American College of Medical Genetics and Genomics (ACMG) criteria.

Patient 2 is a 14-year-old male and the only child of healthy parents. At 3 years of age, he displayed isolated dysarthria because of oromandibular dystonia; an expressive language disorder was initially diagnosed. By 9 years of age writing dystonia and abnormal postures of neck and trunk become evident. At 13 years of age, on examination, he exhibited segmental dystonia with prominent cranial and cervical involvement and normal cognitive function. Treatment with anticholinergic (trihexyphenidyl 18 mg/day) resulted in mild improvement with no side effects. A concomitant brain MRI showed bilateral pallidal hypointensity on T2-weighted images, and a brain CT scan excluded intracranial calcifications (Fig. 1). Sanger sequencing of the *THAP1* gene disclosed an in-frame deletion (c.207_209delCAA; p.Asn69del) inherited from the asymptomatic mother, confirming the clinical suspicious of DYT6. This variant, classified as supporting/moderate pathogenesis (PM2-PP5) according to ACMG criteria, was previously found in 3 related and 2 unrelated patients with childhood- or adolescent-onset dystonia initially affecting the cervical muscles or the upper limbs; generalization of dystonia was reported in 4.[2,3] One adult patient exhibited generalized chorea induced by trihexyphenidyl that persisted after drug withdrawal.[3]

In accordance with the neuroradiological finding, pathogenic variants in NBIA-associated genes (*PLA2G6, PANK2, FTL, WDR45, COASY, C19orf12, FA2H*) and *KMT2B* were excluded in both patients.

Globus pallidus T2 hypointensities are the radiological hallmark of NBIA and reflects the accumulation of iron in the basal ganglia.[4] Currently, 10 genes have been associated with NBIA (*ATP13A2*, *C19orf12*, *COASY*, *CP*, *DCAF17*, *FA2H*, *FTL*, *PANK2*, *PLA2G6*, and *WDR45*), but MRI findings resembling NBIA have been described in other conditions.[5] Brain MRI is usually unrevealing in isolated monogenic dystonia, except for *KMT2B*-related dystonia (DYT28); specifically, approximately 25% of reported cases revealed abnormalities ranging from subtle and symmetric hypointense lateral streaks in the external globus pallidus to NBIA features.[6,7] Our findings expand the radiological spectrum associated with *DYT6* dystonia and advise including this condition with NBIA imitators.

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Application of the Updated Movement Disorder Society Criteria for Prodromal Parkinson's Disease to a Population-Based 10-Year Study

In 2015, a Task Force of the Movement Disorder Society (MDS) proposed evidence-based, probabilistic research diagnostic criteria for prodromal Parkinson's disease (PD).[1] Studies that applied the criteria to existing longitudinal population-based cohorts, including our own evaluation in the Bruneck Study, consistently report high specificity and negative predictive values (NPV).[2-4] However, sensitivity and positive predictive values (PPV) varied substantially

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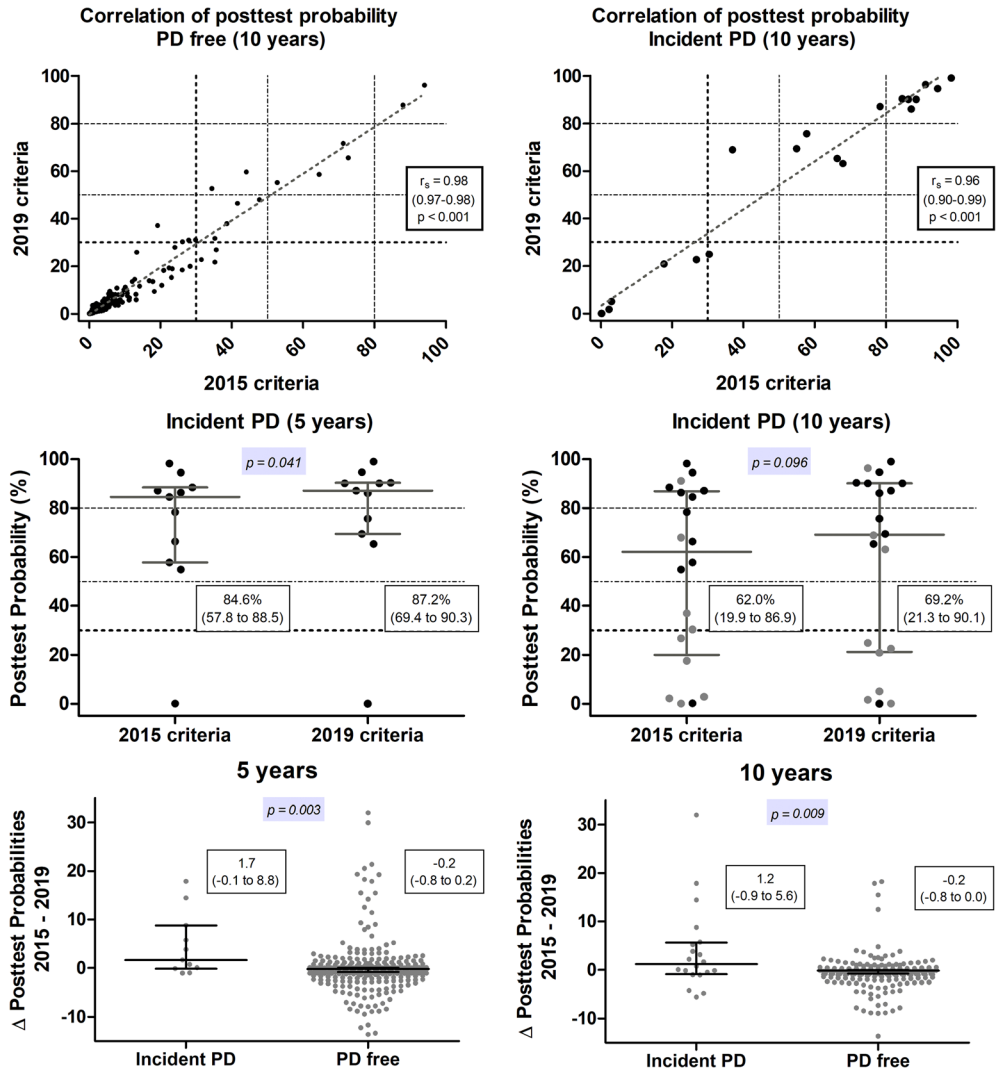

