

Parkinson's disease and dementia with Lewy Bodies: Biological definition



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A biological definition of neuronal α -synuclein disease. towards an integrated staging system for research

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See [Comment](#) pages 129 and 133

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Parkinson's disease and dementia with Lewy bodies are currently defined by their clinical features, with α -synuclein pathology as the gold standard to establish the definitive diagnosis. We propose that, given biomarker advances enabling accurate detection of pathological α -synuclein (ie, misfolded and aggregated) in CSF using the α -synuclein amplification assay, it is time to redefine Parkinson's disease and dementia with Lewy bodies as neuronal α -synuclein disease rather than as clinical syndromes. This major shift from a clinical to a biological definition of Parkinson's disease and dementia with Lewy bodies takes advantage of the availability of tools to assess the gold standard for the diagnosis of neuronal α -synuclein (n- α syn) in human beings during life. Neuronal α -synuclein disease is defined by the presence of pathological n- α syn species detected in vivo (S; the first biological anchor) regardless of the presence of any specific clinical syndrome. On the basis of this definition, we propose that individuals with pathologi-

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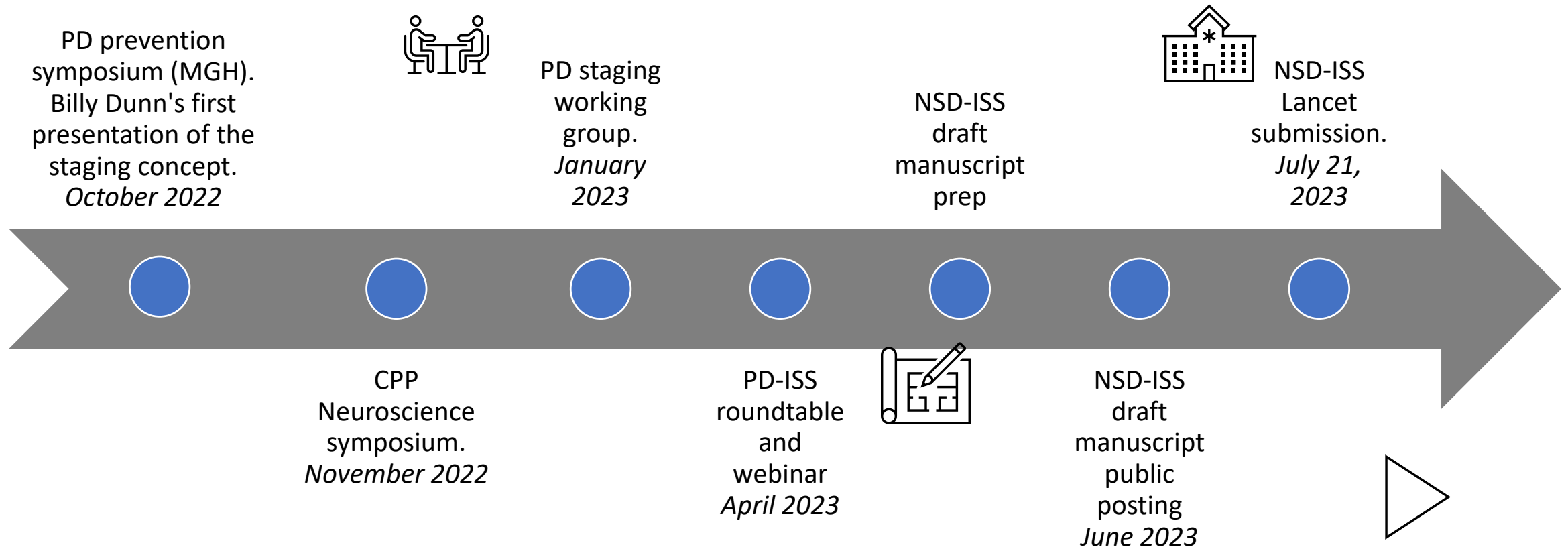
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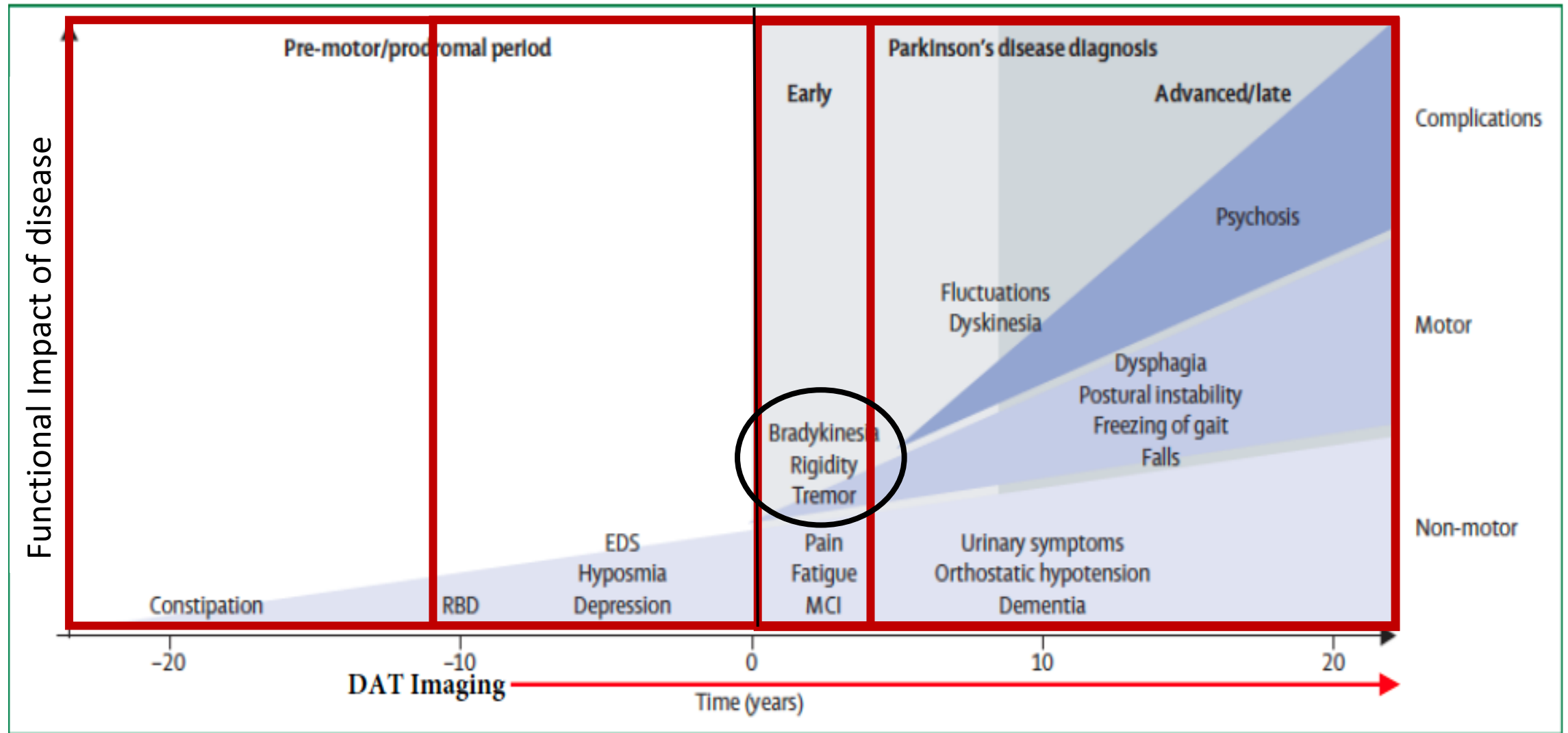
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High level timeline



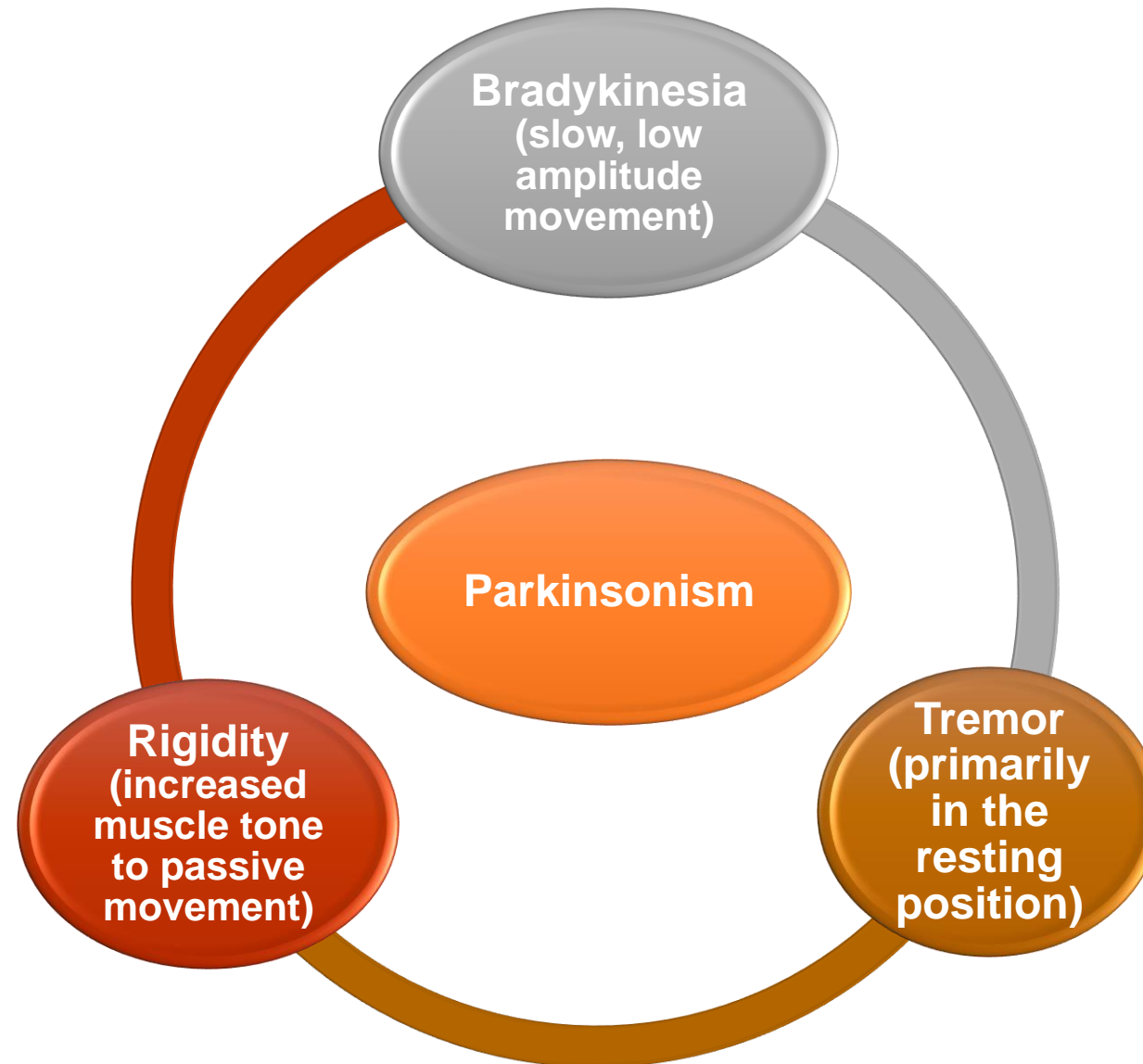


Simuni T, Chahine LM, Poston K et al “A biological definition of neuronal α -synuclein disease: towards an integrated staging system for research”, *The Lancet Neurology* (2024), Volume 23, Issue 2, Pages 178-190.



