

REVIEW

Update of the MDS Research Criteria for Prodromal Parkinson's Disease

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ABSTRACT: The *MDS Research Criteria for Prodromal PD* allow the diagnosis of prodromal Parkinson's disease using an evidence-based conceptual framework, which was designed to be updated as new evidence becomes available. New prospective evidence of predictive values of risk and prodromal markers published since 2015 was reviewed and integrated into the criteria. Many of the predictive values (likelihood ratios, LR) remain unchanged. The positive likelihood ratio notably increase for olfactory loss and decreased for substantia nigra hyperechogenicity. Negative likelihood ratio remained largely unchanged for all markers. New levels of diagnostic certainty for neurogenic and symptomatic orthostatic hypotension have been added, which substantially differ in positive likelihood ratio from the original publication. For intermediate strength genetic variants, their age-related penetrance is now incorporated in the calculation of the positive likelihood ratio. Moreover, apart

from prospective studies, evidence from cross-sectional case-control genome-wide association studies is also considered (given their likely lack of confounding and reverse causation), and to account for the effect of multiple low-penetrance genetic variants polygenic risk scores are added to the model. Diabetes, global cognitive deficit, physical inactivity, and low plasma urate levels in men enter the criteria as new markers. A web-based prodromal PD risk calculator allows the calculation of probabilities of prodromal PD for individuals. Several promising candidate markers may improve the diagnostic accuracy of prodromal PD in the future. © 2019 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; prodromal; evidence-based; Bayesian classifier; risk marker

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The *MDS Research Criteria for Prodromal PD*,¹ published in 2015, provides an evidence-based methodological framework to statistically estimate the likelihood that an individual has prodromal PD. It uses a naive Bayesian classifier approach and considers age (as “prior” probability of prodromal PD) and predictive information from risk and prodromal markers. The criteria have now been validated in prospective cohort studies of the general population,² REM sleep behavior disorder (RBD) patients,³ and *LRRK2* mutation carriers.⁴ These studies show relatively high specificity and positive predictive values for conversion from probable prodromal PD to clinical PD, with variable sensitivity of detecting prodromal PD that depends on the depth of marker assessment and the time from marker assessments to PD diagnosis.⁵ To improve the accuracy of prodromal PD diagnosis, the framework was designed to integrate new prospective

evidence of predictive values of prodromal and risk markers. Because of the rapidly evolving field of prodromal PD research, the diagnostic criteria need to be continually updated. Here we present the first *Update of the MDS Research Criteria for Prodromal PD* that incorporates evidence published after the original presentation. The new markers and updated predictive values largely confirm the concept of prodromal PD and may increase the diagnostic accuracy of prodromal PD.

Selection of Markers

Evidence from prospective studies of risk and prodromal markers newly published since the first criteria in 2015 were identified based on a literature review using a step-wise approach: (1) PubMed searches, (2) supplemented by review of reference lists of articles, and (3) suggestions by experts; for more information, see Supporting Methods. Markers not included previously entered the revised criteria if evidence from 2 prospective studies was now available. The median positive likelihood ratio (LR+) and median negative likelihood ratio (LR-) of all available evidence of a respective marker was used as the revised predictive value. One newly introduced exception of this inclusion criterion concerns evidence from cross-sectional case-control genome-wide association studies. Associations of genetic variants with PD likely lack confounding with other factors and reverse causation, which for other markers may compromise the interpretation of effects and quality of evidence. Therefore, evidence from cross-sectional case-control genome-wide association studies of genetic PD risk factors also is considered.

New Evidence and Revision of LRs

The revised marker LRs and newly added markers are provided in Table 1 and Table 2. For detailed calculations, see the Supporting Methods section, and for a comprehensive overview of marker evidence, see Supporting Information Table S1, S2, and S3.