FIG. 1. Upper row: scatterplot and Spearman rank correlation analyses with original probabilities (2015 criteria) plotted on the x-axis and updated probabilities (2019 criteria) on the y-axis. Numbers in parentheses indicate 95% confidence intervals. The upper dashed lines represent the 80% probability cutoff for probable prodromal Parkinson's disease (PD) as defined per Movement Disorder Society (MDS) research criteria, the middle dash-dotted and the lower dotted lines represent 50% and 30% probability cutoffs, also mentioned by the MDS Task Force.[1,7] Middle row: scatterplots of the absolute baseline posttest probability for prodromal PD, illustrated for cumulative cases with incident PD at 5-year and 10-year follow-ups. Incident cases at respective follow-ups are shown in black and incident cases from previous follow-ups in are shown in lighter gray. The resulting predictive accuracy measures are given in Table S2. Lower row: scatterplots of the relative change in posttest probabilities with the two criteria versions (probability according to updated criteria minus probability according to original criteria) in the various groups. In the middle and lower rows, single values are given with the respective group median (25^{th} to 75^{th} percentiles) and p-values were calculated with the paired Wilcoxon signed-rank test (middle row) or Mann-Whitney U test (lower row). [Color figure can be viewed at wileyonlinelibrary.com]

dependent on the type of study population (enriched risk vs. population-based), depth of marker assessment, and length of follow-up time. In 2019, a first update of the criteria was presented,[5] which incorporated new evidence for risk and prodromal markers. It adapted likelihood ratios (LRs) for markers already included and supplemented them with four new markers.

We have now applied the updated criteria to the Bruneck Study cohort and assessed differences in original versus updated probabilities for prodromal PD within and across groups. Detailed information on the study population, design, and assessments including the application of the original criteria for prodromal PD was published previously[3,6] and is additionally outlined in the Appendix. In brief, 539 participants without PD or secondary parkinsonism at baseline in 2005 (55–94 years; 290 females) were reassessed after 5.0 (range: 4.9–5.0) and 10.4 (10.4–10.5) years for incident PD.[3] Baseline probabilities were modeled retrospectively including 16 of the 18 risk and prodromal markers originally included by the MDS Task Force.[1] For the present updated analysis, all four newly included markers[5] were available and integrated into the algorithm: type 2 diabetes mellitus (clinical diagnosis, antidiabetic medication, and/or glycated hemoglobin [HbA1c] values >6.4%), physical inactivity (according to the Baecke physical activity questionnaire), low plasma urate in men, and global cognitive deficit (Mini-Mental State Examination [MMSE] <25/30 points).

While median baseline probabilities for prodromal PD decreased from 2.4% (25^{th}–75^{th} percentile: 0.6%–8.7%) using original criteria to 1.8% (0.4%–8.1%; $P < 0.001$) with

updated criteria, 12 participants met the ≥80% probability threshold for probable prodromal PD using original criteria as compared with 16 using updated criteria. A correlation analysis between original probabilities and updated probabilities is presented in upper row of Fig. 1. Updated probabilities in participants with incident PD were higher than the original ones (Fig. 1, middle row), while in participants who remained free of PD during follow-up, updated probabilities were lower than the original ones ($P < 0.001$; Table S1). However, these significant divergent changes (Fig. 1, lower row) did not translate into higher predictive accuracies of the updated criteria for incident PD in our sample, as in absolute numbers only a few participants with incident PD were reclassified (Tables S1 and S2).

In summary, we previously reported our findings of the original criteria in the unselected population-based Bruneck Study cohort showing a moderate to high predictive accuracy in identifying cases of incident PD over up to 10 years of follow-up.[3] Predictive accuracy did not change when using the updated criteria, probably due to the low sample size and thus low number of converters despite the long follow-up time. Nevertheless, the updated MDS criteria were superior to the original MDS criteria with regard to separating individuals with low and high probabilities likely indicating presence of prodromal PD. Therefore, together with one other study published to date that has applied the updated criteria,[4] our findings speak to the MDS Task Force Bayesian classifier methodology that allows for sequential inclusion of new markers as they become available. The results of the present study should be confirmed by larger prospective population-based studies, which should include markers with high LR.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Phenoconversion from Possible REM Sleep Behavior to Parkinsonism in the Population-Based CLSA

Rapid eye movement sleep behavior disorder (RBD) is a strong prodromal marker of synucleinopathy. No population-based studies have estimated to what degree questionnaire-screened RBD (possible RBD) is associated with risk of future diagnosis of parkinsonism.

We analyzed the 30,097-person comprehensive subset of the Canadian Longitudinal Study on Aging (CLSA), a population-based cohort of adults age 45 to 85 recruited between 2012 to 2015.[1] Those with self-reported diagnosis of parkinsonism or dementia at baseline were excluded. Dream enactment behavior/possible RBD (DEB/pRBD) at baseline was defined as a positive response to the single-question RBD-1Q during the

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