Kalia LV, Lang AE et al, *Lancet* 2015

Cardinal clinical features of Parkinson's disease



Other Neurodegenerative Syndromes:
Multiple System Atrophy (MSA),
Progressive Supranuclear Palsy (PSP),
Corticobasal Degeneration (CBD),
Others..



Secondary
(Drug induced, Vascular,
Toxic, Infectious)

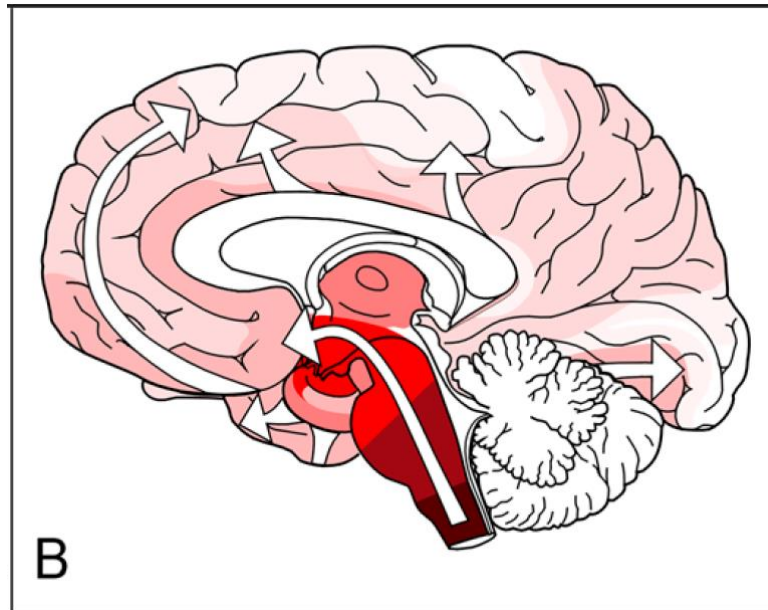
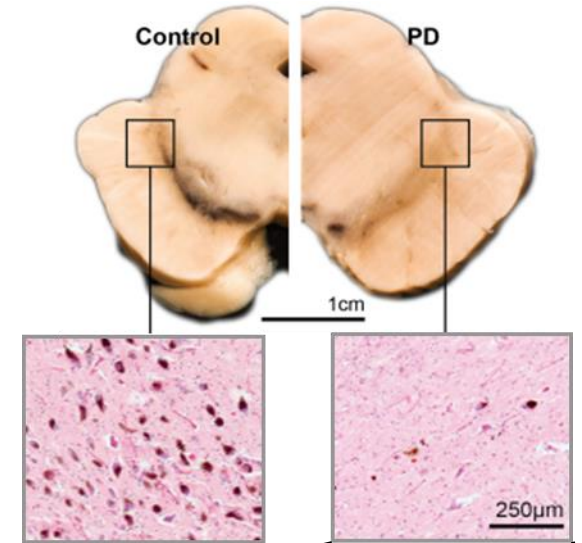
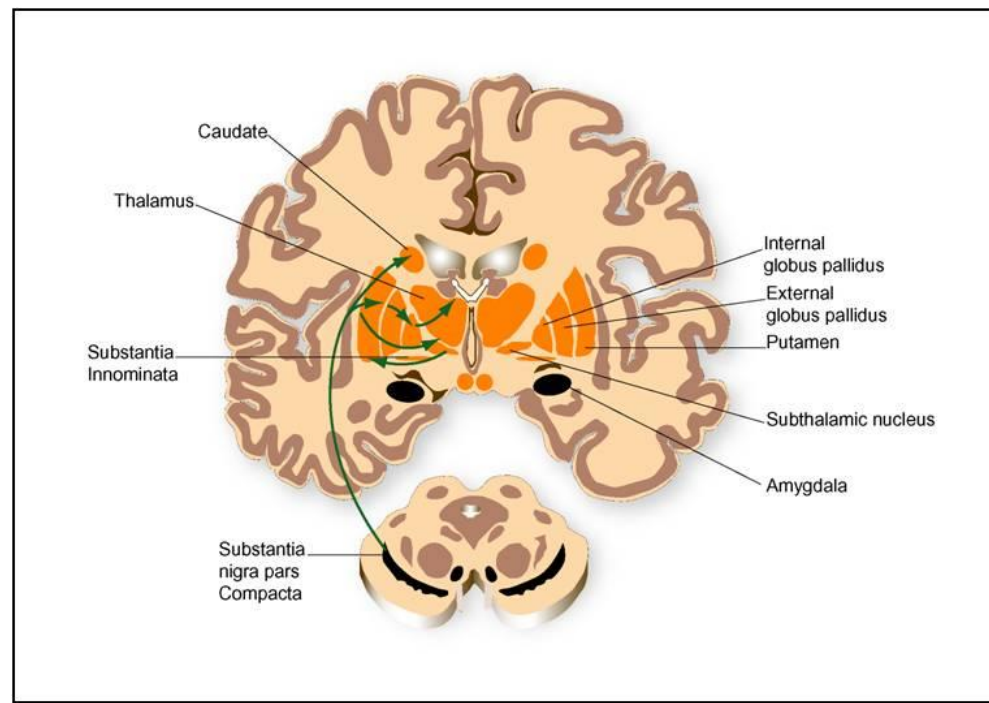


**Clinical
parkinsonism**

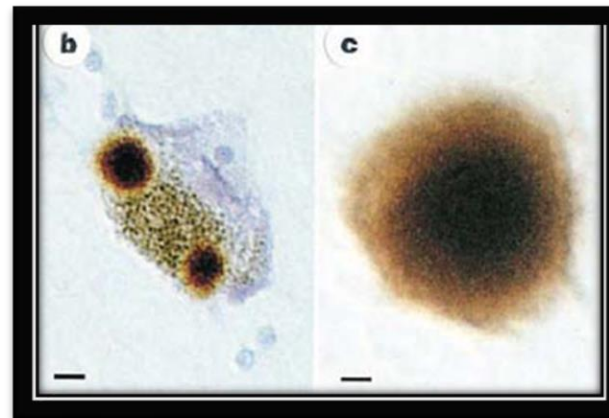
**Parkinson's
disease (PD)**



How do we know it's actually Parkinson's disease?

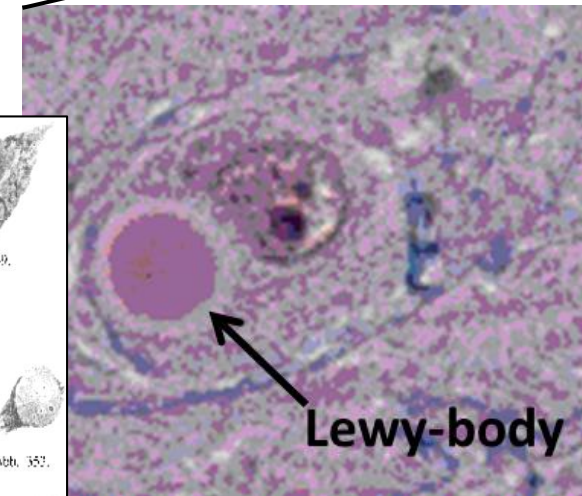
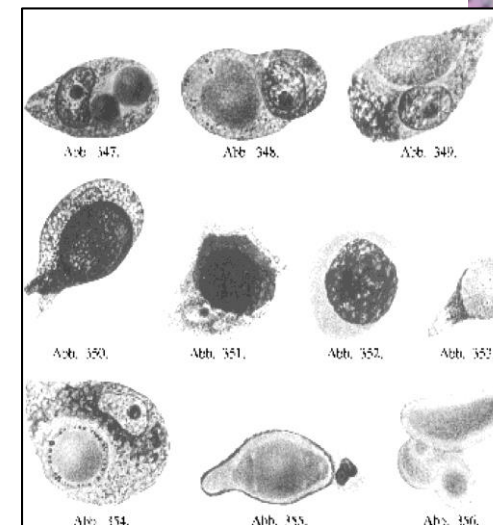


