

Supplementary Table 1. NSD Staging Criteria*

	Biologic anchors			Anchors of clinical signs or symptoms (stages 2A and 2B) and functional impairment (stages 3-6) ^{1,2}	
Stage	S	D ^a	G	Domain	Anchor(s)
Stage 0	-	-	<i>SNCA</i> ^b	—	—
Stage 1A	+	-	±	(1) Cognitive	(1) MDS-UPDRS item 1.1 = 0; and (2a) Does not have subthreshold parkinsonism ^c ; and (2b) is not on PD meds; and (3a) Does not have RBD; and (3b) is not hyposmic ^d
Stage 1B	+	+	±	(2) Motor (3) Other non-motor	
Stage 2A	+	-	±	(1) Cognitive	(1) Item 1.1 = 1 AND MoCA ≥ 25; or (2a) Has subthreshold parkinsonism ^c ; or (2b) is on PD meds ^e ; or (3a) Has RBD; or (3b) is hyposmic ^d
Stage 2B	+	+	±	(2) Motor (3) Other non-motor	
Stage 3	+	+	±	(1) Cognitive (2) Motor	(1a) Item 1.1 = 1 AND MoCA ≤ 24; or (1b) Item 1.1 = 2 AND MoCA ≥ 25; or (2) MDS-UPDRS-II = 3-13 AND either subthreshold parkinsonism ^c or PD meds ^e
Stage 4	+	+	±	(1) Cognitive (2) Motor (3) Other non-motor	(1a) Item 1.1 = 2 and MoCA ≤ 24; or (1b) item 1.1 = 3 AND MoCA ≥ 25; or (2) MDS-UPDRS-II = 14-26; or (3) MDS-UPDRS-I (excluding item 1.1) = 13-24 ^f
Stage 5	+	+	±	(1) Cognitive (2) Motor (3) Other non-motor	(1a) Item 1.1 = 3 AND MoCA ≤ 24; or (1b) item 1.1 = 4 AND MoCA ≥ 25; or (2) MDS-UPDRS-II = 27-39; or (3) MDS-UPDRS-I (excluding item 1.1) = 25-36
Stage 6	+	+	±	(1) Cognitive (2) Motor (3) Other non-motor	(1) Item 1.1 = 4 AND MoCA ≤ 24; or (2) MDS-UPDRS-II ≥ 40; or (3) MDS-UPDRS-I (excluding item 1.1) ≥ 37

* Adapted from: Simuni T, Chahine LM, Poston K, et al. A biological definition of neuronal alpha-synuclein disease: towards an integrated staging system for research. *Lancet Neurol.* 2024 Feb;23(2):178-90.

¹ Presence of qualifying signs/ symptoms in any single domain qualifies for stage 2 but individuals can have combination in all 3 domains.

² Presence of qualifying functional impairment in any single domain qualifies for stage 3-6 but individuals can have combination in all 3 domains.

^a D positivity defined as < 75% age/sex-expected lowest putamen SBR.

^b Only fully penetrant pathogenic *SNCA* variants qualify for Stage 0.

^c Subthreshold parkinsonism defined as MDS-UPDRS-III ≥ 5 excluding postural and action tremor.

^d Hyposmia defined as UPSIT percentile ≤ 15 (age and sex adjusted).

^e Presence of PD medication is determined by the MDS-UPDRS Item III question 3a.

^f MDS-UPDRS-I (excluding item 1.1) ≥ 13 is sufficient for stage 4 provided that stage 2 criteria are met.

Supplementary Table 2: Milestone criteria*

Progression milestone	Assessment(s)	Criteria
Domain 1: Walking and balance		
Walking and balance	MDS-UPDRS item 2.12	Response ≥ 3
Freezing	MDS-UPDRS item 2.13	Response ≥ 3
Gait	MDS-UPDRS item 3.10	Response ≥ 3 (ON or OFF)
Freezing of gait	MDS-UPDRS item 3.11	Response=4 (ON or OFF)
Postural instability	MDS-UPDRS item 3.12	Response ≥ 3 (ON or OFF)
Hoehn and Yahr stage	Hoehn and Yahr Stage	Response ≥ 4 (ON or OFF)
Domain 2: Motor complications		
Dyskinesias	MDS-UPDRS items 4.1 and 4.2	Response ≥ 3 (on <i>both</i> items)
Fluctuations (functional impact)	MDS-UPDRS item 4.4	Response ≥ 3
Fluctuations (complexity)	MDS-UPDRS item 4.5	Response ≥ 3
Domain 3: Cognition		
Cognitive impairment (MoCA)*	MoCA	Score<21
Cognitive impairment (MDS-UPDRS)	MDS-UPDRS item 1.1	Response ≥ 3
Hallucinations	MDS-UPDRS item 1.2	Response ≥ 3
Apathy	MDS-UPDRS item 1.5	Response ≥ 3
Dementia (clinical diagnosis)*	Site investigator assessment	PDD (per Investigator)
Dementia (composite)*	(1) Cognitive testing	Impairment [†] on ≥ 2 cognitive domains; and
	(2) Site investigator assessment	Functional impairment (per investigator)
Domain 4: Autonomic dysfunction		
Urinary incontinence**	(1) MDS-UPDRS item 1.10	Response ≥ 3 ; and
(2) SCOPA-AUT items 8 and 9	Response ≥ 2 (on <i>either</i> item)	
Orthostatic hypotension**	(1) SCOPA-AUT item 15	Response ≥ 2 ; and
(2) Systolic blood pressure	Change of ≥ 20 mm Hg (sitting to standing); and	
(3) Diastolic blood pressure	Change of ≥ 10 mm Hg (sitting to standing)	
Syncope (MDS-UPDRS)	MDS-UPDRS item 1.12	Response=4
Syncope (SCOPA-AUT)**	SCOPA-AUT item 16	Response ≥ 1
Domain 5: Functional dependence		
Schwab &England	Schwab &England	Response<80
Domain 6: Activities of daily living		
Choking	MDS-UPDRS item 2.3	Response ≥ 3
Eating	MDS-UPDRS item 2.4	Response ≥ 3
Dressing	MDS-UPDRS item 2.5	Response ≥ 3
Hygiene	MDS-UPDRS item 2.6	Response ≥ 3
Speech	MDS-UPDRS item 3.1	Response ≥ 3 (ON or OFF)

