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CONNECTING EXPERTS IN PD

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Parkinson's Disease Education Day 2023

June 2023

GB_XAD_711

EXTENDING CHOICE
CONNECTING EXPERTS IN PD

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What Do We Know About Early Parkinson's Disease?

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As presented in May 2023 (GB_XAD_690)

Early PD

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GB_XAD_690 May 2023

Disclosures

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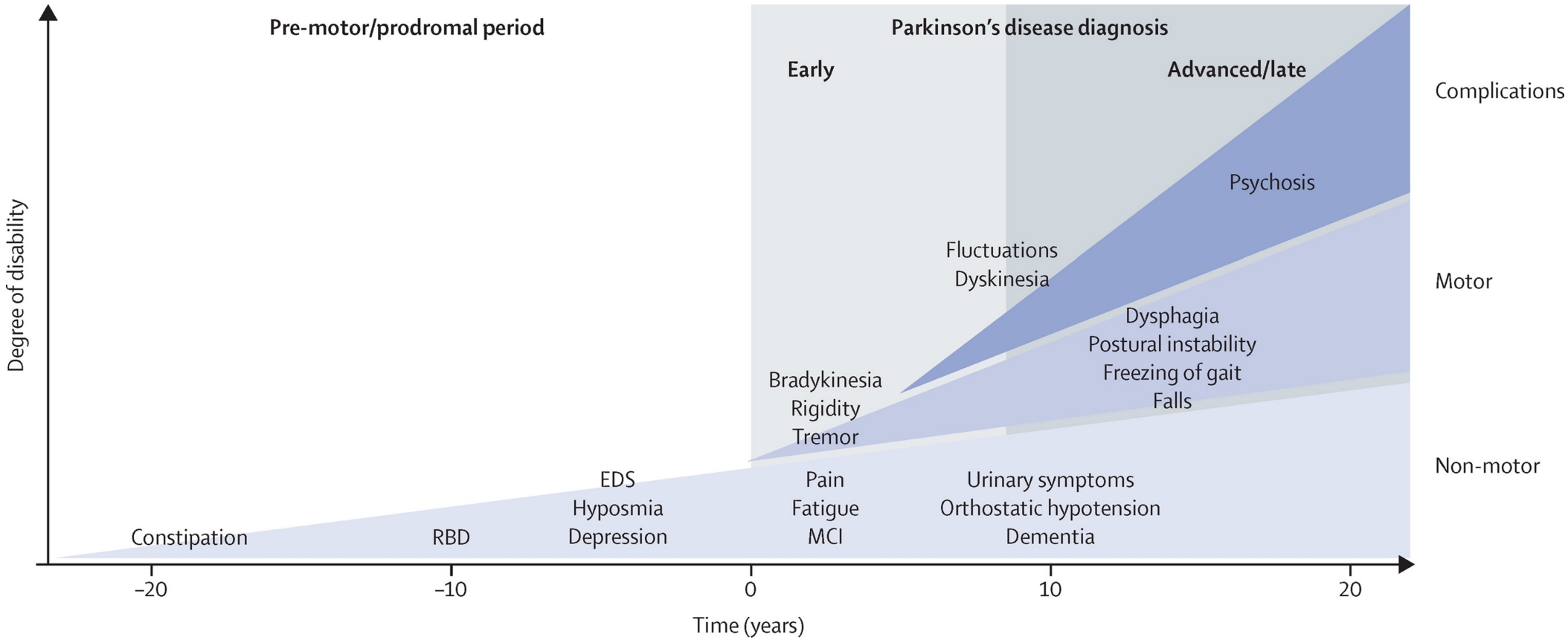
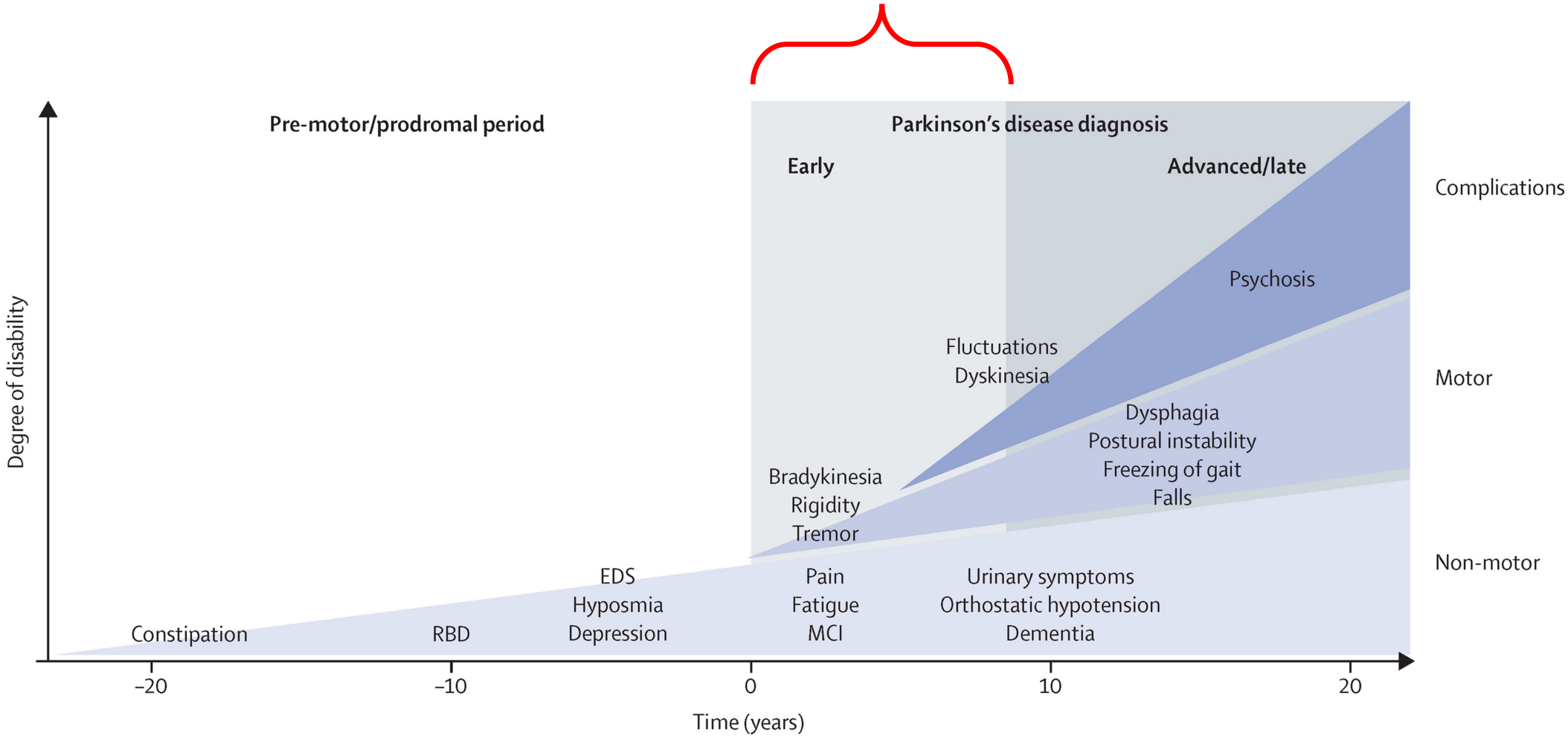
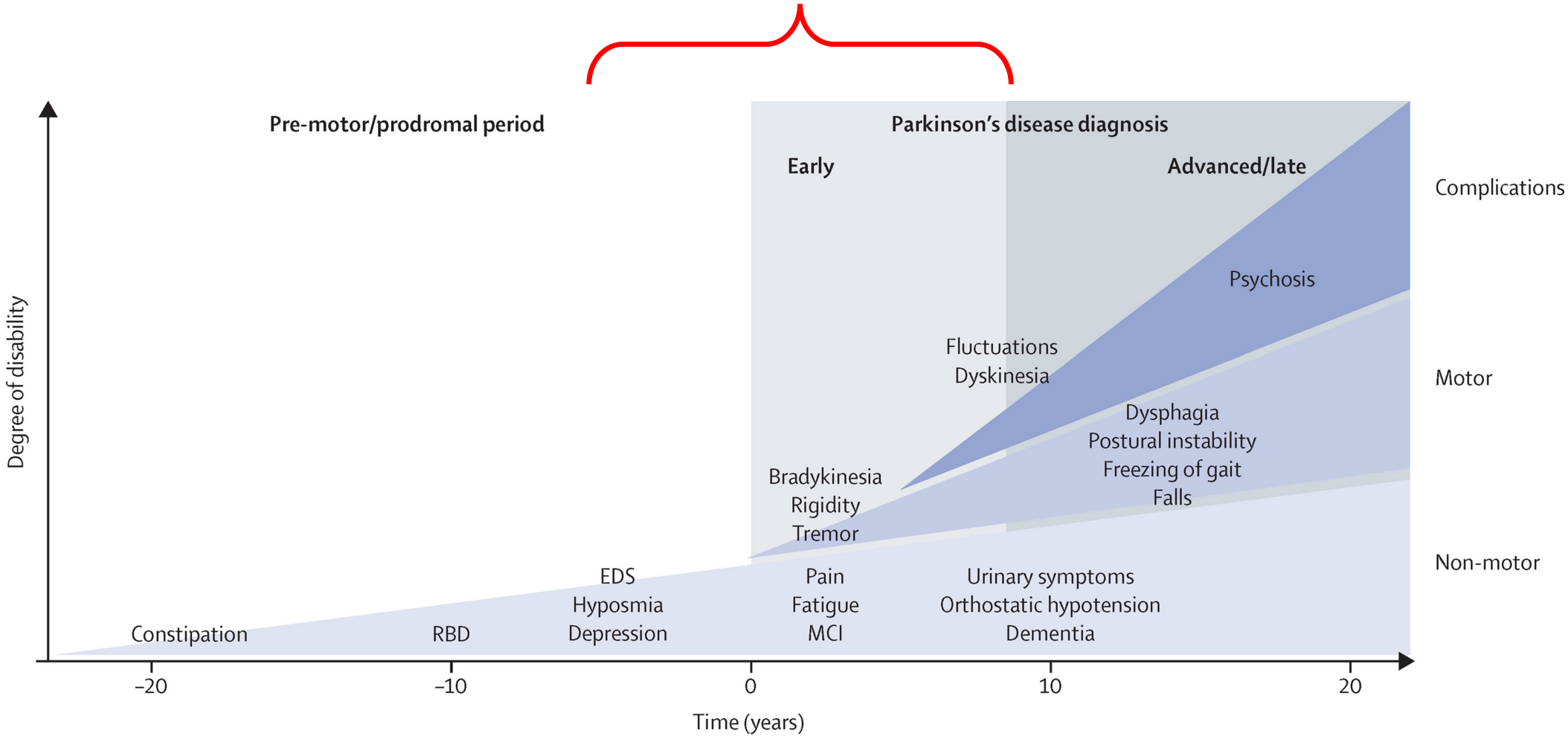
GB_XAD_690 May 2023