Year: 1998



Alpha (α) - synuclein

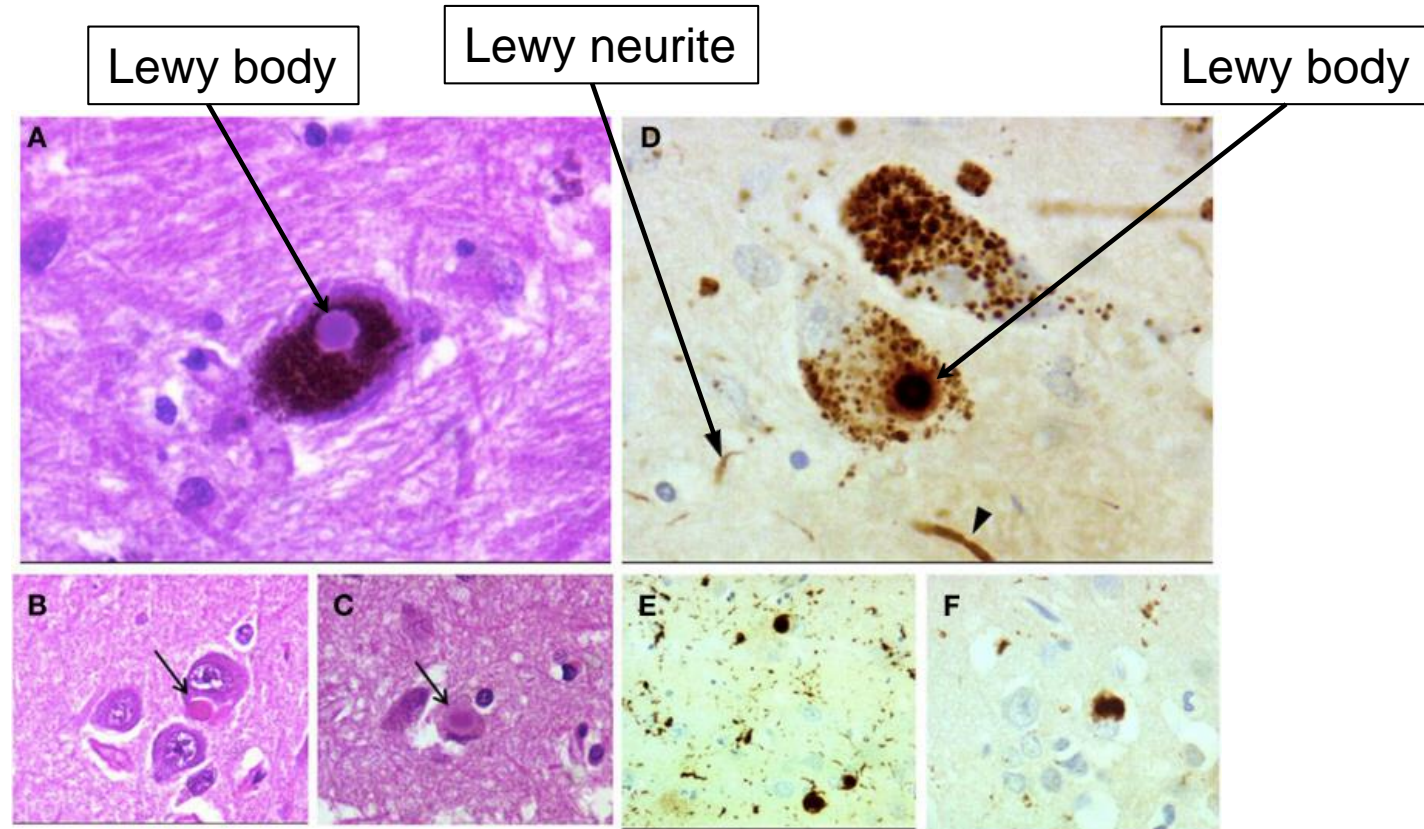
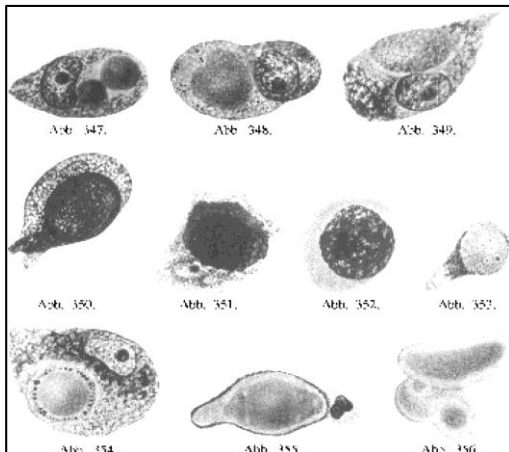
Year: 1912



Deposits of α -synuclein are found in people with Parkinson's disease and in people with dementia with Lewy bodies



Lewy (1912) described concentric inclusion bodies especially in the nucleus basalis, the substantia innominata and the dorsal motor nucleus of the vagus



A) Lewy body in a neuron of the substantia nigra, B) in a pyramidal cell of CA1 area of the hippocampus, and C) in cingulate cortex (C) (arrows). Lewy body (arrow) and Lewy neurites (arrowheads) in the substantia nigra (D). Cortical Lewy bodies (E,F). (A-C) hematoxylin-eosin; (D-F) anti- α -synuclein immunostaining.

Taipa R et al. *Front Neurol*. 2019

Other Neurodegenerative Syndromes:
Multiple System Atrophy (MSA),
Progressive Supranuclear Palsy (PSP),
Corticobasal Degeneration (CBD),
Others..



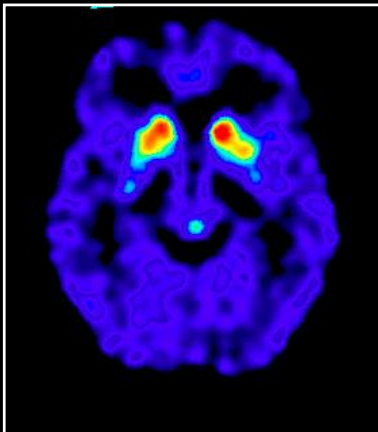
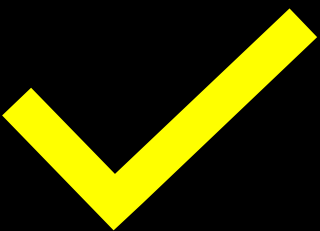
Secondary
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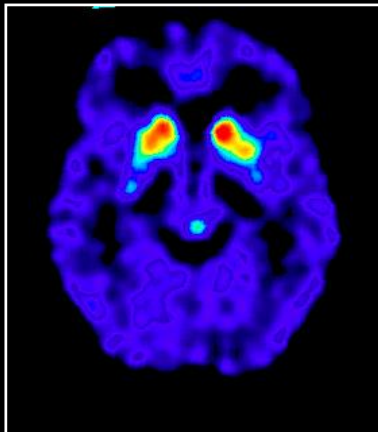
**Clinical
parkinsonism**

**Parkinson's
disease (PD)**

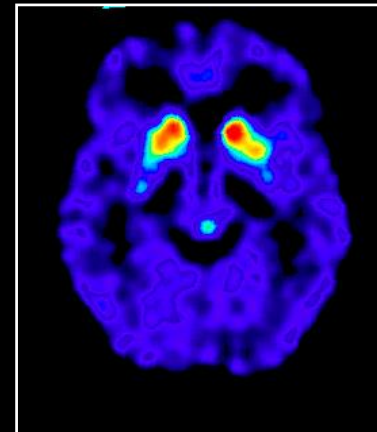




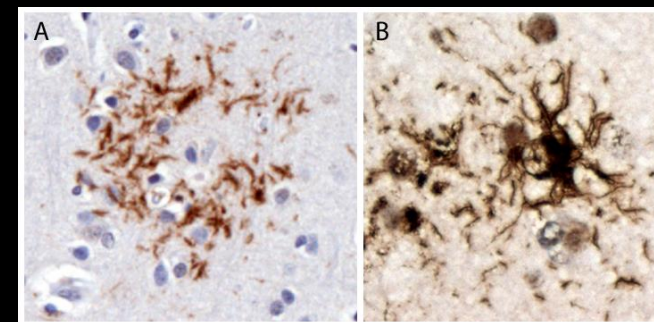
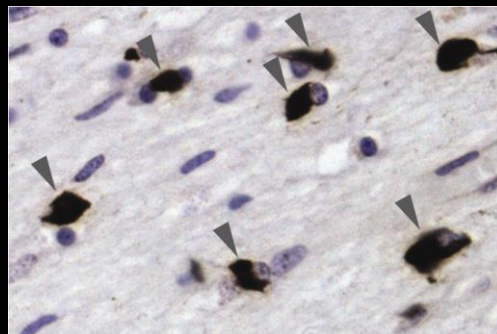
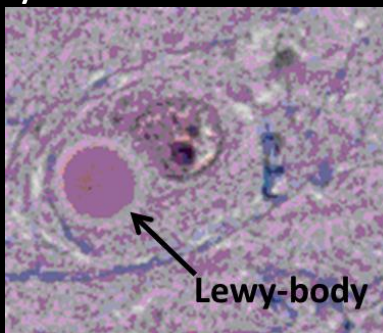
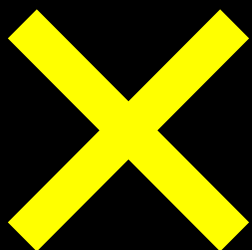
α -synuclein in the Neuron



α -synuclein in the Glial Cell



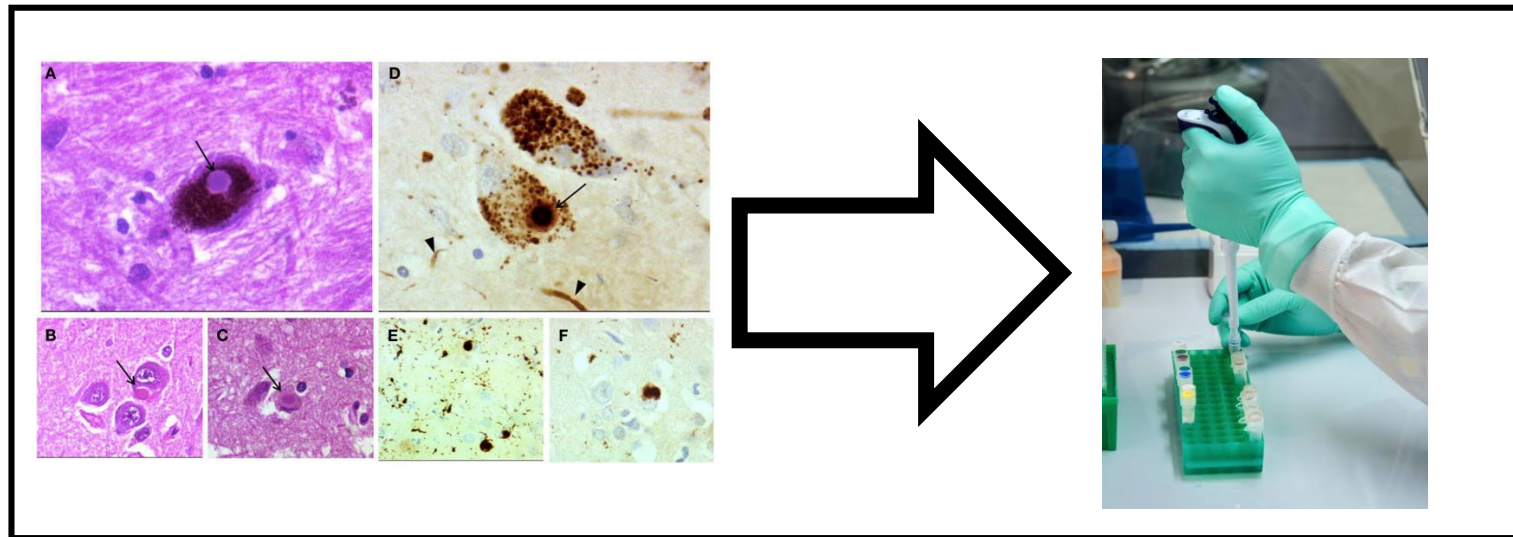
Tau in the Neuron



Multiple
System
Atrophy
(MSA)