For most risk and prodromal markers included in the previous version, new evidence allowed the revision of positive and negative likelihood ratio (LR) estimates (see Table 1, and Supporting Information). Abnormal dopaminergic PET/SPECT scan (43.3, previously 40.0) and olfactory loss (6.4, previous 4.0) have substantial increases in LR+ relative to their previous value, as new evidence is considered. Modest increases in LR+ are observed for possible RBD (questionnaire-based; LR+ = 2.8, previous = 2.3), constipation (2.5, previous = 2.2), excessive daytime somnolence (2.7, previous = 2.2), symptomatic hypotension (3.2, previous = 2.1), and erectile dysfunction (3.4, previous = 2.0). Relative decreases in LR+ are calculated for: substantia nigra (SN) hyperechogenicity (3.4, previous = 4.7), subthreshold parkinsonism on expert examination/

(MDS-)UPDRS-III (9.6, previous = 10.0), and depression, with/without anxiety (1.6, previous = 1.8). LR- only changed slightly for all markers.

For risk markers of male sex, regular pesticide and occupational solvent exposure, and nonuse of caffeine, no new prospective evidence has, to our knowledge, been published that would have changed their LRs.

Moreover, new prospective evidence allows for differentiation of neurogenic and symptomatic orthostatic hypotension (OH). Neurogenic OH refers to clinically diagnosed OH with confirmation based on quantitative assessments of supine/sitting and standing blood pressure drop with alternative causes of OH (dehydration, cardiac disease, autonomic neuropathy, medication, etc.) eliminated after comprehensive clinical assessment. Symptomatic OH is based on clinical OH diagnosis or a positive orthostatic hypotension questionnaire without comprehensive diagnostic investigation regarding the cause. Neurogenic OH is LR+ = 18.5, LR- = 0.88; symptomatic OH is LR+ = 3.2, LR- = 0.80.

Genetic Risk Markers

Individuals with rare high-penetrance genetic mutations or duplications/triplications with dominant (SNCA, VPS35) or recessive (parkin, PINK1, DJ1) inheritance (for an overview, see Supporting Table S2) are considered to form distinct subgroups of (prodromal) monogenetic PD. Their prodromal characteristics are likely to differ from sporadic cases, and for high-penetrance gene mutation carriers the criteria should not be applied.

For intermediate-strength genetic factors, such as mutations in *GBA* and *LRRK2*, the (prodromal) PD risk is age dependent. Therefore, the LR+ of these risk factors is estimated based on the age-related penetrance of the particular mutation and the age-related PD risk in the general population (see Table 2).^{6,7} For instance, the cumulative PD risk of a *GBA* mutation carrier is ~18% at 65 years of age but only 2% in the general population. Using these risk values as estimates of sensitivity and specificity of the marker, the LR+ can be calculated (LR+ = 9). In the absence of a genetic marker no LR- is applied — LR- = NA.

For common genetic risk- and protective genetic variants of low individual effect strength, their cumulative predictive effect is considered in the criteria. In the latest meta-analysis of genome-wide association studies, more than 80 of those risk loci have been identified.⁸ Depending on the number of risks increasing or decreasing variants, a polygenic risk score (PRS) can be calculated (without considering mutations with high/intermediate penetrance). Individuals in the quartile with the highest PRS have a 3.51-fold increased risk of PD compared with those in the lowest quartile.⁸ For large samples with genetic panel data a PRS can be calculated, and based on the sample-specific PRS distribution, cutoff values of quartiles can be determined. LR+ should be