Kalia and Lang, Lancet, 2015



Kalia and Lang, Lancet, 2015



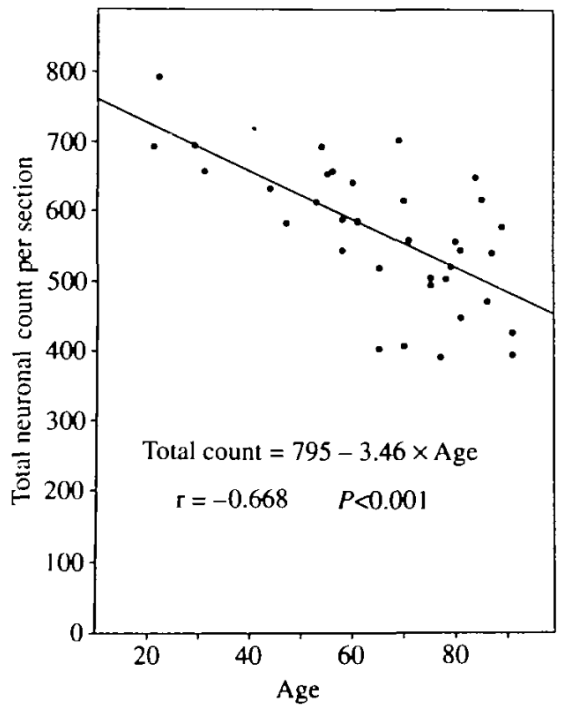
Kalia and Lang, Lancet, 2015

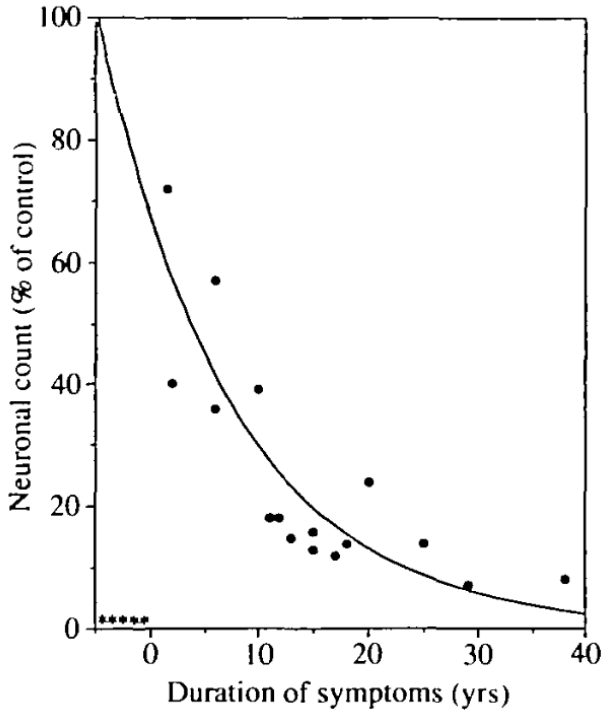
Brain (1991), **114**, 2283–2301

AGEING AND PARKINSON'S DISEASE: SUBSTANTIA NIGRA REGIONAL SELECTIVITY

by JULIAN M. FEARNLEY *and* ANDREW J. LEES

(*From the National Hospital, Queen Square, London, UK*)





Prediagnostic presentations of Parkinson's disease in primary care: a case-control study

Anette Schrag, Laura Horsfall, Kate Walters, Alastair Noyce, Irene Petersen

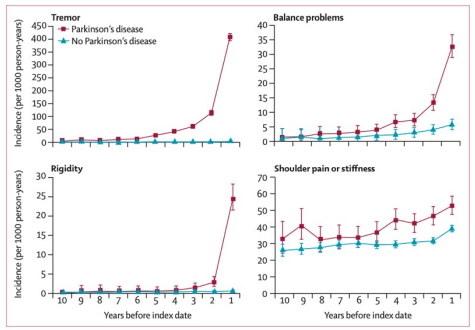


Figure 1: **Incidence of motor symptoms of Parkinson's disease**
Bars are 95% CIs, based on the sample size of each group. Neck pain and stiffness symptoms are not shown because the difference between groups was not significant at any year.

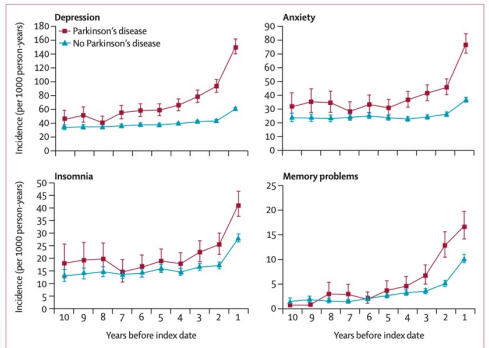


Figure 2: **Incidence of neuropsychiatric symptoms and insomnia**
Bars are 95% CIs, based on the sample size of each group.

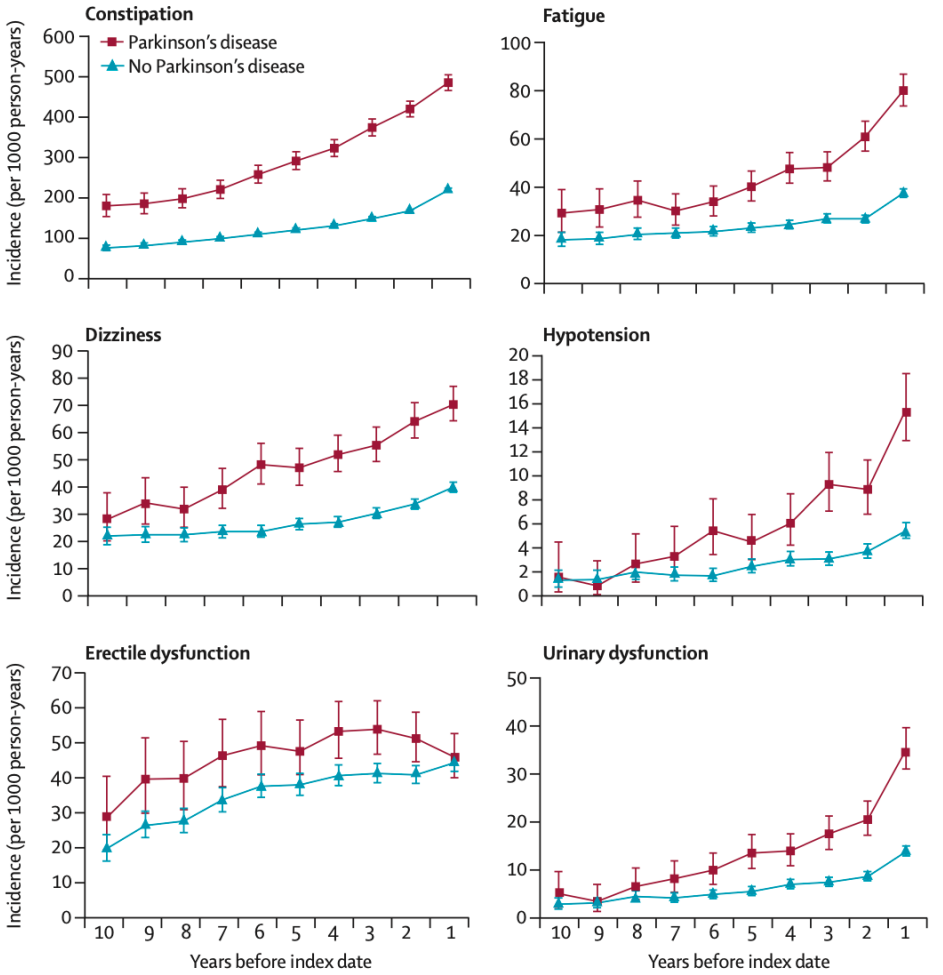


Figure 3: **Incidence of autonomic symptoms and fatigue**
Bars are 95% CIs, based on the sample size of each group.

JAMA Neurology | Original Investigation

Assessment of Risk Factors and Early Presentations of Parkinson Disease in Primary Care in a Diverse UK Population

Cristina Simonet, MD; Jonathan Bestwick, MSc; Mark Jitlal, MSc; Sheena Waters, PhD; Aaron Ben-Joseph, MBBS; Charles R. Marshall, PhD; Ruth Dobson, PhD; Soha Marrium, MSc; John Robson, MSc, MD; Benjamin M. Jacobs, MSc; Daniel Belete, MBChB; Andrew J. Lees, MD; Gavin Giovannoni, PhD; Jack Cuzick, PhD, CBE; Anette Schrag, PhD; Alastair J. Noyce, PhD

Table 1. Demographic Information on PD Cases and Unmatched Controls in East London Primary Care Data

Variable	No. (%)		Prevalence, % PD cases per group
	PD (n = 1055)	Controls (n = 1 009 523)	
Age, mean (SD), y	72.9 (11.3)	40.3 (15.2)	NA
Female	423 (40.1)	492 661 (48.8)	0.09
Male	632 (59.9)	516 862 (51.2)	0.12
Ethnicity[a]			
Black	166 (15.7)	134 629 (13.3)	0.12
South Asian	208 (19.7)	216 763 (21.5)	0.10
White	537 (50.9)	441 522 (43.7)	0.12
Other	88 (8.3)	114 503 (11.3)	0.08
Unknown	56 (5.3)	102 106 (10.1)	0.05
IMD			
1-2 (Most deprived)	472 (44.7)	453 747 (44.9)	0.10
3-4	419 (39.7)	424 944 (42.1)	0.10
5-6	68 (6.4)	76 773 (7.6)	0.09
7-8	25 (2.4)	19 258 (1.9)	0.13
9-10 (Least deprived)	16 (1.5)	6895 (0.7)	0.23
Unknown	55 (5.2)	27 906 (2.8)	0.20

Table 3. Matched Case-Control Analysis for Prodromes and Motor Markers[a]

