain monogenetic forms of PD. Note also that even with a 100% penetrant gene, there still must be prodromal markers in order for a prodromal PD diagnosis to apply; for single-gene mutations, a minimum combined $LR^+$ of 4.0 for prodromal markers must also be present.
7. Abnormal hyperechogenicity of the SN: This is based on a prospective, population-based study[10] and a study in idiopathic RBD[26]. Note that SN ultrasound is considered to be a risk marker, given evidence that it can be observed in young adults and does not progress in PD[27]; however, this evidence is not definitive, and it may, in fact, be a prodromal marker. Also, note that SNpc ultrasound requires adequate training of technicians to be considered reliable for prodromal PD.
   - $LR^+$ 4.7, $LR^-$ 0.45

## Other Candidates Not Included

Several putative risk/protective factors for PD were not included, either because prospective cohort-based evidence was limited, because ORs were insufficiently strong to substantially change risk estimates, or because of concerns of nonindependence (e.g., pesticides and farming as occupation are likely nonindependent). Notable excluded risk factors were farming,

rural living, and well-water use (RR likely <1.5, and nonindependent), use of alcohol (RR = 0.90[22]), nonsteroidal anti-inflammatory drugs (RR = 0.83[22]), urate, head injury, and calcium-channel blockers (conflicting evidence/low amplitude effect).

## Prodromal Markers

### A. Clinical Nonmotor Markers

1. PSG-proven idiopathic RBD: This has been based upon five prospective studies documenting >75% conversion to neurodegenerative synucleinopathy.[13-17] Note that some of the converters had MSA, which is eliminated from calculations (see above). DLB conversions are calculated as PD conversions, owing to the fact that studies have documented substantial overlap in manifestations and levodopa-responsive parkinsonism in the majority of patients diagnosed with DLB emerging from idiopathic RBD.[4] Note that some studies included mild cognitive impairment; because this cannot be considered PD, actual conversion is lower than the study estimate of >90% conversion (although most MCI patients would eventually develop DLB and/or PD, suggesting >75% is accurate). For this, and all subsequent markers, the LR should not be applied if there is a likely alternate explanation for the marker's presence. Therefore, RBD caused by medications or secondary to narcolepsy should not be included. To use this $LR^+$, diagnosis must be unequivocal (i.e., clear decrease in REM atonia according to standardized measures[28,29]); if polysomnography (PSG) diagnosis is at all uncertain, use the lower level of certainty.
   - $LR^+$ 130, $LR^-$ 0.62

or

Positive response to a screening test for RBD with documented specificity 80% to 99% (the border of 1st and 2nd quartiles [85%] was used for calculation of LR).

   - $LR^+$ 2.3, $LR^-$ 0.76
2. Olfactory dysfunction on standardized objective testing, adjusted for age and sex. This is based upon seven prospective studies, including three population-based[9,30,31] and four performed in at-risk populations.[19,32-34]
   - $LR^+$ 4.0, $LR^-$ 0.43
3. Constipation (requiring treatment more than once per week, or spontaneous bowel movement frequency $\geq\leq$1 per 2 days). This is based upon six population-based studies.[35-40]
   - $LR^+$ 2.2, $LR^-$ 0.80
4. Excessive daytime somnolence. This is based upon two population-based studies.[35,37]
   - $LR^+$ 2.2, $LR^-$ 0.88
5. Symptomatic hypotension. Although this is based upon only one population-based study,[39,40] numerous studies document orthostatic hypotension early in PD,[41] suggesting high biological plausibility. Symptoms should not be due to excessive treatment with antihypertensive agents, and for $LR^-$ to be applied, there must be no signs of orthostatic hypotension on examination (i.e., orthostatic blood pressure drop <10 mm Hg).
   - $LR^+$ 2.1, $LR^-$ 0.90
6. Erectile dysfunction of sufficient severity to require medical intervention in order to engage in sexual activity. This is based upon two population-based studies, which had notably divergent estimates.[40,42] Note that the study with the higher LR had only a 3% prevalence of erectile dysfunction, which is a much lower estimate than most estimates of erectile dysfunction prevalence.[43] Considering these factors, the task force considered only severe erectile dysfunction for inclusion, with a conservative $LR^+$ of 2.0, pending further study. $LR^-$ should only be applied if erectile function is considered normal.
   - $LR^+$ 2.0, $LR^-$ 0.90
7. Urinary dysfunction. This is based upon two population-based studies.[39,40] Urinary dysfunction was not specifically defined in this study; however, for reasons of biological plausibility, this should not include long-standing (>10 years) stress incontinence in women. For $LR^-$ to be applied, urinary function must be directly queried.
   - $LR^+$ 1.9, $LR^-$ 0.90
8. Diagnosis of depression. This is based upon five population-based studies.[40,44-47] There have also been three population-based studies examining anxiety as a risk factor.[40,48,49] These produced LRs that were relatively low (1.12–1.6), and anxiety is often comorbid with depression in PD; therefore, isolated anxiety without comorbid depression will not be added to the criteria. However, do not apply the $LR^-$ for absence of depression if the patient has symptoms of anxiety.
   - $LR^+$ 1.8, $LR^-$ 0.85