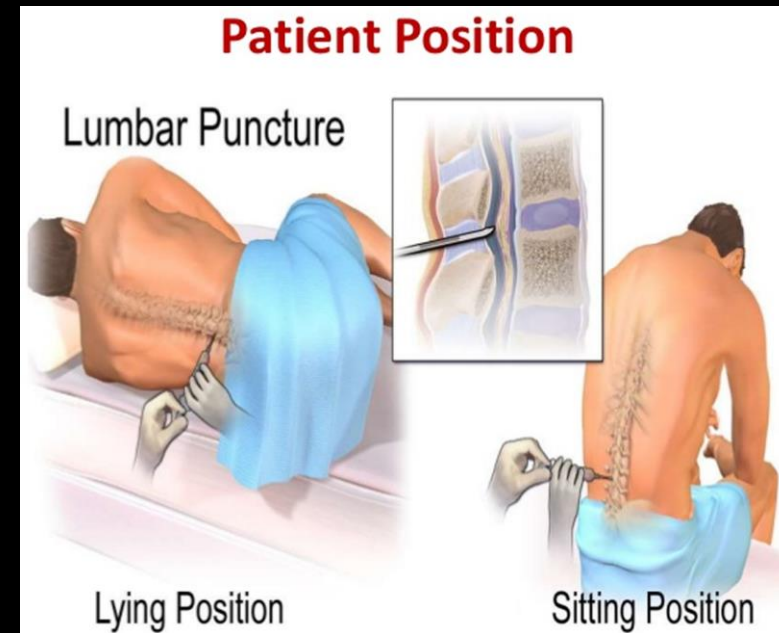
Progressive
Supranuclear Palsy (PSP)
and Corticobasal
Degeneration (CBD)

What is the status of assessing α -synuclein pathology in living people?



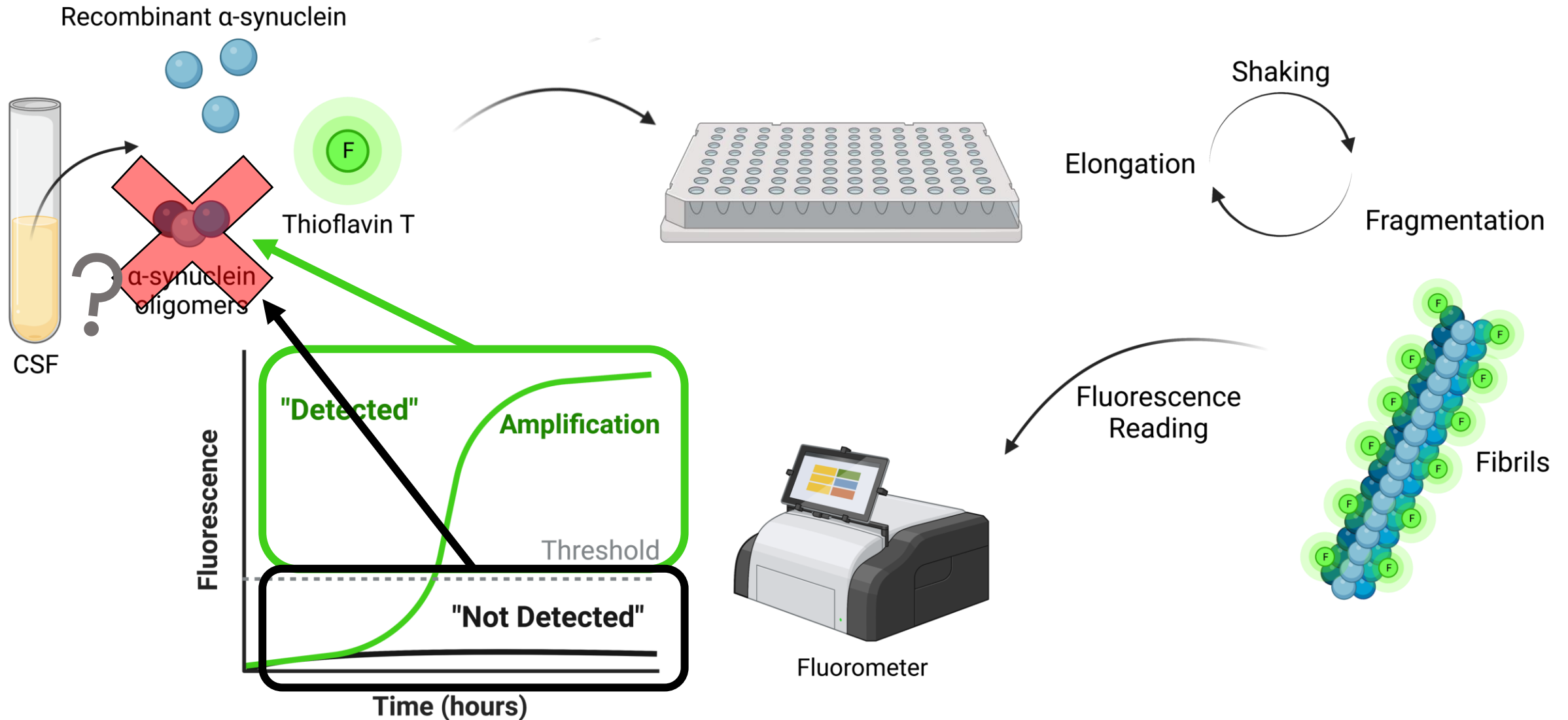
- Traditional ELISA-based assays trying to detect α -synuclein in people living with Parkinson's disease has had limitations
- The new biomarker addresses these limitations and can finally detect α -synuclein in living people.

- Requires a lumbar puncture (or spinal tap), which is done by a physician.
- Physician removes a few tablespoons of cerebrospinal fluid (CSF).
- CSF can be studied for different proteins or other chemicals that come from the brain.



Seed Amplification Assay (SAA) = RT-QulC and PMCA assays

Real-Time Quaking-Induced Conversion (RT-QulC) and Protein-Misfolding Cyclic Amplification (PMCA)



Synuclein Pathology

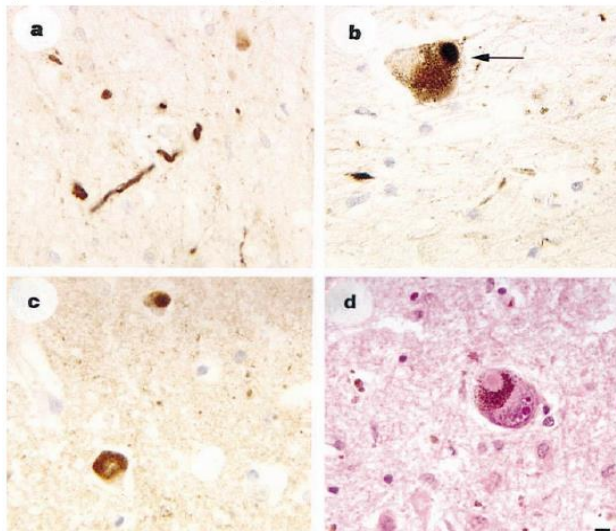


Synuclein seed amplification assay

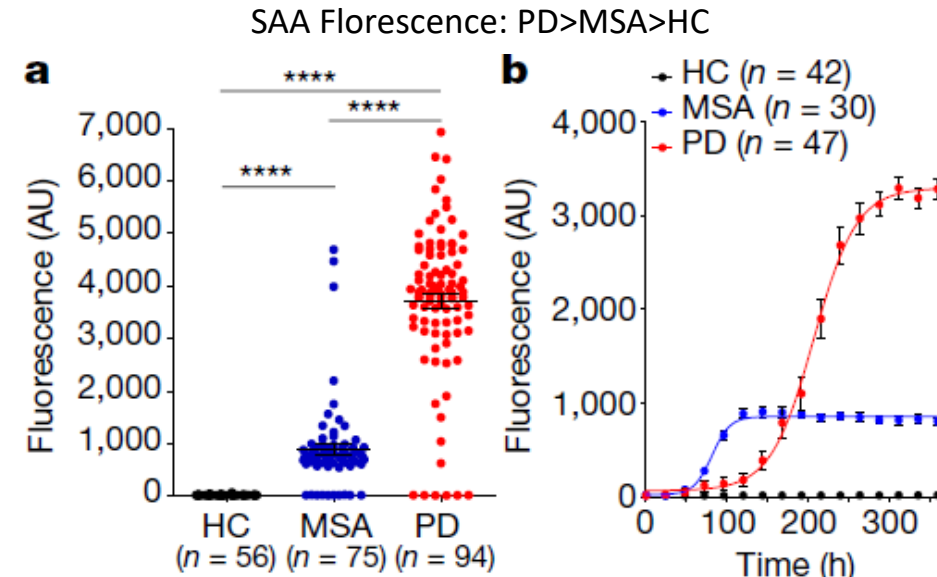
For now!