Category	Time period								
	<2 y			2 to <5 y			5 to 10 y		
	No. (%) [PD: controls]	OR (95% CI)		No. (%) [PD: controls]	OR (95% CI)		No. (%) [PD: controls]	OR (95% CI)	
		Unadjusted	Adjusted		Unadjusted	Adjusted		Unadjusted	Adjusted
Metabolic									
Underweight	7 (0.7): 26 (0.2)	2.73 (1.17-6.37)	2.58 (1.1-6.02)	4 (0.4): 49 (0.5)	0.81 (0.29-2.25)	0.78 (0.28-2.18)	10 (0.9): 69 (0.7)	1.45 (0.74-2.83)	1.44 (0.74-2.82)
Autonomic									
Hypotension	13 (1.2): 19 (0.2)	6.84 (3.38-13.85)	6.81 (3.35-13.8)	12 (1.1): 25 (0.2)	4.88 (2.44-9.77)	4.73 (2.36-9.5)	6 (0.6): 30 (0.3)	2.01 (0.83-4.85)	1.9 (0.79-4.6)
Constipation	44 (4.2): 140 (1.3)	3.29 (2.32-4.66)	3.29 (2.32-4.67)	53 (5): 205 (1.9)	2.68 (1.97-3.66)	2.66 (1.95-3.63)	53 (5): 188 (1.8)	2.96 (2.16-4.06)	2.97 (2.16-4.07)
Erectile dysfunction	21 (3.3): 185 (2.9)	1.14 (0.72-1.80)	1.14 (0.72-1.8)	34 (5.4): 302 (4.8)	1.13 (0.79-1.64)	1.13 (0.78-1.63)	51 (8.1): 350 (5.5)	1.51 (1.11-2.05)	1.52 (1.12-2.08)
Neuropsychiatric									
Depression	24 (2.3): 52 (0.5)	4.69 (2.88-7.63)	4.61 (2.82-7.52)	18 (1.7): 111 (1.1)	1.65 (0.99-2.73)	1.64 (0.98-2.72)	28 (2.7): 144 (1.4)	1.97 (1.31-2.97)	1.94 (1.29-2.92)
Anxiety	32 (3): 106 (1)	3.08 (2.06-4.60)	3.01 (2.02-4.5)	18 (1.7): 137 (1.3)	1.32 (0.8-2.18)	1.29 (0.78-2.13)	37 (3.5): 243 (2.3)	1.55 (1.09-2.21)	1.53 (1.07-2.18)
Insomnia	21 (2): 97 (0.9)	2.18 (1.36-3.51)	2.17 (1.35-3.48)	25 (2.4): 137 (1.3)	1.85 (1.20-2.85)	1.87 (1.21-2.88)	24 (2.3): 164 (1.6)	1.48 (0.96-2.28)	1.47 (0.95-2.27)
Fatigue	26 (2.5): 138 (1.3)	1.91 (1.25-2.93)	1.86 (1.21-2.85)	27 (2.6): 194 (1.8)	1.41 (0.93-2.13)	1.4 (0.93-2.11)	26 (2.5): 243 (2.3)	1.08 (0.71-1.63)	1.06 (0.7-1.6)
Dizziness	36 (3.4): 229 (2.2)	1.59 (1.11-2.27)	1.57 (1.09-2.24)	54 (5.1): 276 (2.6)	2.01 (1.49-2.71)	1.99 (1.47-2.68)	60 (5.7): 369 (3.5)	1.68 (1.27-2.24)	1.66 (1.25-2.21)
Memory symptoms	52 (4.9): 63 (0.6)	8.6 (5.91-12.49)	8.73 (6.0-12.7)	18 (1.7): 59 (0.6)	3.08 (1.81-5.24)	3.09 (1.81-5.26)	8 (0.8): 39 (0.4)	2.06 (0.96-4.42)	2.01 (0.93-4.31)
Sensory									
Hearing loss	23 (2.2): 140 (1.3)	1.66 (1.06-2.58)	1.65 (1.06-2.58)	29 (2.7): 170 (1.6)	1.73 (1.16-2.57)	1.73 (1.16-2.57)	24 (2.3): 163 (1.5)	1.48 (0.96-2.29)	1.46 (0.95-2.26)
Sensory/indirect motor									
Shoulder pain	31 (2.9): 142 (1.3)	2.23 (1.5-3.3)	2.25 (1.52-3.33)	39 (3.7): 212 (2)	1.88 (1.33-2.66)	1.89 (1.33-2.68)	45 (4.3): 348 (3.3)	1.32 (0.96-1.81)	1.31 (0.95-1.80)
Neck pain	26 (2.5): 188 (1.8)	1.39 (0.92-2.11)	1.39 (0.92-2.11)	32 (3): 235 (2.2)	1.38 (0.95-2.01)	1.37 (0.94-1.99)	36 (3.4): 300 (2.8)	1.21 (0.85-1.72)	1.21 (0.85-1.72)
Motor									
Tremor	267 (25.3): 26 (0.2)	145.96 (90.55-235.28)	151.24 (93.74-244.02)	42 (4): 29 (0.3)	14.48 (9.02-23.25)	14.51 (9.02-23.3)	26 (2.5): 24 (0.2)	11.66 (6.59-20.64)	11.4 (6.43-20.22)
Rigidity	13 (1.2): 1 (0)	129.99 (17.01-993.63)	124.84 (16.3-956.36)	1 (0.1): 4 (0)	2.5 (.28-22.37)	2.48 (0.28-22.26)	2 (0.2): 2 (0)	10 (1.41-71.0)	8.27 (1.14-59.8)
Balance difficulties	44 (4.2): 187 (1.8)	2.42 (1.73-3.39)	2.4 (1.71-3.36)	42 (4): 202 (1.9)	2.14 (1.52-3.01)	2.1 (1.49-2.95)	33 (3.1): 223 (2.1)	1.51 (1.04-2.19)	1.49 (1.02-2.17)

Abbreviations: OR, odds ratio; PD, Parkinson disease.

[a] Matched case-control analysis: matching patients with PD (n = 1055) with 10 controls (n = 10 550) for each case according to age and sex (unadjusted) and adjusted for ethnicity and Index of Multiple Deprivation. Time spans refer to years before PD diagnosis or index date.

Simonet et al, JAMA Neurol 2022

What is a disease?

- An abnormal condition that negatively affects the structure or function of all or part of an organism, and that is not immediately due to any external injury.
- May be classified by cause, pathogenesis, or by symptom(s).
- Classical classification of human disease derives from the observational correlation between pathological analysis and clinical syndromes.

Making a diagnosis

Journal of Neurology, Neurosurgery, and Psychiatry 1988;**51**:745–752

Occasional review

The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease

W R G GIBB, A J LEES

From the Department of Neuropathology, National Hospitals for Nervous Diseases, Maida Vale, London, UK

STEP 1. Diagnosis of PARKINSONIAN SYNDROME.

BRADYKINESIA (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions).

And at least one of the following:

a. muscular rigidity

b. 4–6 Hz rest tremor

c. postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

STEP 2. Exclusion criteria for Parkinson's disease.

history of repeated strokes with stepwise progression of Parkinsonian features
history of repeated head injury
history of definite encephalitis
oculogyric crises
neuroleptic treatment at onset of symptoms
more than one affected relative
sustained remission
strictly unilateral features after three years
supranuclear gaze palsy
cerebellar signs
early severe autonomic involvement
early severe dementia with disturbances of memory, language and praxis
Babinski sign
presence of a cerebral tumour or communicating hydrocephalus on CT scan.
negative response to large doses of levodopa (if malabsorption excluded)
MPTP exposure

STEP 3. Supportive prospective positive criteria for PARKINSON'S DISEASE. Three or more required for diagnosis of definite Parkinson's disease.

unilateral onset
rest tremor present
progressive disorder
persistent asymmetry affecting the side of onset most
excellent response (70–100%) to levodopa
severe levodopa-induced chorea
levodopa response for 5 years or more
clinical course of 10 years or more

Gibb & Lees. JNNP 1988;51:745-752.

GB_XAD_690 May 2023

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

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

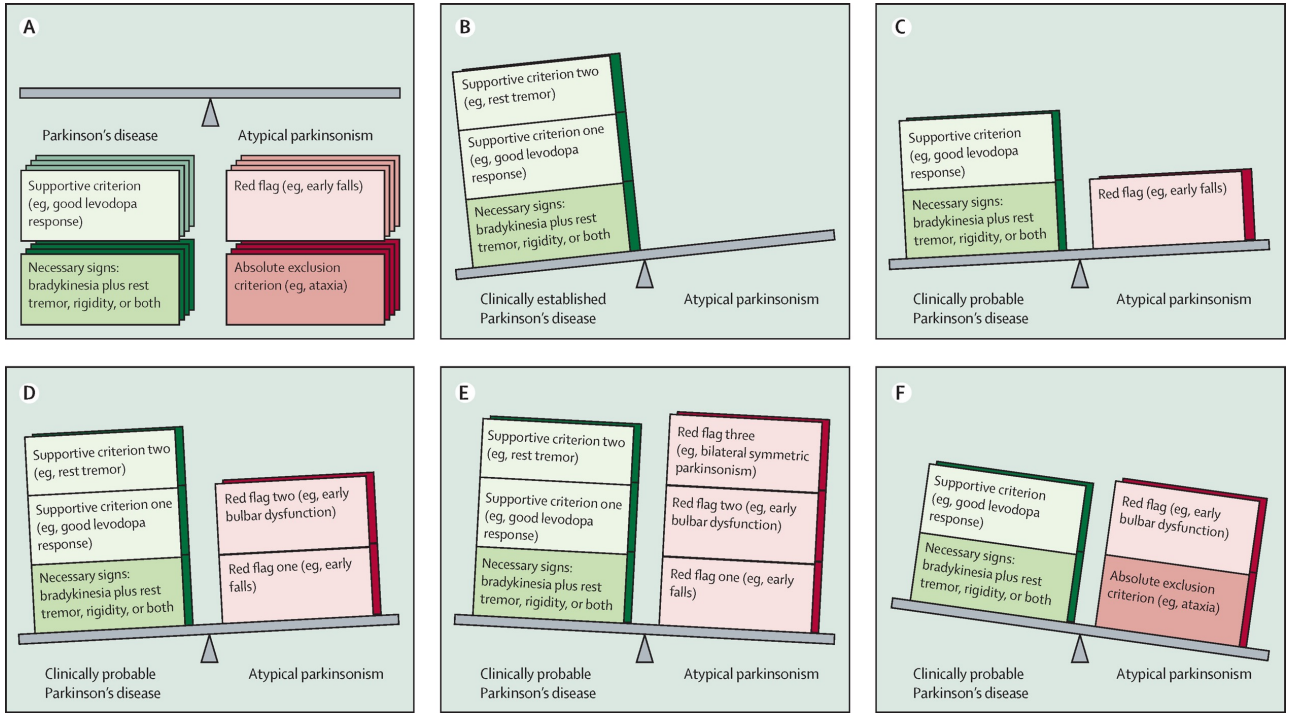
The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of **Clinically Established PD** requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category



Postuma et al. Mov Disord 2015;30(12):1591-1599.
Bloem et al. Lancet 2021

GB_XAD_690 May 2023

REVIEW

CME

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and Günther Deuschl, MD[18]

Supportive criteria
(Check box if criteria met)

☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
☐ 2. Presence of levodopa-induced dyskinesia
☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Postuma et al. Mov Disord 2015;30(12):1591-1599.