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	NA
	Occupational solvent exposure	1.5	NA
	Nonuse of caffeine	1.35	0.88
	Nonsmoking		
	Current smoker	NA	0.51
	Never smoker	1.2	NA
	Former smoker	NA	0.91
	First-degree relative with PD	2.5	NA
	or	LR+ dependent on age-related penetrance, see Table 2	NA
	Known gene mutation (with intermediate-strength penetrance)		
	or	1.57 (highest quartile of PRS scores)	0.45 (lowest quartile)
	Polygenic risk score (PRS)		
	SN hyperechogenicity	3.4	0.38
Prodromal markers	Diabetes mellitus (type II)	1.5	0.97
	Physical inactivity	1.3	0.91
	Low plasma urate levels	1.8 (in men)	0.88 (in men)
	PSG-proven RBD	130	0.65
	Possible RBD (questionnaire)	2.8	0.89
	Dopaminergic PET/SPECT clearly abnormal (eg, <65% normal, 2 SDs below mean)	43.3	0.66
	Subthreshold parkinsonism (UPDRS-III >3 excluding action tremor or MDS-UPDRS-III >6 excluding postural and action tremor)	9.6	0.55
	or	3.5	0.60
	Abnormal quantitative motor testing		
	Olfactory loss	6.4	0.40
	Constipation	2.5	0.82
	Excessive daytime somnolence	2.7	0.86
	Orthostatic hypotension (OH) – neurogenic OH	18.5	0.88
	Symptomatic OH	3.2	0.80
	Erectile dysfunction	3.4 (in men)	0.87 (in men)
	Urinary dysfunction	2.0	0.90
	Depression (\pm anxiety)	1.6	0.88
Global cognitive deficit	1.8	0.88	

NA, not applicable.

TABLE 2. Age-related penetrance of intermediate-strength genetic mutations

Age groups (years)	PD risk at different ages				
	Noncarriers	<i>GBA</i> mutation carriers ⁶ (eg, N370S, L444P)	<i>GBA</i> : LR+	<i>LRRK2</i> mutation carriers ⁷ (p.G2019S)	<i>LRRK2</i> : LR+
50–54	0.4%	8%	20.0	~1%	2.5
55–59	0.75%	11%	14.7	3%	4.0
60–64	1.25%	14%	11.2	7%	5.6
65–69	2.0%	18%	9.0	15%	7.5
70–74	2.5%	21%	8.4	29%	11.6
75–79	3.5%	25%	7.1	32%	9.1
80+	4%	30%	7.5	42%	10.5

applied to individuals in the highest PRS quartile, and LR– to individuals in the lowest quartile. Those in the middle 2 quartiles are considered intermediate or borderline (LR = 1) — LR+ = 1.57, LR– = 0.45 — see Supporting Table S3.

Alternatively, in the absence of a defined genetic abnormality, a positive family history of PD can be considered

a genetic risk marker (note that one should not combine genetic findings as outlined above with family history). When a sibling or parent of an individual has been diagnosed with PD, an OR of 2–3.5 is estimated,^{9,10} and an LR+ = 2.5 is considered. In the previous criteria, individuals with a sibling diagnosed with early-onset (<50 years)

PD were considered at higher PD risk ($LR+ = 7.5$). However, as these individuals would likely be recessively inherited PD cases¹¹ with an onset before the age range for prodromal criteria (ie, <50 years), we now consider all positive family history as $LR+ = 2.5$.

Newly Added Markers

1. Diabetes mellitus (type II) has been shown to be associated with PD risk in multiple population-based prospective studies.¹²⁻¹⁴ The collective evidence of diabetes as PD risk marker results in $LR+ = 1.5$ and $LR- = 0.97$.

2. Cognitive deficits have been shown to be associated with increased PD risk in 2 prospective studies investigating global cognition¹⁵ and cognitive decline.¹⁶ In a third study, global cognition was numerically but not statistically worse in hyposmics with incident PD compared with those who remained PD free.¹⁷ Based on those studies, the prodromal marker of (global) cognitive deficits has $LR+ = 1.8$ and $LR- = 0.88$.

3. Physical activity is associated with a lower risk for PD (relative risk, 0.79; 95% CI, 0.68-0.91) in a recent meta-analysis¹⁸ of 8 prospective studies.¹⁹⁻²⁵ Conversely, physical inactivity can be considered as a risk (or prodromal) marker. Based on 2 high-quality population-based studies, the LRs of physical inactivity could be calculated: $LR+ = 1.3$, $LR- = 0.91$. For purposes of the criteria, low physical activity is defined as less than 1 hour per week of activity causing increased respiratory or heart rate or sweating.