### B. Clinical Motor Markers

Possible subthreshold parkinsonism on expert examination (supported by two prospective studies[30,50]): defined as a UPDRS (1987 version) score >3 excluding action tremor,[30,50] or MDS-UPDRS score >6, excluding postural and action tremor,[51] evaluated by an examiner experienced in PD assessment. The UPDRS was developed as a rating scale within PD, and instructions are to "rate what you see." However, for the purposes of these criteria, the examiner should consider confounds. For example, if the expert examiner feels that the UPDRS bradykinesia assessment is falsely elevated by arthritis, or stooped posture is a

result of osteoporotic kyphosis, they should remove this factor from UPDRS scoring before applying $LR^+$. On the other hand, $LR^-$ should only be applied if UPDRS is <3 *including* any potentially confounded scores (in case the confound is not the true explanation for the abnormality). Sensitivity was adjusted downward from published estimates, given that this has an estimated 4- to 5-year prodromal interval.[50]

- $LR^+$ 10, $LR^-$ 0.7
or

Abnormalities of quantitative motor tests according to defined thresholds, with performance >1 standard deviation (SD) below age-adjusted normal values. The motor test must be clearly demonstrably abnormal in clinical PD, with specificity compared to controls of ≥80%. If multiple quantitative motor tests are performed, the individual must score below threshold on ≧50% of them. Uncertain or borderline test results should not be included (use evaluator judgment). See calculations above.

- $LR^+$ 3.5, $LR^-$ 0.6

These are not independent markers. If both abnormalities have been evaluated and are present, use the higher $LR^+$. If both are absent, use the lower $LR^-$. If they are contradictory (e.g., a quantitative test is slower than normal, but examination by an expert finds normal UPDRS), the $LR^+$ of one (e.g., $LR^+$ 3.5) and the $LR^-$ of the other (e.g., LR –0.7) should both be added to the final calculation.

### C. Neuroimaging/Biomarkers

Clearly abnormal tracer uptake of the presynaptic dopaminergic system (SPECT or PET); that is, a highly standardized quantification method with clearly defined reference values demonstrates abnormal uptake, at least 2 SDs below mean values. This is based upon two studies. In the PARS study, a decrease to <65% predicted values (reference = >80% expected values) was used to indicate parkinsonian degeneration. After adjustment for biases created by using high-risk groups and using a conservative estimate of predictive value in imputed groups (see Supporting Methods), the $LR^+$ is 48 and $LR^-$ is 0.41. In the Iranzo study,[52] a cutoff of 2 SDs below the mean was used. After adjustment for high-risk groups, $LR^+$ is 33 and $LR^-$ is 0.37. As with motor examination, dopamine transporter scanning is almost certainly less sensitive in early prodromal stages[53]; therefore, $LR^-$ was adjusted to reflect the entire 10-year prodromal period.

- $LR^+$ 40, $LR^-$ 0.65

## Combining LR and Prior Probability to Estimate Probability of Prodromal PD

Once all relevant information is obtained, LRs can then be multiplied together to generate a total LR of prodromal PD for an individual patient. Both $LR^+$ and $LR^-$ should be combined. Effort should be made to collect all available info (e.g., sex should always be added to the model, and easily assessed factors such as smoking/constipation should be available in the large majority of patients). However, if no information for a prodromal marker is present, it is not added to the equation. The final estimate is generated by multiplying all available LRs by one another to generate a "total" LR. This total LR now can be combined with baseline probability to calculate the final post-test probability for the individual.