REVIEW

CME

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and Günther Deuschl, MD[18]

Red flags

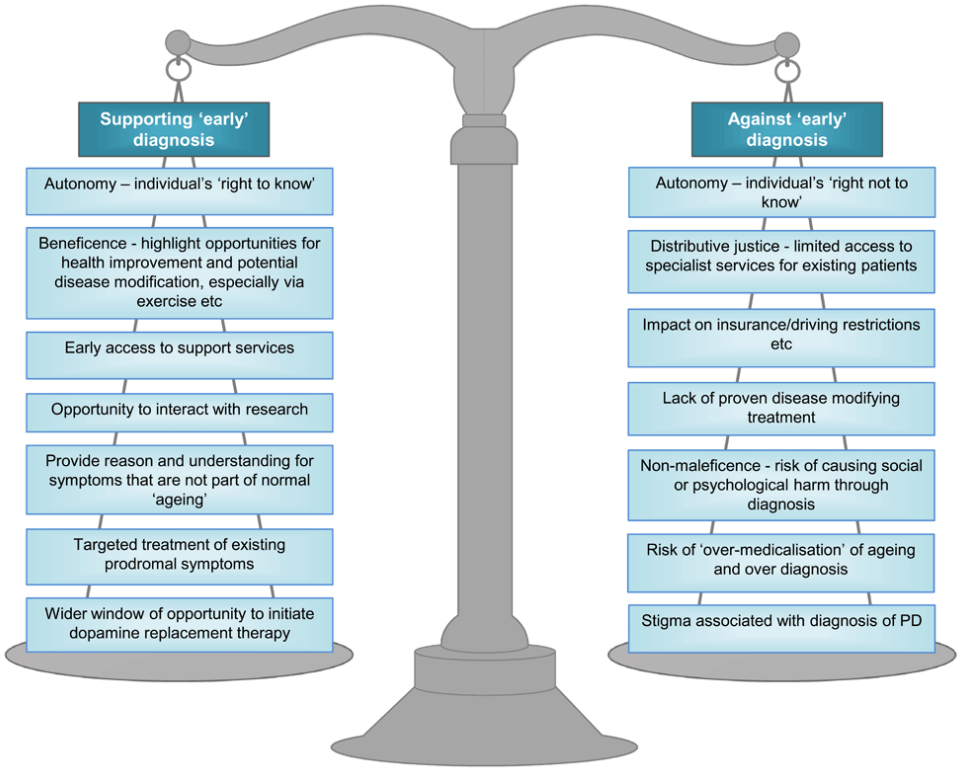
- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: **severe** dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  - a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  - b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, **and** no side predominance is observed on objective examination

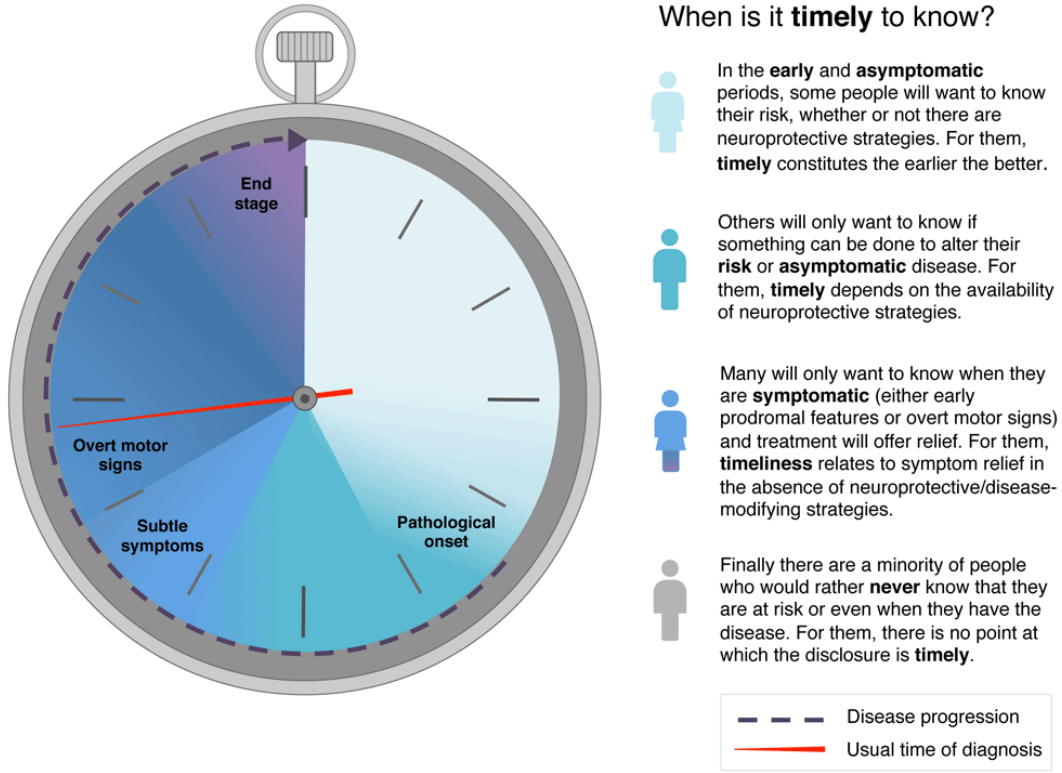
Postuma et al. Mov Disord 2015;30(12):1591-1599.

REVIEW

An early diagnosis is not the same as a timely diagnosis of Parkinson's disease [version 1; referees: 2 approved]

Richard Nathaniel Rees[1], Anita Prema Acharya[2], Anette Schrag[1], Alastair John Noyce[3,4]





Rees et al. F1000 Research 2018

GB_XAD_690 May 2023

ARTICLE

Patients' views on the ethical challenges of early Parkinson disease detection

Eva Schaeffer, MD,* Annette Rogge, MD,* Katharina Nieding, Vera Helmker, Christa Letsch, Björn Hauptmann, MD, and Daniela Berg, MD

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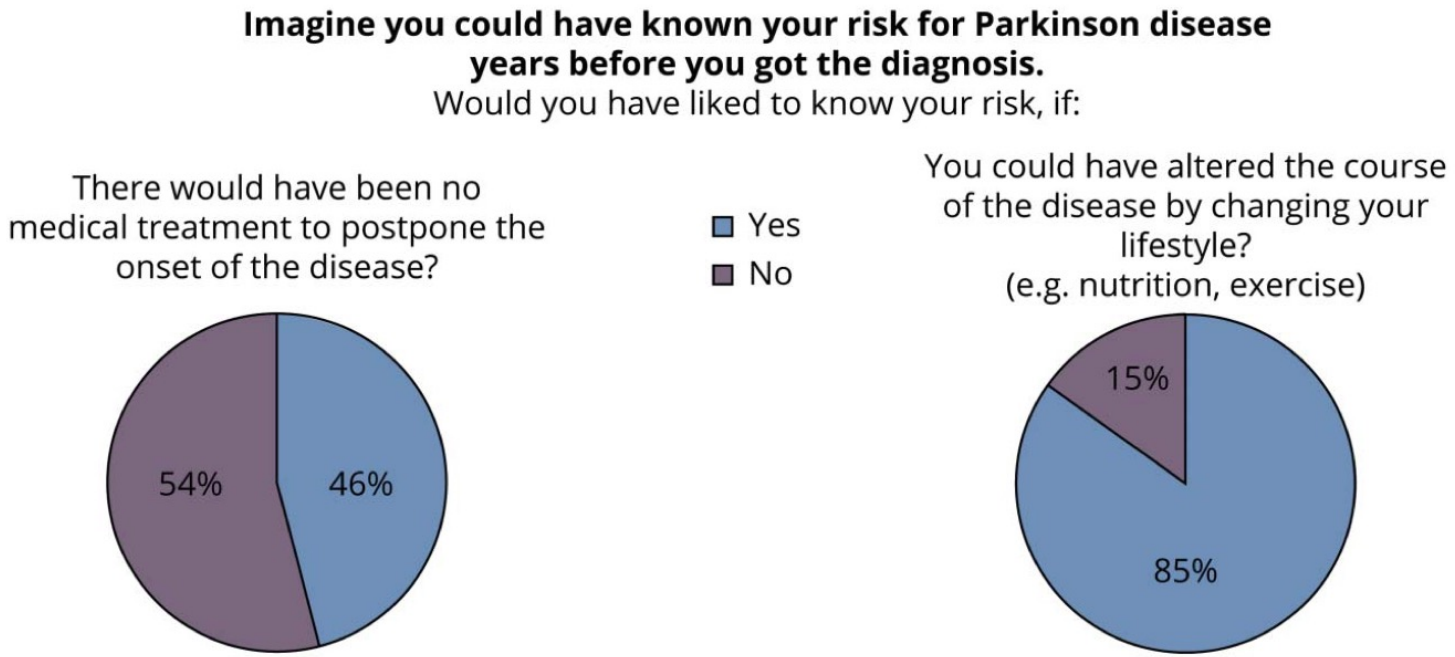
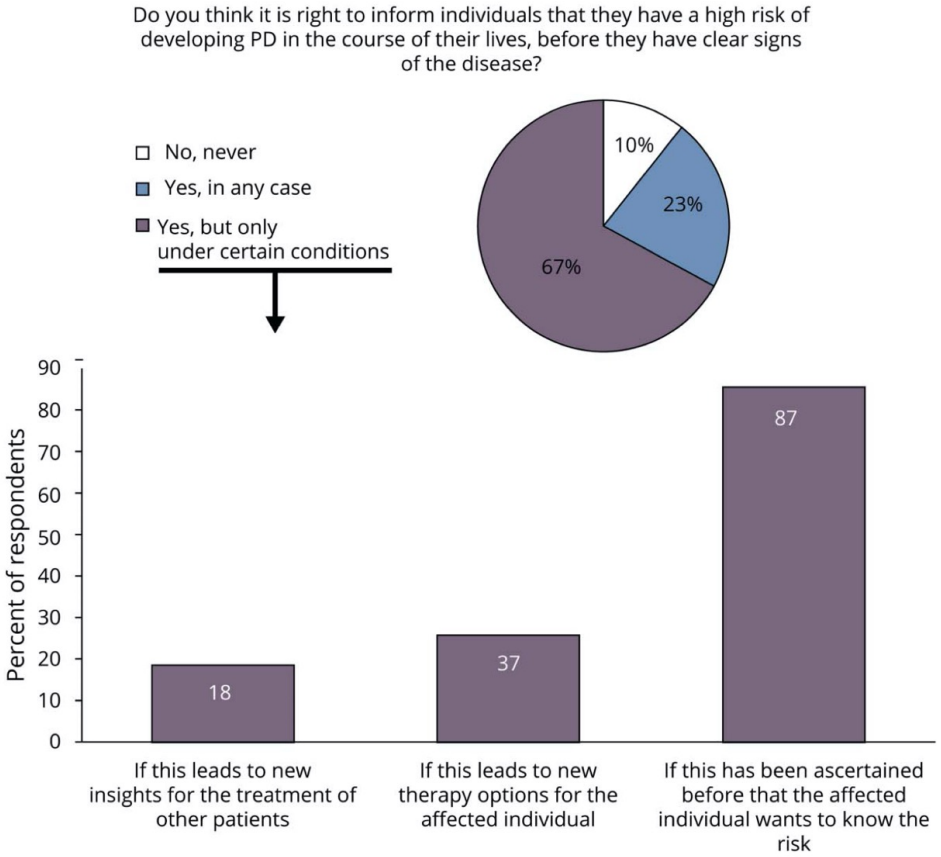
Neurology® 2020;94:e2037-e2044. doi:10.1212/WNL.0000000000009400





BRIEF REPORT

The Views of Patients with Isolated Rapid Eye Movement Sleep Behavior Disorder on Risk Disclosure