* Adapted from: Brumm MC, Siderowf A, Simuni T, et al. Parkinson's Progression Markers Initiative: A Milestone-Based Strategy to Monitor Parkinson's Disease Progression. J Parkinsons Dis. 2023;13(6):899-916.

Unless otherwise specified, milestones were assessed at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months.

*Assessed at annual visits only. **Assessed at 6 months and annual visits only. [†]Impairment defined as a test score ≥ 1.5 standard deviations below the standardized mean score. MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; PDD, Parkinson's Disease Dementia; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic.

Supplementary Table 3. Cox Regression Model Results

Outcome	Hazard Ratio (95% Wald CL)	Hazard Ratio P-value
Death		
BL Stage 3 vs 2b	1.89 (0.22, 16.30)	0.5619
BL Stage 4 vs 2b	7.07 (0.62, 80.67)	0.1153
Disability (S&E < 80%)		
BL Stage 3 vs 2b	2.15 (0.95, 4.83)	0.0655
BL Stage 4 vs 2b	6.73 (2.51, 18.05)	0.0001
H&Y ≥ 3		
BL Stage 3 vs 2b	1.70 (0.65, 4.47)	0.2808
BL Stage 4 vs 2b	5.64 (1.86, 17.10)	0.0022
Cognitive Decline		
BL Stage 3 vs 2b	1.84 (1.07, 3.18)	0.0281
BL Stage 4 vs 2b	4.62 (2.27, 9.44)	<0.0001
Domain 1: Walking & Balance		
BL Stage 3 vs 2b	2.96 (0.68, 12.93)	0.1486
BL Stage 4 vs 2b	9.86 (1.97, 49.41)	0.0054
Domain 2: Motor Complications		
BL Stage 3 vs 2b	1.56 (0.52, 4.69)	0.4255
BL Stage 4 vs 2b	5.38 (1.50, 19.29)	0.0098
Domain 3: Cognition		
BL Stage 3 vs 2b	1.40 (0.67, 2.91)	0.3725
BL Stage 4 vs 2b	3.05 (1.16, 7.98)	0.0234
Domain 4: Autonomic Dysfunction		
BL Stage 3 vs 2b	1.20 (0.56, 2.55)	0.6365
BL Stage 4 vs 2b	4.86 (1.88, 12.58)	0.0011

Supplementary Table 4: List of Acronyms and abbreviations

Acronym	Definition
α Syn	Alpha-synuclein
A β 1–42	Amyloid-beta 1–42
ATN(PD)	Amyloid/Tau/Neurodegeneration framework for Parkinson's Disease
CSF	Cerebrospinal fluid
CSF-SAA	Cerebrospinal fluid synuclein seed amplification assay
DAT	Dopamine transporter
D+ / D–	Dopaminergic dysfunction present / absent
GDS	Geriatric Depression Scale
H&Y	Hoehn and Yahr scale
LEDD	Levodopa Equivalent Daily Dose
MCI	Mild cognitive impairment
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment
NfL	Neurofilament light chain
NSD	Neuronal Synuclein Disease
NSD-ISS	Neuronal Synuclein Disease – Integrated Staging System
PDD	Parkinson's Disease Dementia
RBDSQ	REM Sleep Behavior Disorder Screening Questionnaire
S+ / S–	Synuclein seed amplification assay positive / negative
S&E	Schwab & England Activities of Daily Living Scale
SAA	Seed amplification assay
SBR	Striatal binding ratio
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease–Autonomic Symptoms
SNCA	Alpha-synuclein gene
UPSIT	University of Pennsylvania Smell Identification Test

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