To meet the probability threshold of 80% for probable prodromal PD, the approximate minimum required total LR is:

1000 from ages 50 to 54;
515 from ages 55 to 59;
300 from ages 60 to 64;
180 from ages 65 to 69;
155 from ages 70 to 74;
110 from ages 75 to 79; and
95 age 80 and over.

Example 1: A 62-year-old man with occupational pesticide exposure, drinks coffee, and was never a regular smoker. He has idiopathic RBD, olfactory loss, no constipation, no depression or anxiety, and no daytime somnolence. Quantitative motor testing was in the borderline/low-normal range (no expert examination available). One would then calculate as follows:

Step 1: Establish the prior from the table = 1.25%
Step 2: Calculate total LR = 1.2 (male) × 1.5 (pesticide) × 0.88 (coffee) × 1.25 (nonsmoker) × 130 (RBD) × 4.0 (olfaction) × 0.8 (no constipation) × 0.85 (no depression or anxiety), 0.88 (no somnolence) × 1.0 (borderline motor testing – result omitted) = 616.
Step 3: Calculate post-test probability, using one of two methods:

a. Make an exact quantitative probability calculation using calculators. Result = 89%, or
b. From Table 2, LR must be 300. Actual LR >300, so patient meets criteria for probable prodromal PD.

Example 2: A 67-year-old female recruited from an epidemiological study who had occupational pesticide exposure on a farm, drinks coffee, but never smoked. Her brother had PD with onset age 65. She endorses constipation, urinary dysfunction, and has olfactory

**TABLE 2.** Previous probability and required LR for prodromal PD

| Age | Prior Probability (%) | LR for Probable Prodromal PD |
|---|---|---|
| 50–54 | 0.4 | 1,000 |
| 55–59 | 0.75 | 515 |
| 60–64 | 1.25 | 300 |
| 65–69 | 2.0 | 180 |
| 70–74 | 2.5 | 155 |
| 75–79 | 3.5 | 110 |
| ≧80 | 4.0 | 95 |

loss on examination. There is no somnolence or depression/anxiety. Motor examination and other testing have not been performed.

Step 1: Establish the prior from the table (age 67) = 2.0%

Step 2: Calculate total LR = 0.8 (female) × 1.5 (pesticide) × 0.88 (coffee) × 1.25 (nonsmoker) × 2.5 (family history) × 2.2 (constipation) × 1.9 (urinary dysfunction) × 4.0 (olfactory loss) × 0.85 (depression) × 0.88 (somnolence) = 41.3.

Step 3: Calculate post-test probability, using one of two methods:

a. Make an exact quantitative probability calculation using calculators. Result = 46%, or
b. From Table 2, patient does not meet criteria for probable prodromal PD (<180).

Note that addition of missing info could refine diagnosis considerably. For example, if based upon these findings, a neurologist examination was arranged that disclosed an MDS-UPDRS of 9 (excluding action tremor and without evident confounds), LR rises to 413, and patient meets criteria for probable prodromal PD. If that examination is normal, LR drops to 29.

## Ethical Issues

In applying these criteria to an individual patient, caution must prevail. There are important reasons to disclose a diagnosis of prodromal disease, including patient autonomy (all patients have a right to understand their condition), and beneficence (diagnosing early disease stages can facilitate prompt treatment of motor and nonmotor symptoms). However, in the absence of neuroprotective therapy for PD, beneficence is relatively modest, and there is potential for harm (i.e., learning about a prodromal stage of disease is distressing and can cause discrimination regarding work, insurability, and so on). These issues are especially critical in patients who have not sought medical attention for their symptoms (e.g., patients screened from the general population). The task force cannot specifically prescribe the way these criteria are applied or disclosed, but urges full consideration of these issues when discussing findings with patients.

## Limitations

One of the most obvious limitations of these criteria is the quality of the underlying data; there are a limited number of prospective studies that have analyzed markers before patients develop PD. Because most studies have relatively few de novo PD patients, confidence intervals are wide. We generally followed point estimates as published in prospective studies; however, evidence for each marker is quite variable in strength. Obviously, as new information becomes available, these criteria should be updated. In most cases, this can be done within the framework already created.