Lewy (1912) described concentric inclusion bodies especially in the nucleus basalis, the substantia innominata and the dorsal motor nucleus of the vagus



Spillantini, Schmidt, Lee, Trojanowski, Jakes and Goedert, Nature 1997



Shahnawaz et al. Nature, 2020

Accuracy of SAA for PD vs HC

Patients (#)	CTRL (#)	Max Sens	Max Spec	Reference
PD (20)	HC (20)	95%	100%	Fairfoul et al. (2016)
PD (12)	HC (28)	92%	100%	Groveman et al. (2018)
PD (105)	HC (79)	96%	90%	Kang et al. (2019)
PD (15)	HC (11)	100%	100%	Manne et al. (2019)
PD (108)	HC (85)	97%	87%	Orru` et al. (2020)
PD (88)	HC (56)	94%	100%	Shahnawaz et al. (2020)
PD (116)	HC (35)	91%	97%	Quadalti et al. (2021)
PD (30)	HC (30)	96% ^a	100%	Russo et al. (2021)
PD (74)	HC (55)	89%	96%	Poggiolini et al. (2021)
PD (235)	HC (26)	89%	99%	Brockman et al. (2021)

Adapted from: Bellomo G et al. α -Synuclein Seed Amplification Assays for Diagnosing Synucleinopathies: The Way Forward. Neurology; 2022: 99(5)

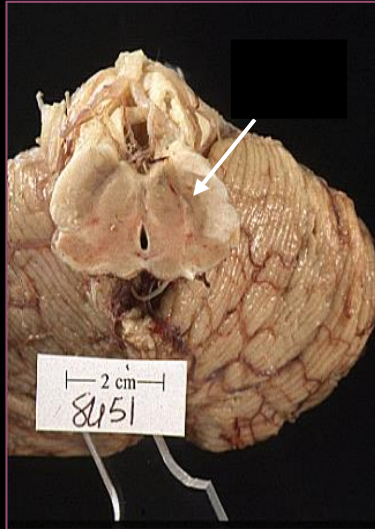
Dopaminergic Dysfunction



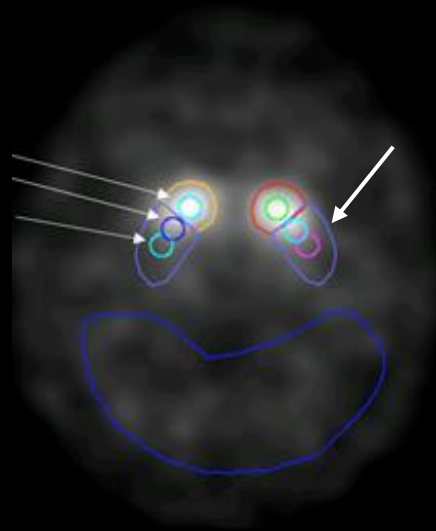
Dopamine imaging

For
now!

Severe loss of dopamine
Neurons (no black stripe)

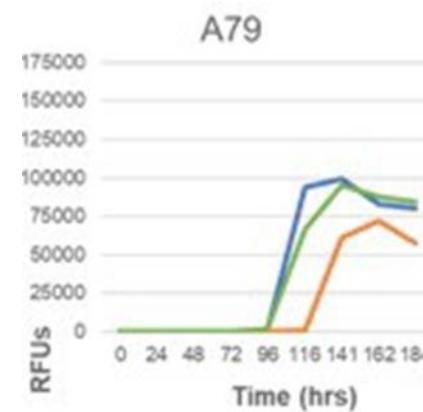
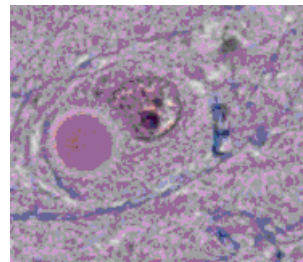
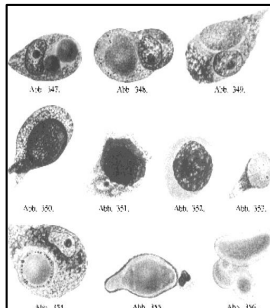
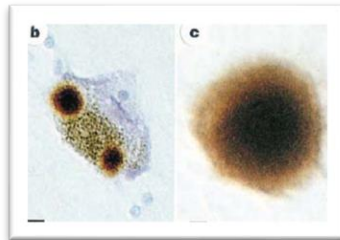


Severe loss of dopamine
production

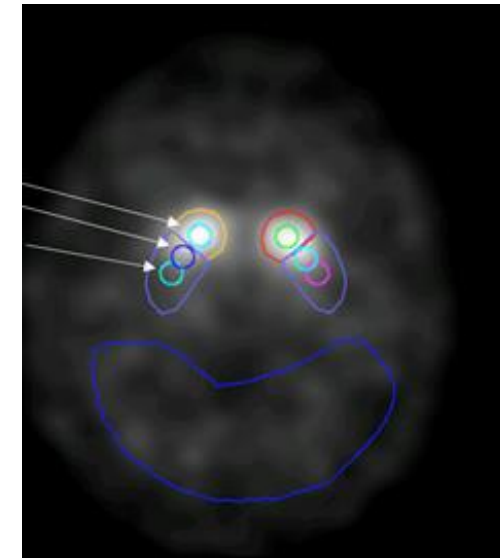


Biologic Definition of Neuronal alpha-Synuclein Disease (NSD)

- Neuronal alpha-Synuclein disease (NSD) is defined by presence of disease specific neuronal a-synuclein pathology and dopaminergic neuronal degeneration



Detected



How does NSD terminology integrate with PD/DLB clinical diagnosis?

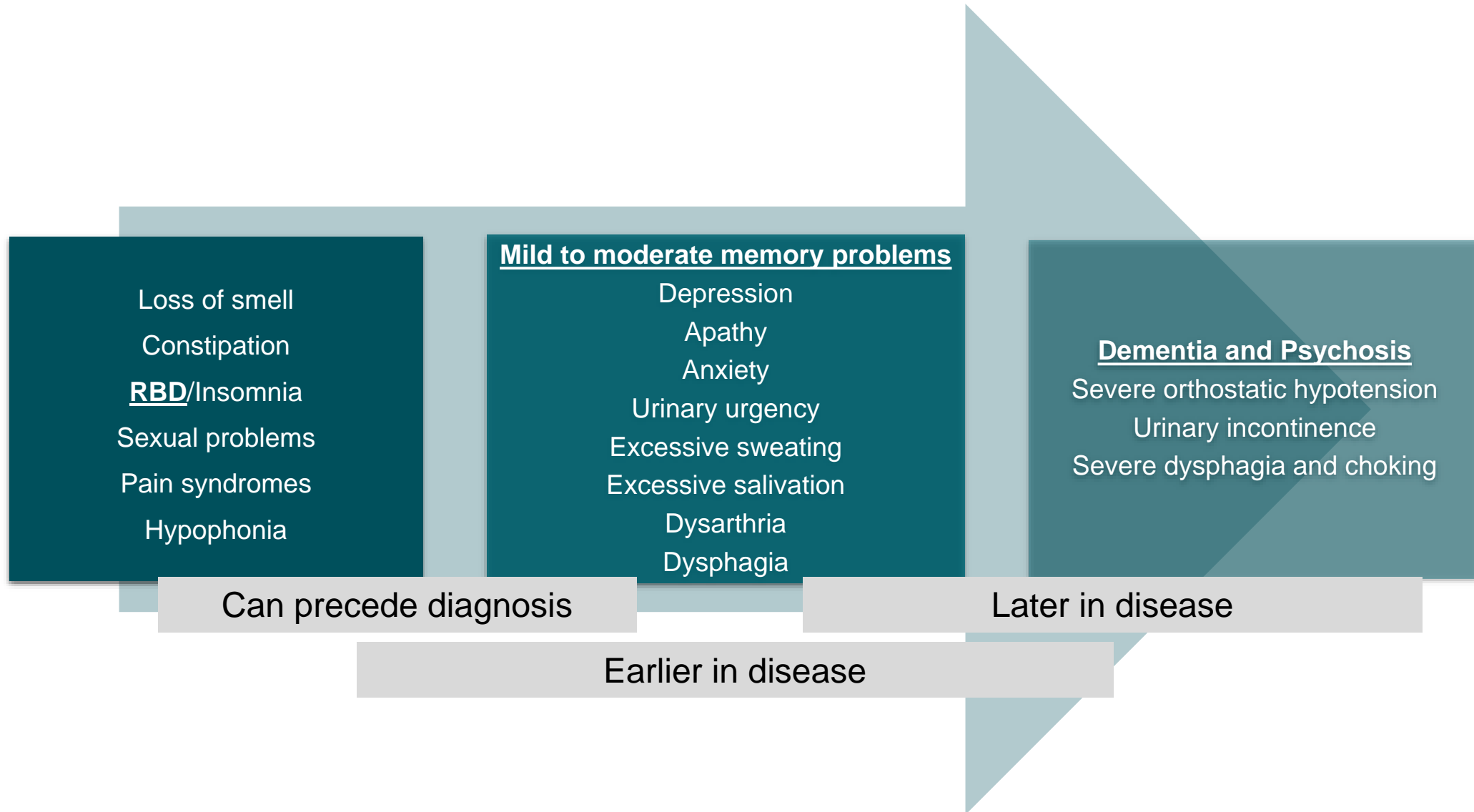
Parkinson's Disease

- Bradykinesia (required) and
 - + Tremor (at rest) or
 - + Rigidity

Dementia with Lewy bodies

- Dementia (required) and
 - 2 of the following:
 - + Parkinsonism
 - + Visual hallucinations
 - + REM sleep behavior disorder
 - + Cognitive fluctuations

The spectrum of Parkinson's Disease non-motor features



DIAGNOSTIC CRITERIA FOR PARKINSON’S DISEASE

DIAGNOSTIC CRITERIA FOR DEMENTIA WITH LEWY BODIES

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

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

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 criteria³¹ 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

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 hypotension³²—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

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria?

If no, neither probable PD nor clinically established PD can be diagnosed. If yes:

2. Are any absolute exclusion criteria present?

If “yes,” neither probable PD nor clinically established PD can be diagnosed. If no:

3. Number of red flags present

4. Number of supportive criteria present

5. Are there at least 2 supportive criteria and no red flags?

If yes, patient meets criteria for clinically established PD. If no:

6. Are there more than 2 red flags?

If “yes,” probable PD cannot be diagnosed. If no:

7. Is the number of red flags equal to, or less than, the number of supportive criteria?

If yes, patient meets criteria for probable PD

Yes☐

No☐

Yes☐

No☐

Yes☐

No☐

Yes☐

No☐

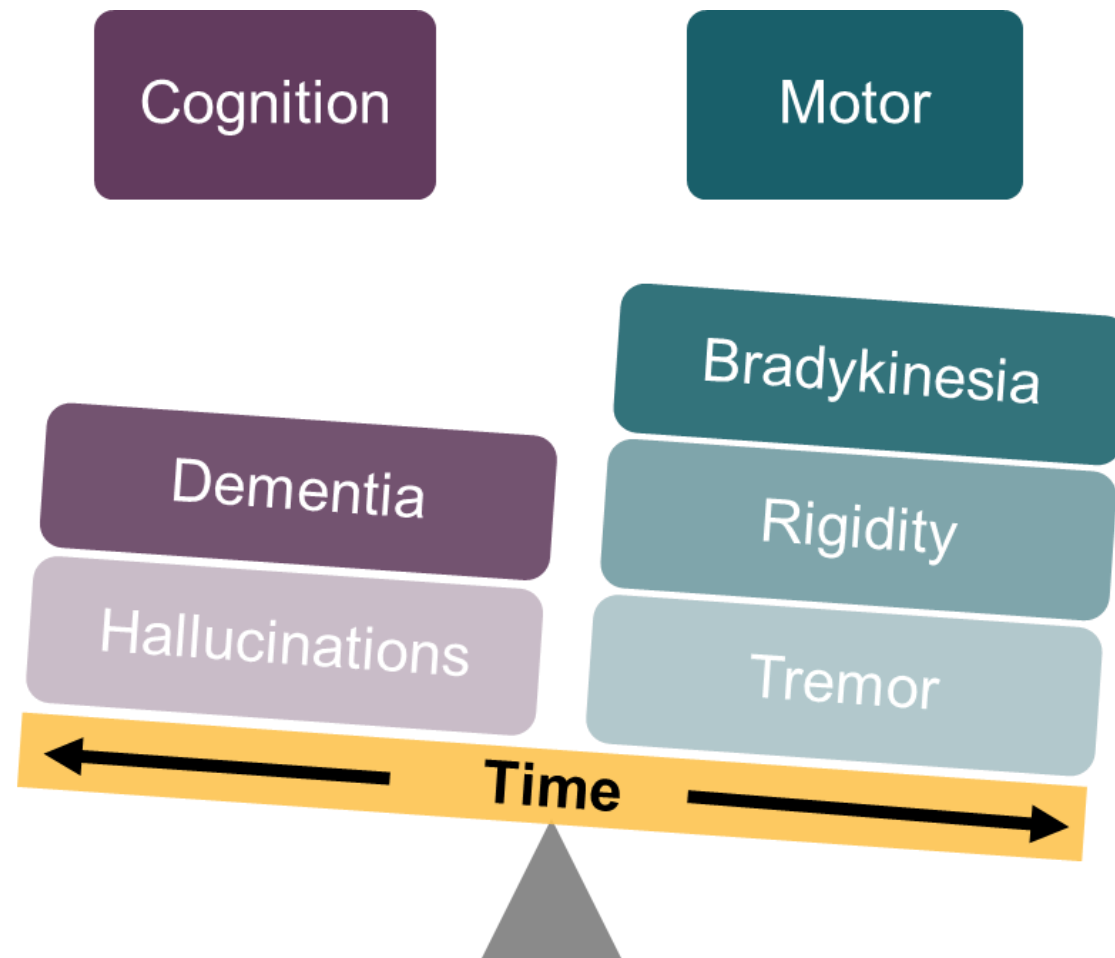
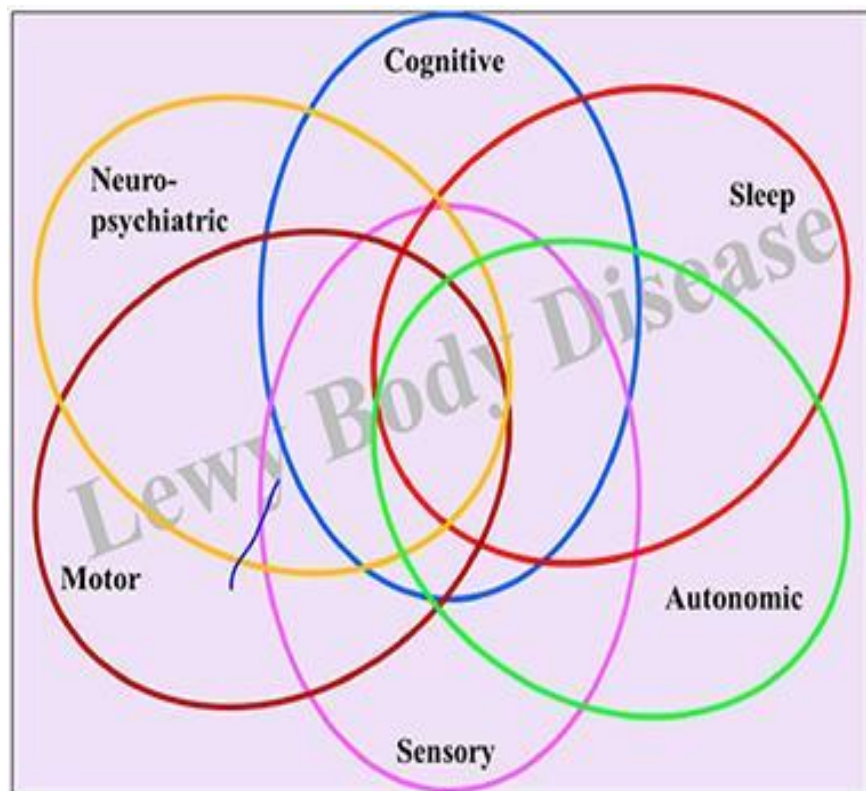
Yes☐

No☐

Yes☐

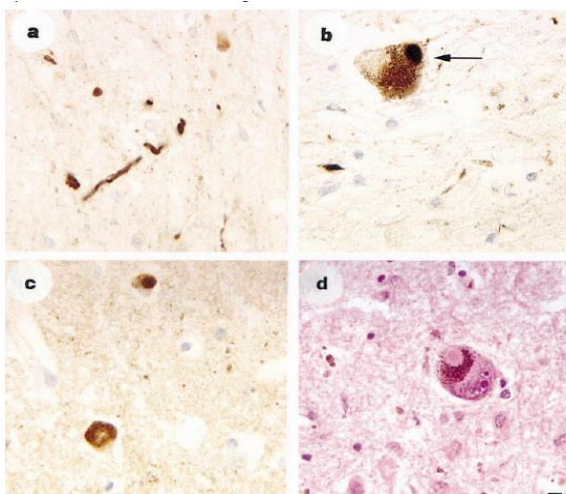
No☐

Table 1	Revised ^{1,2} criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)
Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuo-perceptual ability may be especially prominent and occur early.	
Core clinical features (The first 3 typically occur early and may persist throughout the course.)	
Fluctuating cognition with pronounced variations in attention and alertness. Recurrent visual hallucinations that are typically well formed and detailed. REM sleep behavior disorder, which may precede cognitive decline. One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.	
Supportive clinical features	
Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.	
Indicative biomarkers	
Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. Abnormal (low uptake) ¹²³ Iodine-MIBG myocardial scintigraphy. Polysomnographic confirmation of REM sleep without atonia.	
Supportive biomarkers	
Relative preservation of medial temporal lobe structures on CT/MRI scan. Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging. Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.	
Probable DLB can be diagnosed if:	
a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or	
b. Only one core clinical feature is present, but with one or more indicative biomarkers.	
Probable DLB should not be diagnosed on the basis of biomarkers alone.	
Possible DLB can be diagnosed if:	
a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or	
b. One or more indicative biomarkers is present but there are no core clinical features.	
DLB is less likely:	
a. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or	
b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia.	
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.	



Clinical Terminology conundrum

Parkinson's disease
Dementia with Lewy bodies
Lewy Body Disease
Lewy Body Dementia
PD dementia
Prodromal PD
Prodromal DLB



Weintraub D. "What's in a Name? The Time Has Come to Unify Parkinson's Disease and Dementia with Lewy Bodies." *Mov Disord.* 2023

How does NSD terminology coexist with PD/DLB clinical diagnosis?

- Most people with clinical symptoms or in clinical research will not have biomarker data to determine if the cause of their symptoms is NSD or not.
- For now, the designation of NSD will not change how people with PD or DLB are treated therapeutically (not appropriate for clinical use).
- For now, continuing to use the clinical definitions for diagnosis will be appropriate in most patients, and in people enrolled in clinical trials when biomarker data is not being used. We are not advocating for the abandonment of the term Parkinson's disease at this time.
- Coexistence of NSD and clinical diagnoses in a contextually appropriate way

Reality

Biomarker

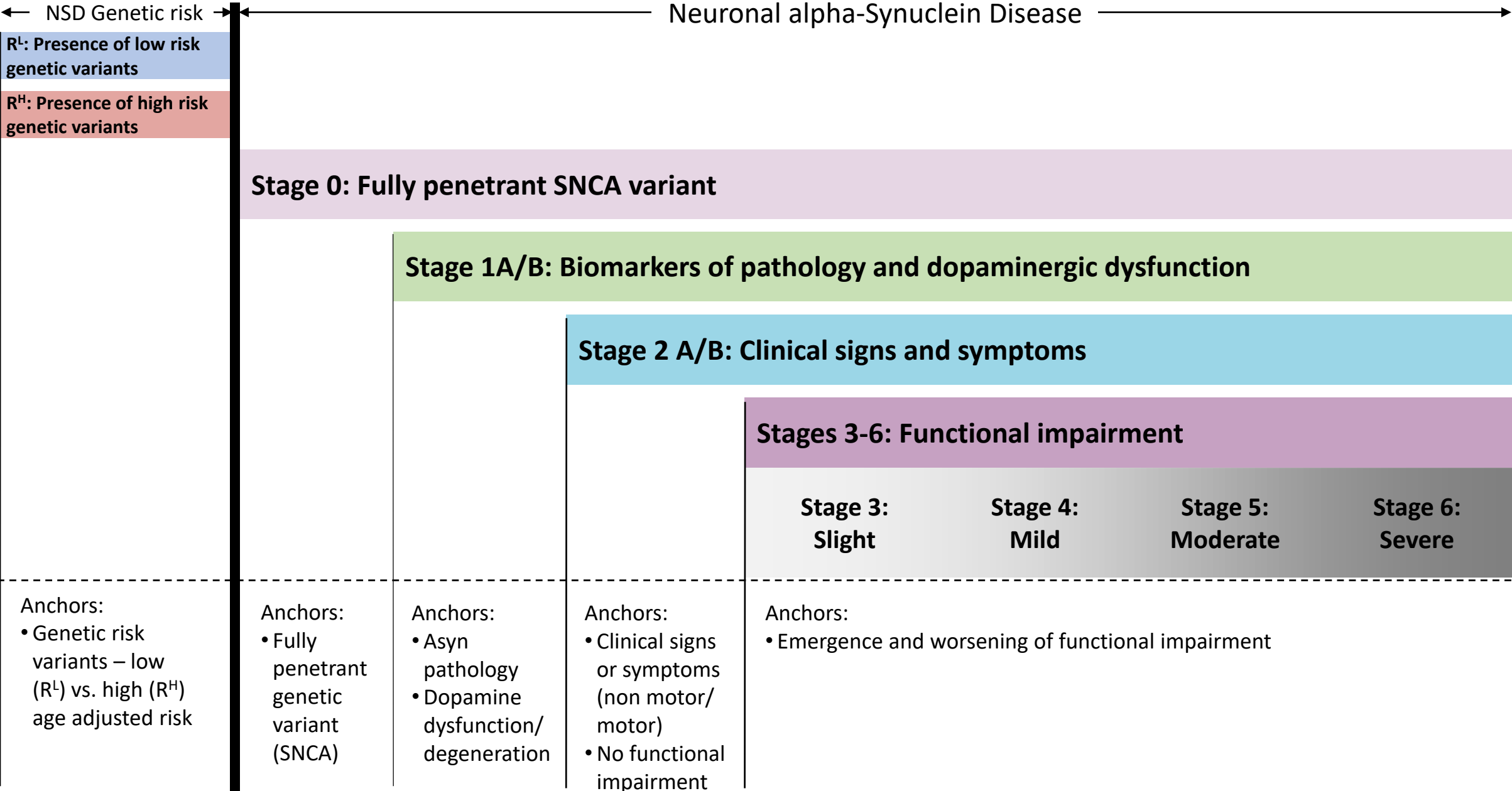
	Disease Positive (Parkinsons)	Disease Negative (Not Parkinsons)
Test Positive (Detected)	<u>True Positive</u>	False Positive
Test Negative (Not Detected)	False Negative	<u>True Negative</u>