4. Low plasma urate levels in men have repeatedly been shown to be associated with higher PD risk in large prospective studies,²⁶⁻²⁸ although it remains unclear if the association is causal.²⁹ Low urate plasma levels (<5 mg/dL) and high levels (>5.6 mg/dL), but not borderline levels (5–5.5 mg/dL), are considered in the criteria. Three prospective studies²⁶⁻²⁸ provided data that allowed LR calculations: $LR+ = 1.8$, $LR- = 0.88$ in men (in women: $LR = 1$).

Promising Candidate Markers

Several innovative markers with compelling and pathophysiologically plausible evidence have been published, which further support the concept of prodromal PD. However, because of the lack of prospective studies, the following promising candidate markers are not yet added to the criteria. Those of particular interest include:

1. *Tissue biopsy*: Phosphorylated α -synuclein in skin biopsy has been shown to be sensitive (55%–100%) as well as highly specific (>90%) for PD and prodromal PD (idiopathic RBD).³⁰⁻³² Similarly, biopsy of the submandibular gland shows considerable promise.³³ However, sensitivity of this marker depends on the

number and location of tissue samples³⁴; specificity may vary between biopsy techniques, and prospective studies proving predictive value are still lacking.

2. *(Neuro)imaging*: Several imaging approaches have potential as sensitive and specific markers of prodromal PD as suggested by associations with RBD, *GBA/LRRK2* mutation carriers, Dementia with Lewy Bodies, and PD.³⁵ Promising techniques include ¹¹C-donepezil PET/CT (cholinergic (parasympathetic) gut innervation), ¹²³I-metaiodobenzylguanidine scintigraphy (cardiac sympathetic denervation),³⁶ susceptibility-weighted and neuromelanin-sensitive MRI (dorsal nigral hyperintensity; integrity of pigmented neurons of the locus coeruleus), ¹¹C-methylreboxetine PET (noradrenergic nerve terminals originating in the locus coeruleus), structural connectivity and functional MRI (striatal or whole-brain function).^{35,37-39} However, for the establishment of prodromal (neuro)imaging markers consensus on specific methods and analyses is needed.
3. *Continuous monitoring*: Technological advances in wearable or smartphone-based sensor technologies have been considerable. Such objective markers might be predictive as well as sensitive to subtle progressive prodromal changes. However, sensor-based quantitative motor^{40,41} and nonmotor markers (eg, cardiac/autonomous dysfunction) in (prodromal) PD⁴¹⁻⁴³ require further prospective evidence and standardization of methods.
4. *Subjective symptoms*: Subjective self-reported symptoms may complement objectively assessed signs in the diagnosis of prodromal PD. Subjective motor complaints have been shown to predict PD,⁴⁴ and self-reported olfactory loss, impaired posture, and gait difficulties have been shown to be sensitive yet less specific prodromal markers because of confounding with depression and cognitive impairment.⁴⁵ Comprehensive time- and cost-efficient self-report tools should be established for large-scale screening for prodromal PD.
5. *Other environmental factors*: Environmental risk factors, such as dietary factors,^{46,47} metal exposure,⁴⁸ and illicit drug use⁴⁹ have been associated with parkinsonism and may aid with PD prediction. However, marker definitions are often inconsistent, and predictive effects may not be independent. Specific pharmacological medical treatments have been associated with PD risk, for example, ibuprofen,⁵⁰ urate-lowering medication,⁵¹ asthma treatment (β -adrenoreceptor agonists),⁵² beta-blockers (β -adrenoreceptor antagonists),⁵² and statins.⁵³ However, more research and independent replications, as well as consideration of confounding (particularly confounding by indication), are needed to evaluate the potential of medication as protective or risk markers in PD.
6. *Gene-environment interactions*: Some evidence suggests that gene-environment interactions may

modulate the effects of risk factors, such as pesticide exposure,⁵⁴ smoking,⁵⁵ or head injury.⁵⁶ For preventive endeavors in public health and improvement of the accuracy of prodromal PD diagnosis, gene-environment interactions should be investigated further.