Laura Pérez-Carbonell, MD,[1]
Cristina Simonet, MD, PhD,[2] Harneek Chohan, MSc,[2]
Aneet Gill, MSc,[2] Guy Leschziner, MD, PhD,[1]
Anette Schrag, MD, PhD,[3] and
Alastair J. Noyce, MD, PhD[2*]

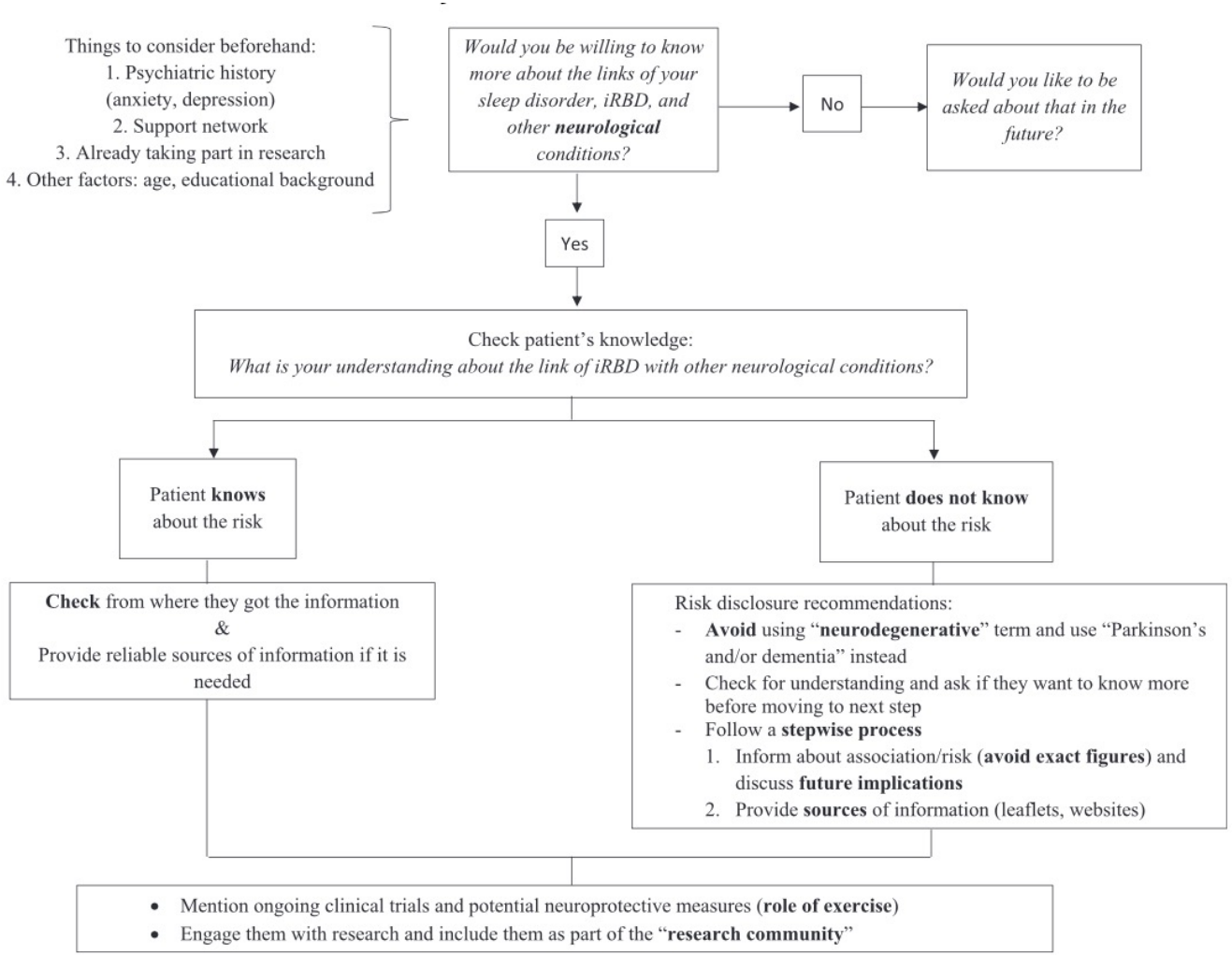
1/3 no information about NDD at Dx

- >50% of these found out online

>90% wanted to receive this information

- All from their clinician

Several suggested that information be disclosed sequentially, starting at the first consultation



Perez-Carbonell et al, MDJ 2023.

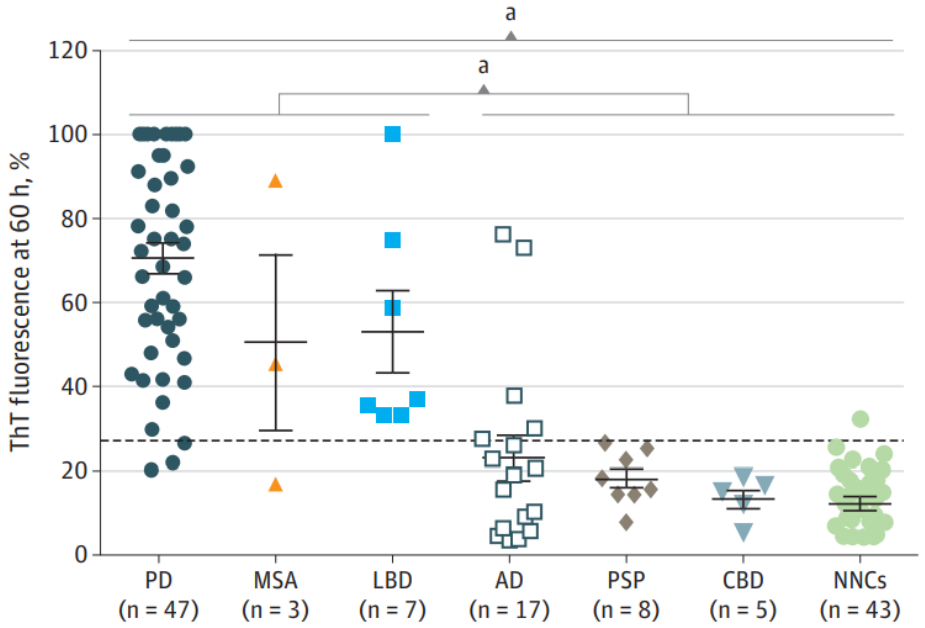
Shifting to a biological definition of disease?

JAMA Neurology | Original Investigation

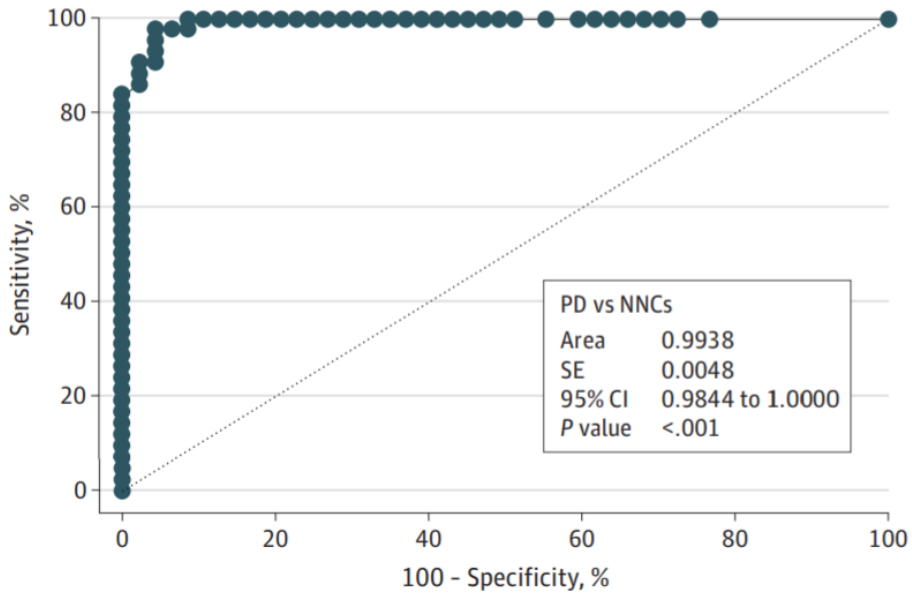
Skin α-Synuclein Aggregation Seeding Activity as a Novel Biomarker for Parkinson Disease

Zerui Wang, MD, PhD; Katelyn Becker, MS; Vincenzo Donadio, MD, PhD; Sandra Siedlak, MS; Jue Yuan, MS; Masih Rezaee, MD; Alex Incensi, MSc; Anastasia Kuzkina, MD; Christina D. Orrú, PhD; Curtis Tatsuoka, PhD; Rocco Liguori, MD; Steven A. Gunzler, MD; Byron Caughey, PhD; Maria E. Jimenez-Capdeville, PhD; Xiongwei Zhu, PhD; Kathrin Doppler, MD; Li Cui, MD, PhD; Shu G. Chen, PhD; Jiyan Ma, MD, PhD; Wen-Quan Zou, MD, PhD

A Scatter graph of RT-QuIC ThT fluorescence intensity of αSyn^P seeding activity of abdominal skin samples from cadavers with and without SOPs



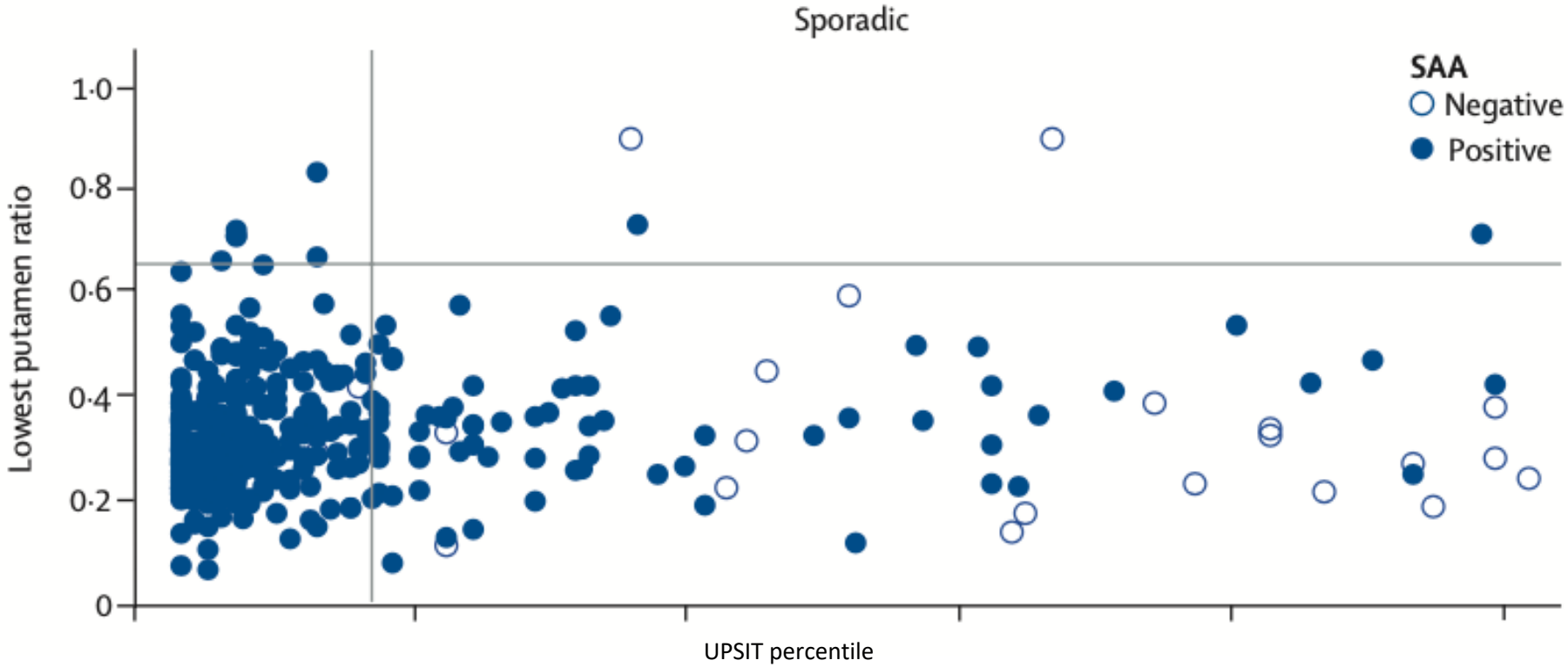
B ROC curve and derived AUC for αSyn^P seeding activity comparisons between patients with PD and controls



Wang Z, et al. JAMA Neurol 2021.

Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study

Andrew Siderowf, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kieburtz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†*



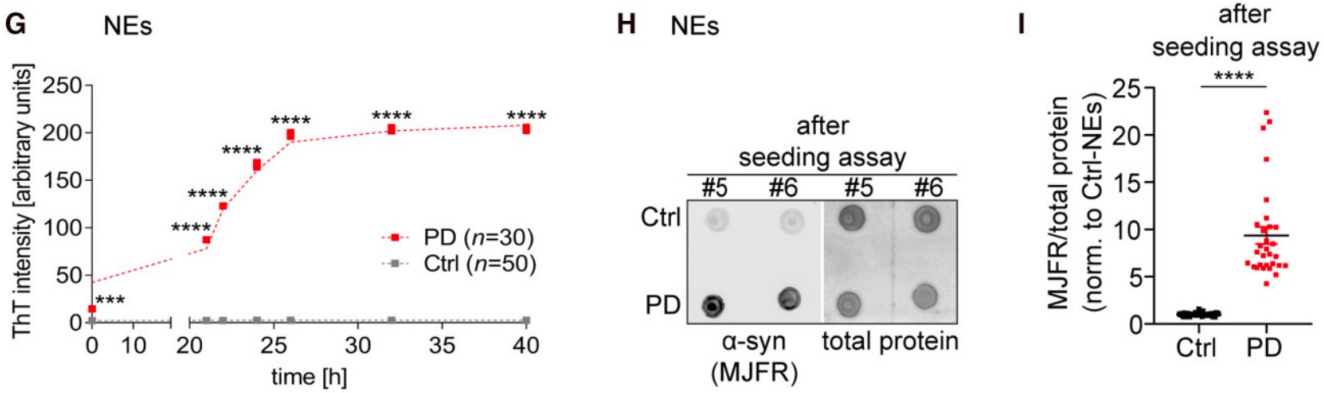
Siderowf A, et al. Lancet Neurol 2023.

https://doi.org/10.1093/brain/awac115 BRAIN 2022: 00; 1–14 | 1

BRAIN
ORIGINAL ARTICLE

Detection of neuron-derived pathological α-synuclein in blood

Annika Kluge,[1] Josina Bunk,[2] Eva Schaeffer,[1] Alice Drobny,[3] Wei Xiang,[3] Henrike Knacke,[1] Simon Bub,[3] Wiebke Lückstädt,[4] Philipp Arnold,[5] Ralph Lucius,[4] Daniela Berg[1,†] and Friederike Zunke[3,†]



For each time point, measurements of all 30 Parkinson's disease patients and all 50 controls were combined and demonstrated as means ± SEM.

doi:10.1093/brain/awab005 BRAIN 2021: 144; 1118–1126 | 1118

BRAIN
A JOURNAL OF NEUROLOGY

Alpha-synuclein seeds in olfactory mucosa of patients with isolated REM sleep behaviour disorder

Ambra Stefani,[1] Alex Iranzo,[2] Evi Holzknecht,[1] Daniela Perra,[3] Matilde Bongianni,[3] Carles Gaig,[2] Beatrice Heim,[1] Monica Serradell,[2] Luca Sacchetto,[4] Alicia Garrido,[2] Stefano Capaldi,[5] Almudena Sánchez-Gómez,[2] Maria Paola Cecchini,[6] Sara Mariotto,[3] Sergio Ferrari,[3] Michele Fiorini,[3] Joachim Schmutzhard,[7] Pietro Cocchiara,[3] Isabel Vilaseca,[8] Lorenzo Brozzetti,[3] Salvatore Monaco,[3] M. Jose Marti,[2] Klaus Seppi,[1] Eduardo Tolosa,[2] Joan Santamaria,[2] Birgit Högl,[1] Werner Poewe[1,2] and Gianluigi Zanusso[3] for the SINBAR (Sleep Innsbruck Barcelona) group

	Isolated RBD		
	α-syn-positive *n* = 28 (44.4%)	α-syn-negative *n* = 35 (55.6%)	*P*-value
Age, years	72 (67–74.8)	67 (60–74)	0.059
Age at diagnosis, years	67 (63–68.8)	60 (56–67)	**0.004**
Age at onset, years	62 (59–67.5)	53 (45–61)	**0.011**
Disease duration, years	4.5 (1.3–8)	6 (2–10)	0.176
Sex, *n* (%)			0.170
Female	6 (21.4)	3 (8.6)	
Male	22 (78.6)	32 (91.4)	
MDS-UPDRS III score	4 (1–7)	4 (2–7)	0.692
SCOPA-AUT score	18 (11–29)	13 (8–21)	0.133
MoCA score	27 (24–28)	27 (24–28)	0.737
Sniffin' Sticks score	7 (5–8)	11 (8–13)	**<0.001**
Olfactory dysfunction, *n* (%)	22 (78.6)	8 (22.9)	**<0.001**
Hoehn and Yahr stage	n.a.	n.a.	n.a.
Rigidity, *n* (%)	n.a.	n.a.	n.a.
Rest tremor, *n* (%)	n.a.	n.a.	n.a.

Kluge A et al. Brain 2022;145:3058–71; Stefani A et al. Brain 2021;144:1118–26.

ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

podcast CrossMark

A biological classification of Huntington's disease: the Integrated Staging System

Sarah J Tabrizi, Scott Schobel*, Emily C Gantman, Alexandra Mansbach, Beth Borowsky, Pavlina Konstantinova, Tiago A Mestre, Jennifer Panagoulias, Christopher A Ross, Maurice Zauderer, Ariana P Mullin, Klaus Romero, Sudhir Sivakumaran, Emily C Turner, Jeffrey D Long, Cristina Sampaio, on behalf of the Huntington's Disease Regulatory Science Consortium (HD-RSC)†*

Lancet Neurol 2022; 21: 632–44

See Comment page 582

The current research paradigm for Huntington's disease is based on participants with overt clinical phenotypes and does not address its pathophysiology nor the biomarker changes that can precede by decades the functional decline.

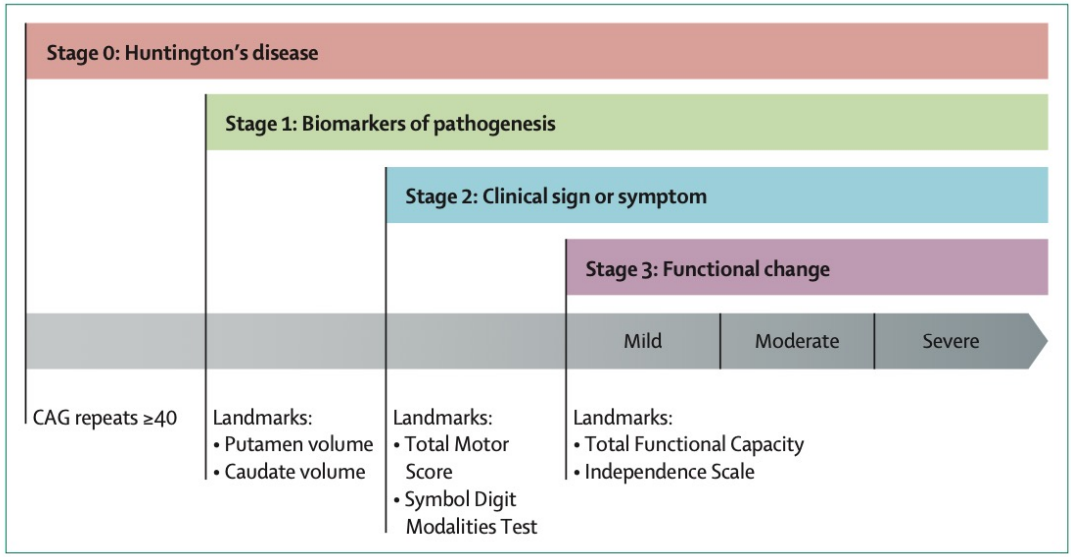
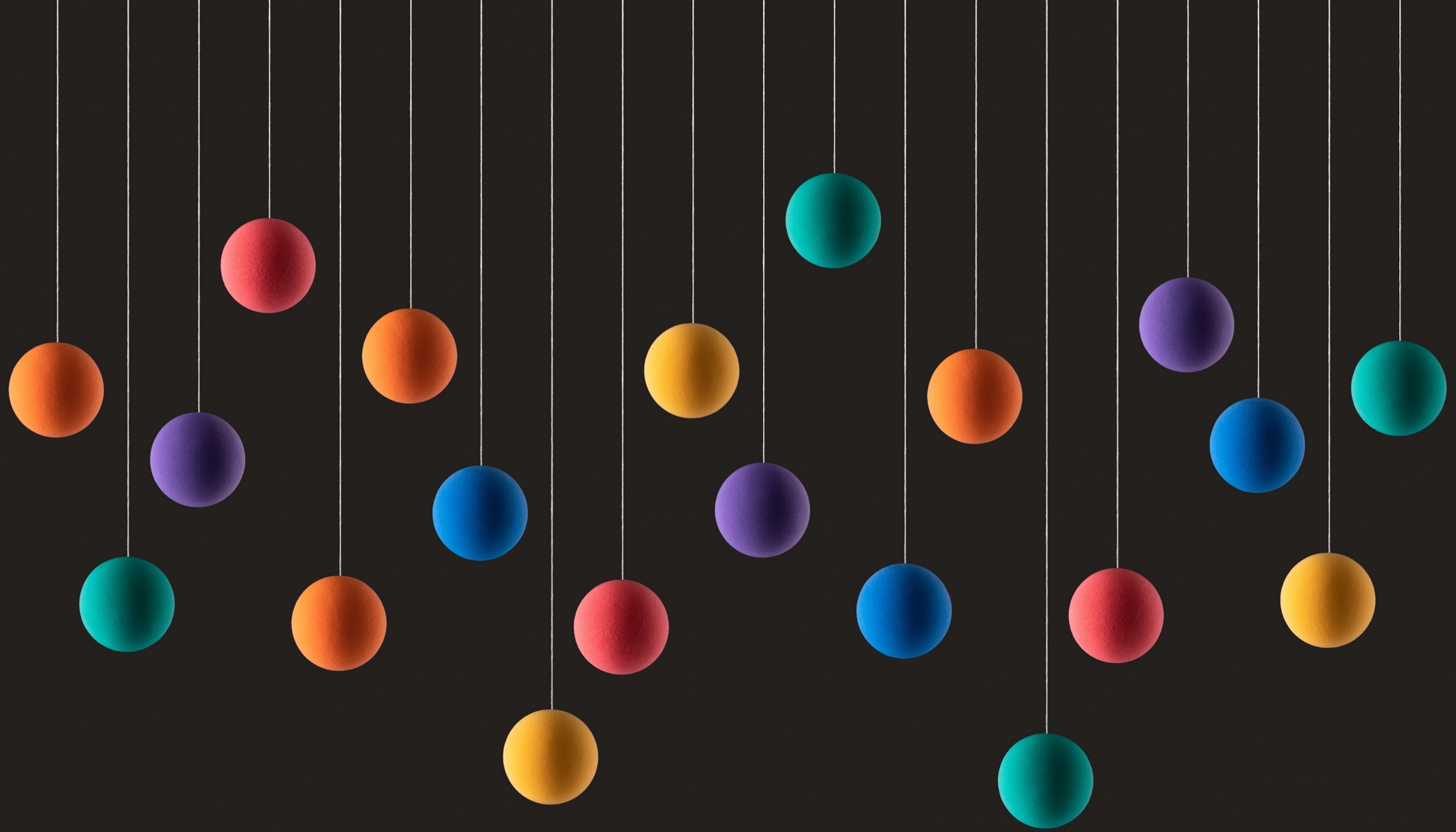