From NSD definition to NSD staging

Purpose of staging

- Provides a framework for therapeutic development across the continuum from earliest stages to more advanced stages of NSD
 - Allows selection of patients with early *biologically defined* disease for enrollment into clinical trials
 - Enables stage-dependent selection of endpoints for clinical trials in these populations

NSD: an integrated staging system



Show me the data...

PPMI

Identify Biomarkers of PD progression to accelerate therapeutics to slow PD disability

- Specific biomarker data set
- Standardization of data acquisition and analyses
- Open access/Data sharing

Study Synopsis

STUDY POPULATION N=4000	ASSESSMENTS/ CLINICAL DATA COLLECTION	BIOLOGIC COLLECTION	SHARED DATA & BIOSAMPLES
<ul style="list-style-type: none">» 1100 PPMI current participants<ul style="list-style-type: none">» 700 PD» 100 HC» 300 Prodromal» 1000 newly enrolled at clinical site<ul style="list-style-type: none">» 900 PD» 100 HC» 2000 Prodromal PD – Enrolled through staged risk paradigm» Subjects followed for 5 to 13 years	<ul style="list-style-type: none">» Motor assessments» Neuropsychiatric/ Neurobehavioral testing» Autonomic, olfaction, sleep» DaTSCAN. MRI – imaging sub-studies» Digital data» Online PROs	<ul style="list-style-type: none">» DNA, RNA» Serum, whole blood and plasma collected at each visit; urine annually» CSF collected at baseline and then annually» IPSC in subset» Skin biopsy» Samples aliquotted and stored in central biorepository» Post-mortem tissue	<ul style="list-style-type: none">» Open-source data» > 10 M data downloads» Biosamples available; 200+ sample requests via BRC» Ancillary study opportunity» Subjects followed for 5 to 18 years

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 Ureña, 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 Cuspell-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†

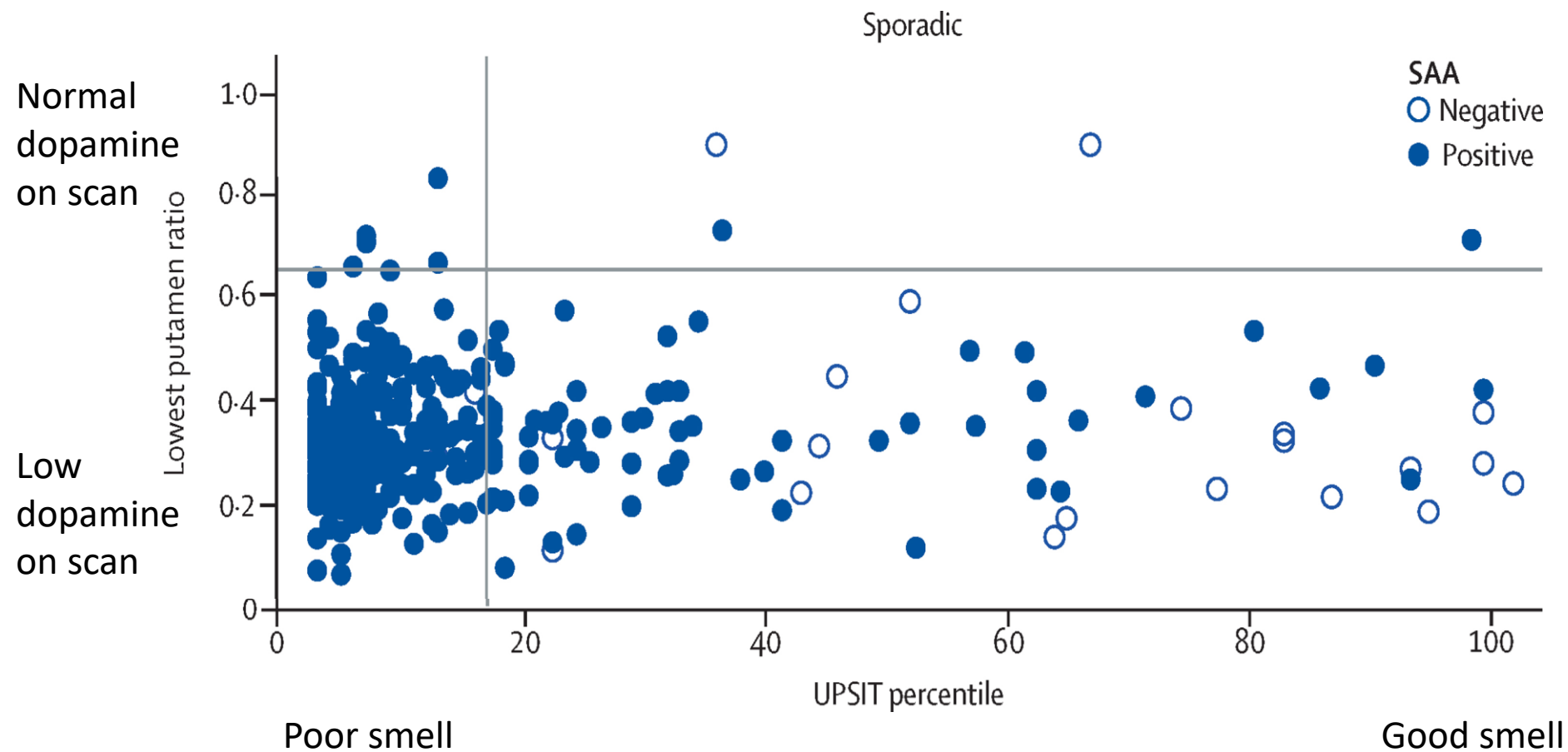
Lancet Neurol 2023; 22: 407–17



Parkinson's
Progression
Markers
Initiative



SAA in PPMI participants with Clinical symptoms present (newly diagnosed PD)

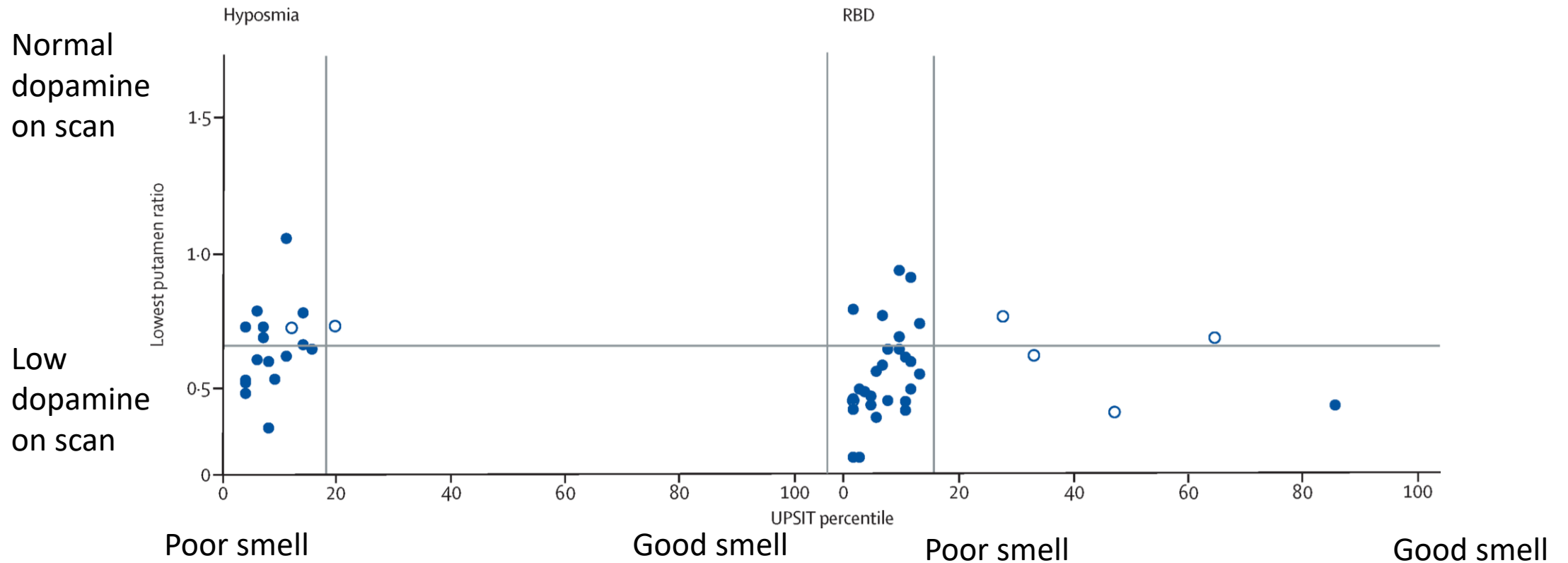


[Research News](#)**Breaking News: Parkinson's Disease Biomarker Found**

April 13, 2023

- The validation was carried out in some 1,123 samples of spinal fluid contributed by PPMI participants over the years.
- The assay proved amazingly accurate, with 93 percent of participants with Parkinson's having an abnormal test. (Very few tests for neurologic disorders are over 90 percent sensitive for disease.)
- The test was abnormal in less than 5 percent of people without Parkinson's.