Another critical caveat is that markers cannot be combined if they are not independent. For example, if every person in the population with constipation also has olfactory loss (and vice versa), then no new information is gained by identifying both factors. Multiplying their LRs together would then overestimate disease risk. Unfortunately, it is impossible to determine whether many markers are truly independent. A recent study suggested independence of some key markers in the general population.[54] Also, we used clinical judgment in consideration of potential dependence; for example, it is difficult to think of a highly prevalent underlying pathology other than prodromal PD in which a person would have combined olfactory loss, constipation, and elevated UPDRS. In situations in which markers were likely correlated, they were combined into one criterion (e.g., quantitative motor tests were combined into one category; olfactory discrimination, threshold, and identification were considered as one category). Regardless of these steps, some dependence remains possible, and so some patients determined as >80% likely prodromal PD (i.e., probable) might actually have a lower probability.

Another limitation is that the duration of prodromal PD is unknown. Some studies in cohorts (e.g., RBD cohorts) have clearly documented prodromal durations of >20 years in duration.[14] However, some patients may have considerably shorter prodromal intervals. Based upon an overall assessment of the literature, we posited an average prodromal period of 10 years, but this was extremely subjective; the true value may differ considerably. Also, individual prodromal markers have different lead times, with predictive strength that varies according to interval. For example, motor abnormalities may be strongly predictive of PD over the subsequent 3 years, but may not predict disease well after 10 years (if a person has a motor abnormality for >10 years without developing parkinsonism, an alternate explanation may be more likely). For this reason, individual evaluators can elect to not include a marker that appears to have another explanation, or which occurs in a manner or time course inconsistent with prodromal PD. Normally, specificity is a time-independent feature of a test. However, short-duration studies, in which many test-positive/disease-negative participants would have

continued to develop disease, can underestimate specificity. This can be especially problematic when testing markers in high-risk groups. Using high-risk may also underestimate $LR^+$; because the prevalence of the marker is higher, specificity estimates are biased downward. We adjusted for this in our analysis, but this required making assumptions about disease risk in the non-high-risk population and, in some cases, about the proportion of the population in the high-risk group, adding additional uncertainty to the estimates. Also, the significance of a negative test ($LR^-$) is less for a marker that becomes abnormal only very soon before disease onset; so, combining early markers and late markers can be problematic. In general, it becomes easier to diagnose prodromal PD close to clinical PD onset, given that many later markers will not be present in early prodromal stages. We adjusted for this effect in some cases; when evidence was very strong that the marker is insensitive in early prodromal stages (i.e., motor markers[50] and dopaminergic PET/single-photon emission computed tomography [SPECT][53]), we revised sensitivity estimates downward. However, this was subjective and imprecise. Given this sensitivity issue, if late prodromal markers are borderline/low normal, examiners may elect to not apply $LR^-$. The criteria aimed to assess the probability of prodromal disease being present, not when the patient might develop full motor PD. With more information, it may be possible to identify sets of markers for early versus later prodromal phases and/or sets of markers for progression between these phases. Also, the LR of individual markers may change according to age, sex, and so on. For many markers, there are no clear cutoffs for what is considered an abnormal test; we generally reported findings directly from the article, using the cutoffs delineated by the researchers. Obviously, if cutoffs vary, so will LR, and so it is essential to use well-validated markers whenever available. These criteria generally require patients to have had a relatively thorough evaluation of markers for prodromal PD. If information on markers is unavailable, it will be difficult to meet the threshold for prodromal PD (although the likelihood estimate is not biased in one direction or the other if there is missing information). Finally, it is difficult to distinguish what is a prodromal marker and what is a risk marker, a limitation that is mitigated here by treating prodromal and risk markers similarly. For all of these reasons, further validation of the model will be essential.

Regardless of these limitations, the task force considered that the advantages of using a data-driven approach outweighed the limitations and was superior to other approaches (e.g., expert opinion). Critically, this proposed methodology can be applied for all types of markers (clinical, genetic, neuroimaging, and so on) and provides a scaffold for future revisions, allowing new factors to be added as new findings are reported. The field of prodromal PD is in its relative infancy; many prodromal markers remain to be discovered, and the precise predictive value of each marker remains partially defined. Given that new markers or more-accurate LR ratio estimations become available, criteria should be continuously updated. ■

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