- Inflammatory bowel disease (IBD) has been associated with increased PD risk^{57,58}; however, potential biases of analyses such as surveillance bias⁵⁹ require further investigation of IBD as a PD risk marker. In addition to IBD, inflammatory markers as well as (microbial) gut function in prodromal PD may constitute promising markers and avenues of prodromal PD research.

The MDS Webportal for Prodromal PD Research

As continual update of the prodromal criteria is needed, an MDS Webportal has been designed to foster prodromal PD research by providing a practical calculator of prodromal PD probabilities, applying the most recent criteria (www.movementdisorders.org/pdcalculator). A comment section will also provide the opportunity for researchers to post new evidence and remarks to be considered in further updates of the criteria.

Update of the MDS Research Criteria for Prodromal PD

Here we provide the first update of the *MDS Research Criteria for Prodromal PD* with several key revisions. In addition to updating predictive values of most markers, 4 new risk and prodromal markers enter the criteria. Moreover, to account for differences in marker assessment techniques, certainty categories of symptomatic orthostatic hypotension are newly included. For genetic markers differentiated approaches for considering intermediate-strength genes (based on age-related penetrance) and common low-penetrance variants (based on polygenic risk scores) are newly introduced. Importantly, the presented criteria are still, at this stage, for research purposes only. Further collaborative research across scientific and medical disciplines, methodological and technical advances, and increased societal and political awareness of prodromal PD are needed.

As in the original criteria, several limitations and methodological aspects should be emphasized. First, the individual longitudinal studies have variable strengths and limitations,⁶⁰ yet the criteria largely do not weigh or prioritize evidence based on study characteristics nor do they consider the uncertainties of marker estimates. Data quality of markers (and their sensitivity and specificity) may

partly depend on assessment methods used, and the criteria and certainties of PD diagnosis may vary between studies (eg, register studies using medical record data).

Second, independence of several risk and prodromal markers, a prerequisite for naive Bayesian classifiers, has been shown.⁶¹ However, depression has been shown to be associated with other (self-reported) prodromal markers.^{45,62} The newly introduced markers of diabetes, physical inactivity, and cognitive deficits may, in some individuals, be causally linked to each other. Markers may co-occur because of a common pathological process, for example, in RBD or hyposmics other risk and prodromal markers may be more frequently observed than in the general population. Thus, marker independence might be violated, and for certain marker constellations, prodromal PD probabilities would be either over- or underestimated.

Third, LRs are applied equally to all individuals, but the LR of many single markers likely differs depending on ethnicity⁶³ and according to age and/or sex.⁶⁴ For example, markedly higher LR+ of subthreshold parkinsonism has been observed in younger individuals,⁶⁴ diabetes is associated with higher PD risk specifically in younger diabetics,¹⁴ and olfactory loss is associated with higher relative risk in men than women and in white compared with black individuals.⁶³ Further investigation of marker clustering and interactions with variables such as ethnicity,⁶³ age, and sex⁶⁴ might improve the diagnostic accuracy of prodromal PD.

Finally, clinical PD is a heterogeneous and complex disease with many different possible etiologies.⁶⁵ For example, some evidence suggests that the presence of RBD, orthostatic hypotension, and cognitive deficits is associated with a more malignant PD phenotype, which will likely have a different prodromal state.⁶⁶ Similarly, patients with *LRRK2* mutations often have prominent prodromal gait deficits,⁴⁰ and *LRRK2* carriers with synuclein pathology exhibit more cognitive impairment, anxiety, and orthostatic hypotension than those without.⁶⁷ Heterogeneity of prodromal states should be further investigated and may be important for targeted trial recruitment.⁶⁸

In summary, this *Update of the MDS Research Criteria for Prodromal PD* aims to encourage further research in prodromal PD, in particular, regarding prospective studies of promising candidate markers. Further validation and testing of the criteria and future revisions will be needed to continually improve the diagnostic sensitivity and specificity of the criteria. ■

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Supporting Data

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