Figure 3: **Cumulative staging framework and landmarks of the Huntington's disease Integrated Staging System**



Hyposmia in the clinic

70-90% have hyposmia/anosmia at the point of diagnosis

Subjective and objective olfactory function are loosely correlated

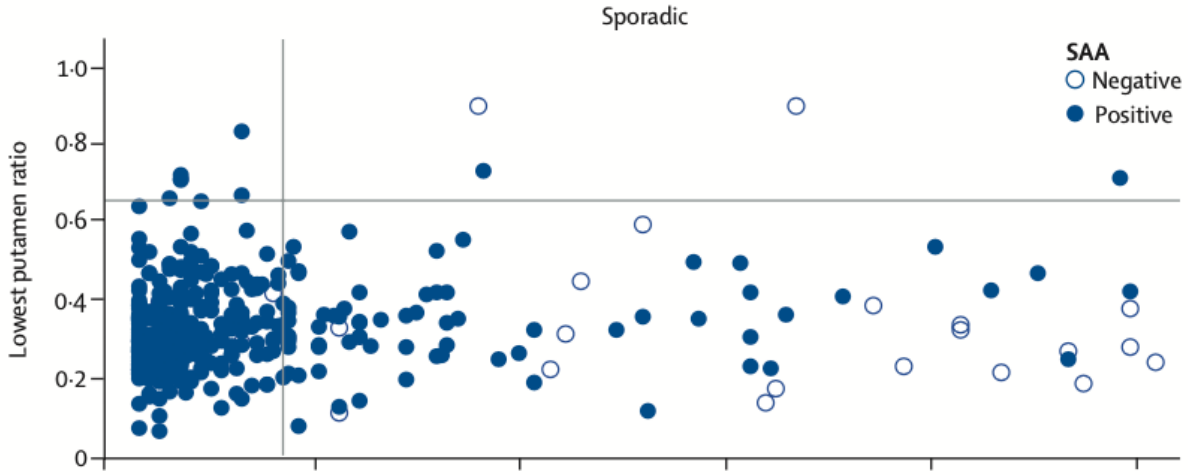
NICE (71) - 2017

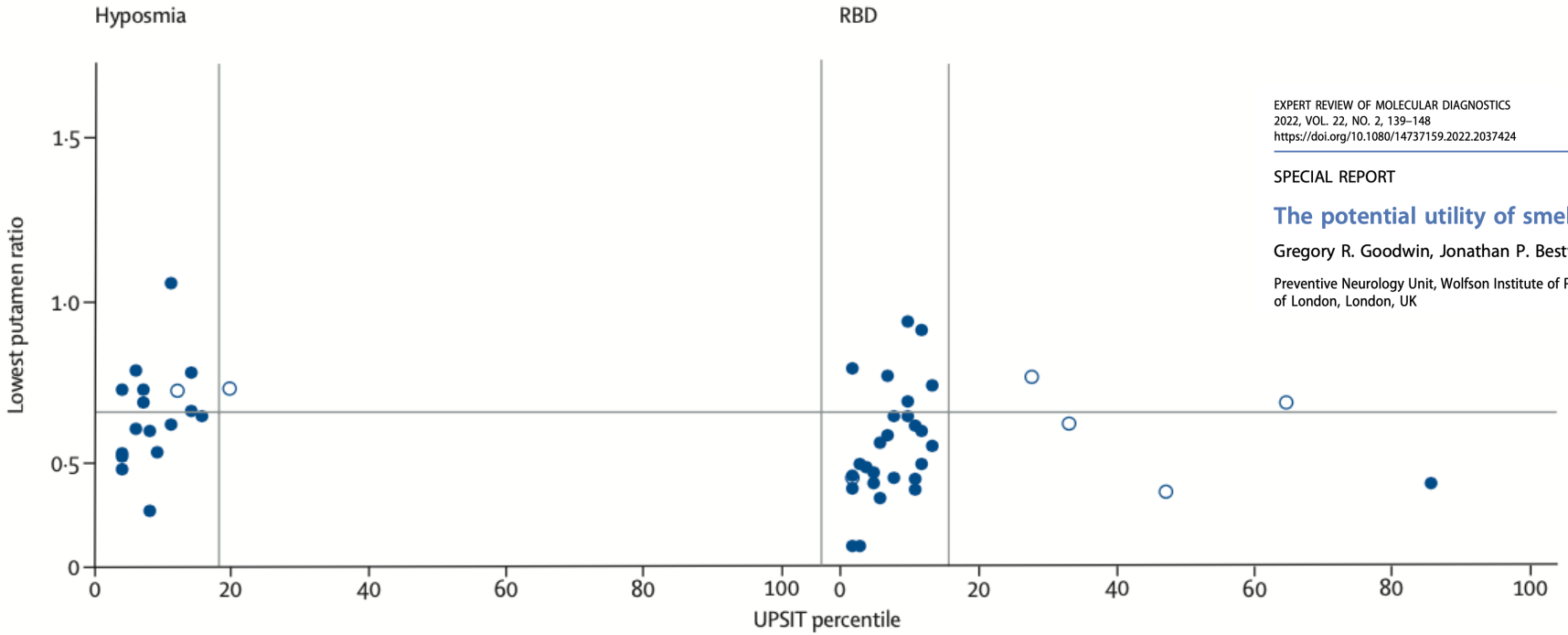
Objective smell testing

1.2.14 Do not use objective smell testing in the differential diagnosis of parkinsonian syndromes, except in the context of clinical trials. **[2006, amended 2017]**

Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study

Andrew Siderowf, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kieburtz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†*





EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
2022, VOL. 22, NO. 2, 139–148
https://doi.org/10.1080/14737159.2022.2037424

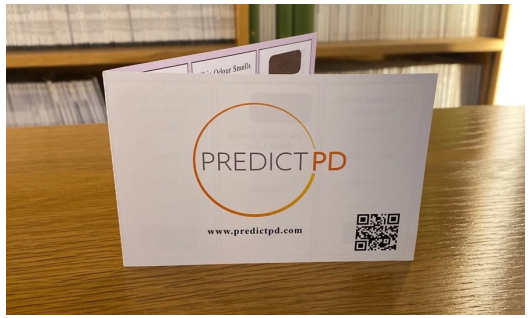
Taylor & Francis
Taylor & Francis Group

SPECIAL REPORT

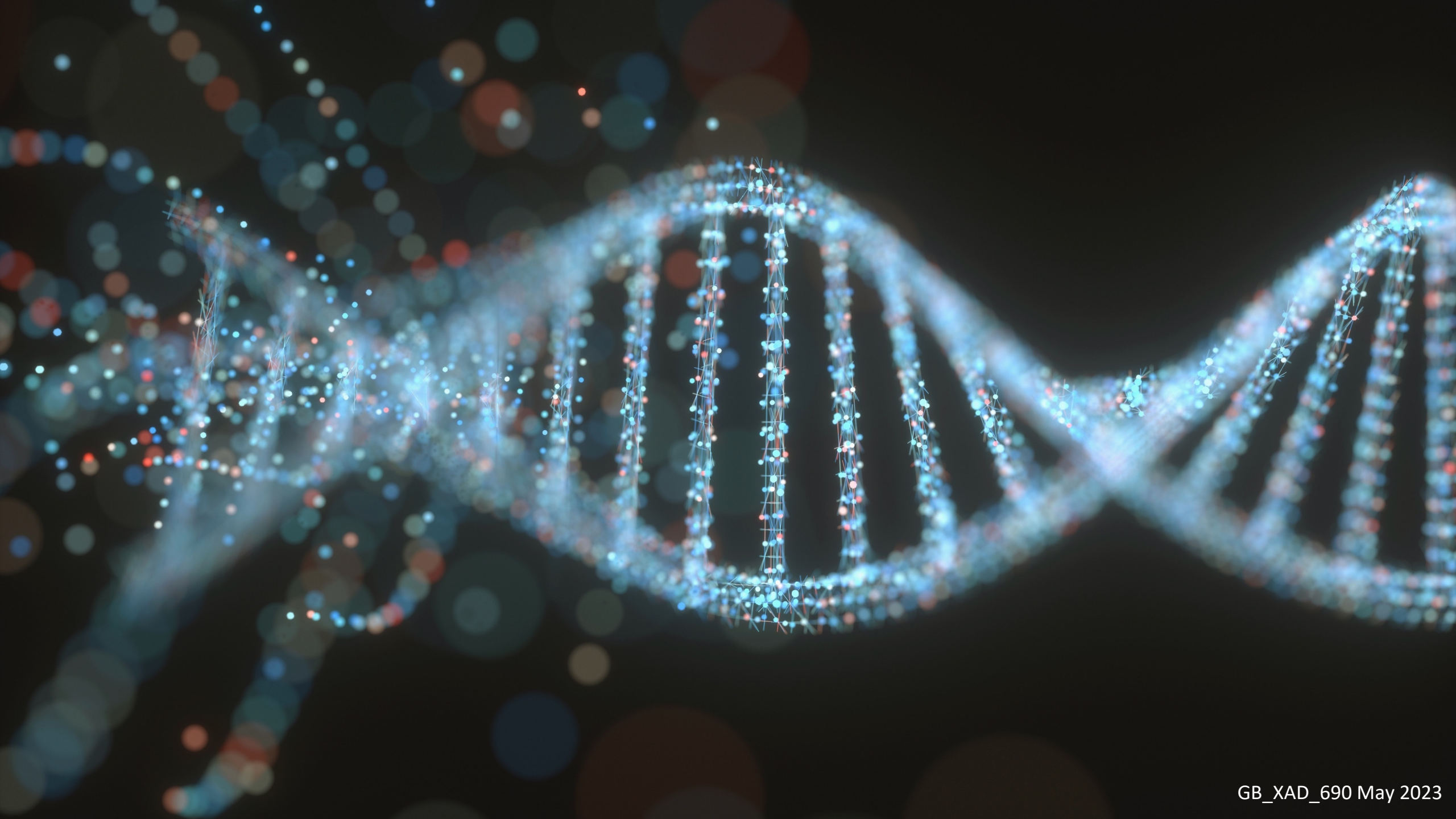
The potential utility of smell testing to screen for neurodegenerative disorders

Gregory R. Goodwin, Jonathan P. Bestwick and Alastair J. Noyce

Preventive Neurology Unit, Wolfson Institute of Population Health, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

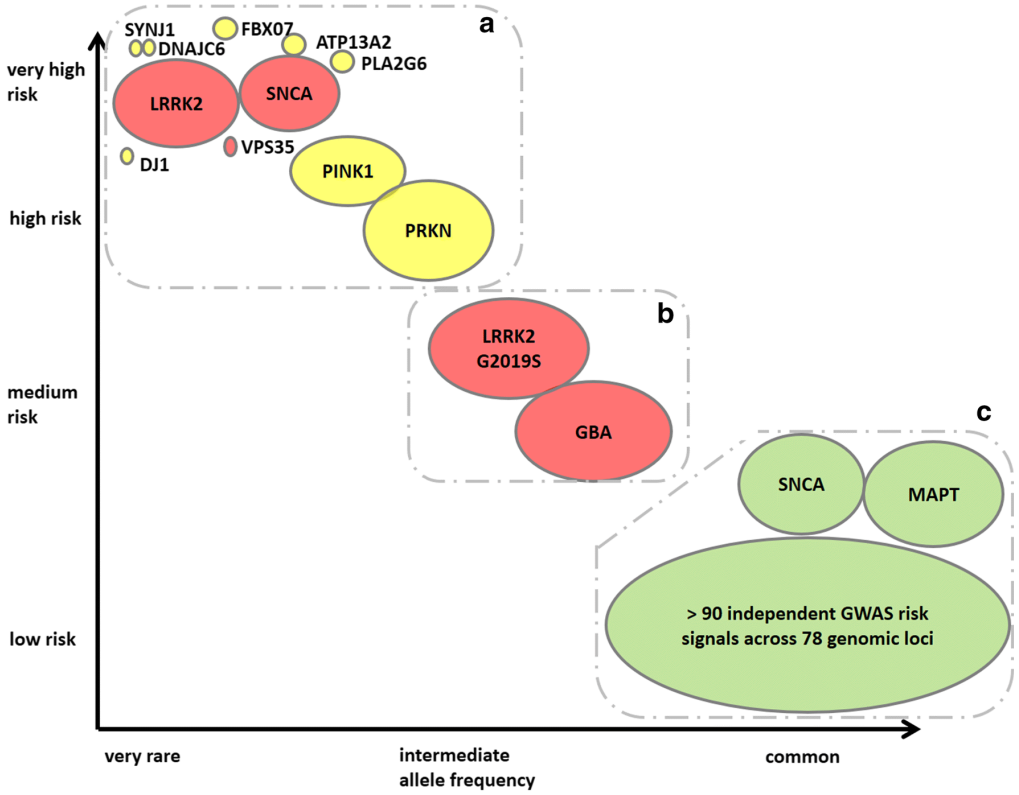


Siderowf A, et al. Lancet Neurol 2023.



GB_XAD_690 May 2023

Monogenic PD 5–10%
Most is ‘sporadic’



MAPT, microtubule-associated protein tau; PRKN, parkin RBR E3 ubiquitin protein ligase; PINK1, PTEN-induced kinase1; SNCA, synuclein alpha; SNP, single nucleotide polymorphism.


THE LANCET
Neurology
ARTICLES | VOLUME 18, ISSUE 12, P1091-1102, DECEMBER 01, 2019
Purchase

Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies

Mike A Nalls, PhD * • Cornelis Blauwendraat, PhD * • Costanza L Vallerga, MS * • Karl Heilbron, PhD * • Sara Bandres-Ciga, PhD * • Diana Chang, PhD * • et al. Show all authors • Show footnotes

Published: December, 2019 • DOI: https://doi.org/10.1016/S1474-4422(19)30320-5 • Check for updates

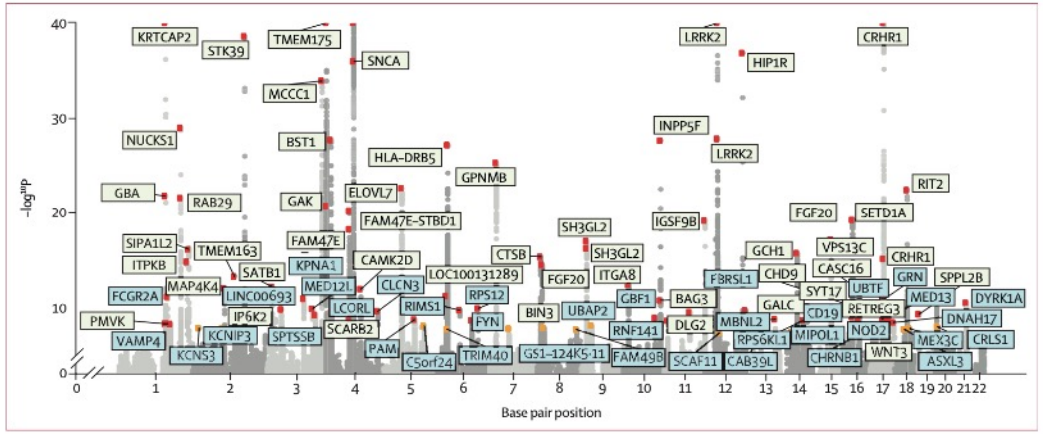


Figure 2: **Manhattan plot for significant variants**
The nearest gene to each of the 90 significant variants are labelled in green for previously identified loci and in blue for novel loci. $-\log_{10}$ p values were capped at 40. Variant points are colour-coded red and orange, with orange representing significant variants at $p=5\times10^{-8}$ and 5×10^{-8} and red representing significant variants at $p<5\times10^{-8}$. The X axis represents the base pair position of variants from smallest to largest per chromosome (1–22), only autosomes were included in this analysis.

7.8M SNPs in 37.7K cases, 18.6K UK Biobank proxy-cases (having a first degree relative with PD), and 1.4M controls.

Schneider SA et al, Neurotherapeutics 2020;17:1378–92
Nalls MA et al, Lancet Neurol 2019;18:1091–102

Genetic testing in the clinic

NICE guidelines

Parkinson's disease in adults

NICE guideline
Published: 19 July 2017
www.nice.org.uk/guidance/ng71

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

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

No mention of genetic analysis in either

International Parkinson and Movement Disorder Society

The objectives of Task Force on Recommendations for Clinical Genetic Testing in Parkinson's Disease are:

- Convene a panel of international experts to review the current state of the field in PD genetic testing and counseling in various regions of the world
- Review the ethical implications of genetic testing, counseling, and variable access to testing
- Build consensus on the policies and recommendations for PD clinical genetic testing and counseling

PD genetics panel

1. NEUROGENETICS UNIT

The Neurogenetics Unit is a department of the UCLH National Hospital for Neurology and Neurosurgery. The laboratory is co-situated with the Great Ormond Street Genetics (GOSH) Service, together forming the Rare & Inherited Disease Genomic Laboratory of the North Thames Genomics Laboratory Hub (GLH). Under this arrangement, for reports issued by Neurogenetics, technical laboratory services are provided by the GOSH laboratory (UKAS accredited medical laboratory no. 7883) and data interpretation and reporting is performed by Neurogenetics (UKAS accredited medical laboratory No. 8040), please check the UKAS website here: http://www.ukas.com/search-accredited-organisations/ for our current accredited scope. The Neurogenetics Unit provides a regional, national and international diagnostic service for inherited neurological disorders. Every test accepted by the laboratory is considered a service level agreement.

Laboratory Director
Professor H. Houlden PhD, MRCP (Clinical lead)
Head of Laboratory
Dr James Polke PhD, FRCPath
Quality Manager
Dr Vaneesha Gibbons PhD

Consultant Neurologists
Professor N.W. Wood PhD, FRCP, FMedSci

Professor M.G. Hanna MD, FRCP
Professor M.M. Reilly MD, FRCPI
Professor S. Tabrizi PhD, MRCP
Professor P. Giunti MD, PhD

Clinical Nurse Specialist
Ms L. Redmond RGN MSc

Note – *GBA* not there

R58.1 Adult onset neurodegenerative disorder PanelApp
GLH Regions Covered: North Thames
Notes: The primary indications for this test are ALS, Dementia, and PD. Any referral received where one of these is clearly the presenting phenotype will be tested with a targeted panel first, if clinically-relevant variants are detected, a report will be issued, if not, the entire Neurodegenerative Diseases panel will be analysed and a report issued from this. See also sections 2 and 3 below.

- PD Slice:

Genes Sequenced: *ATP13A2, ATP1A3, CHCHD2, CSF1R, DCTN1, DNAJC6, FBXO7, GCH1, GRN, LRRK2, MAPT, PANK2, PARK7, PINK1, PLA2G6, PRKN, SNCA, SPG11, SYNJ1, VPS13A, VPS35, WDR45, XPR1*
Other Notes: This test will also include MLPA for exonic deletions / duplications in *SNCA*, *PRKN*, *PINK1* and *PARK7*.

Test Name	Sample Requirements	Reporting Time (Calendar Days)	Testing Strategy	NHS Price * $	GLH Region Covered
Adult onset dystonia, chorea or related movement disorder (Panel) (R56.1)	Blood 5-10ml in EDTA	84	NGS	£1,105**	North Thames
Adult onset hereditary spastic paraplegia (Panel) (R60.1)	Blood 5-10ml in EDTA	84	NGS	£1,105**	North Thames
Adult onset neurodegenerative disorder (ALL Genes: Dementia, ALS, PD, and others) (Panel) (R58.1) #	Blood 5-10ml in EDTA	84	NGS	£1,105**	North Thames

What is Parkinson's disease

We are approaching a point in time where we will be forced to re-examine this question

Until then…