**SAA in PPMI participants at risk for PD but with
no motor symptoms yet
(previously called *Prodromal*)**



In a small group of patients, the test accurately predicted what we found at autopsy

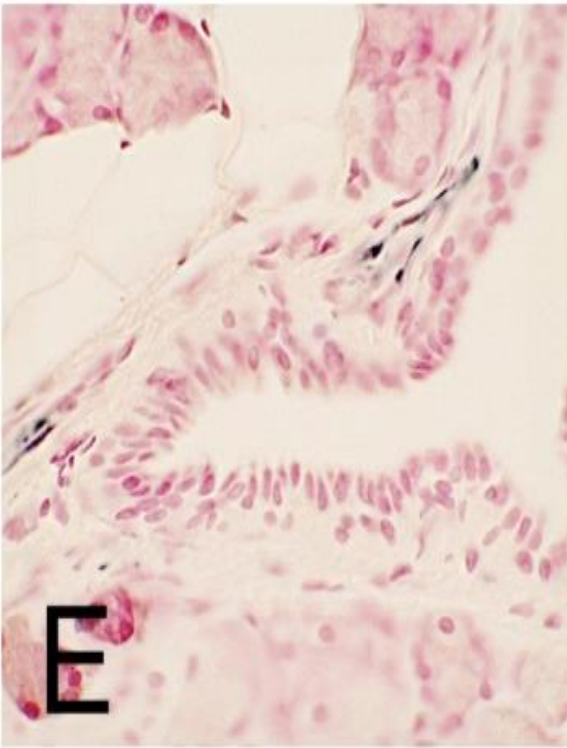
- Of the 19 people who have passed away and donated their brain to research, all 19 have confirmed the accuracy of the SAA assay.
- 17 participants were SAA positive in the CSF at the time of PD diagnosis and all had α -synuclein Lewy body pathology at autopsy
- 2 participants were SAA negative in the CSF at the time of diagnosis and neither of them had α -synuclein Lewy body pathology at autopsy

Can this test only be done with CSF?

- Right now, yes. The test can only be done on CSF.

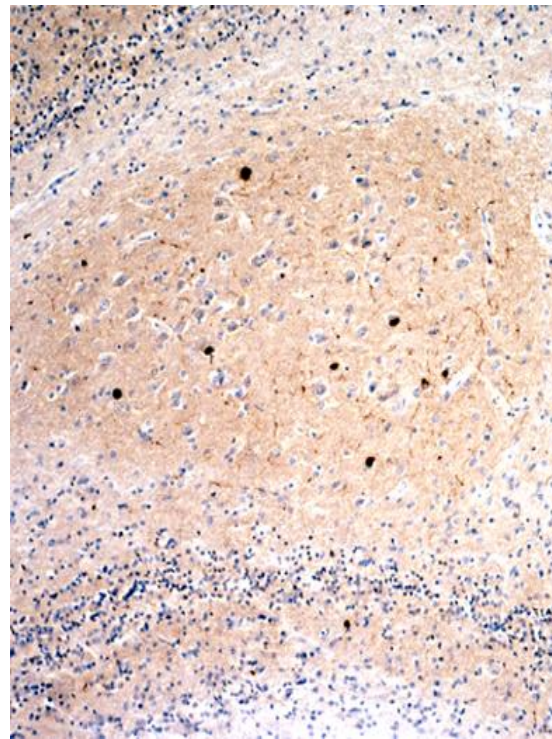
In people with PD, alpha-synuclein can be found in other parts of the body

Salivary gland



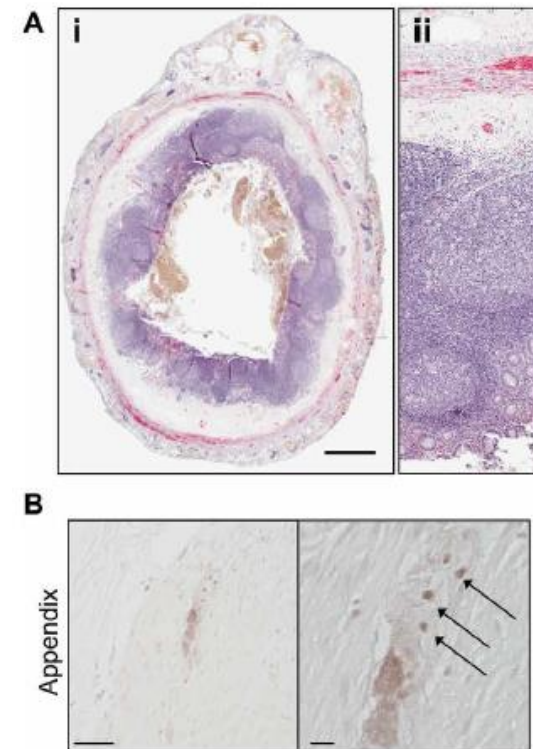
Courtesy of C. Adler MD, presented
at ADPD meeting Florence 2013

Olfactory bulb



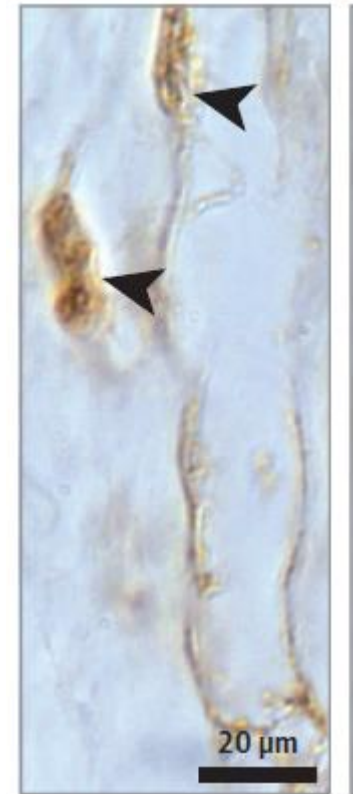
Courtesy of John Duda, MD, and J.
Noorigian, MPH

Appendix



Kilinger et al. Sci Trans Med
2018

Skin



Wang et al. JAMA
Neurology, 2020

SAA in Skin

- Skin biopsy is simple, quick requiring minimal expertise and is well tolerated



Punch biopsy



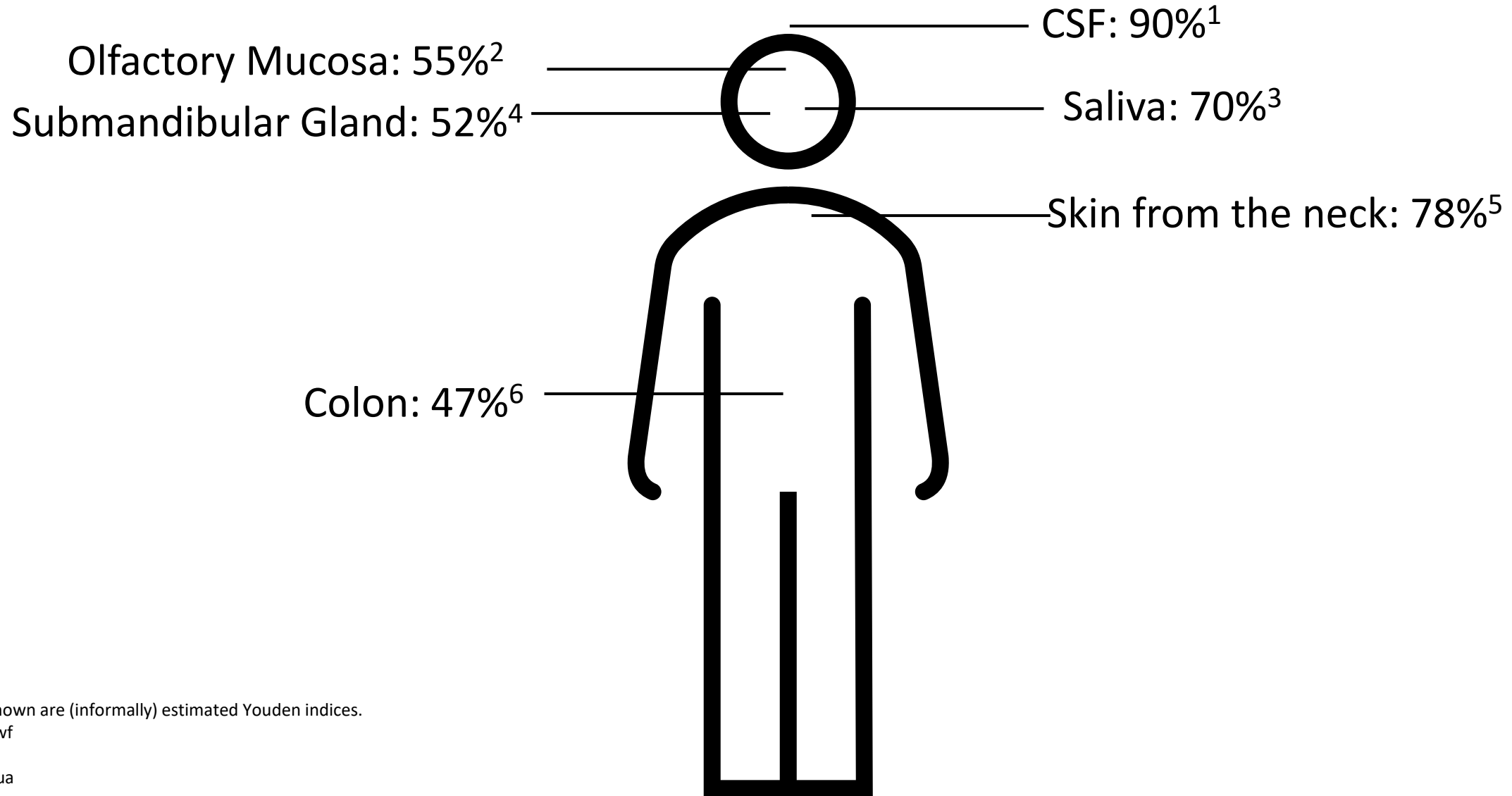
Packing with gel foam (no sutures required)

Relationship between CSF and Skin

31 patients with α -synucleinopathies vs 38 patients with non-synucleinopathies

	CSF SAA	Skin SAA
Sensitivity	78%	86%
Specificity	100%	80%
Accuracy	96%	82%

Accuracy of asyn SAA in peripheral specimens for PD Dx



Values shown are (informally) estimated Youden indices.

1 Siderowf

2 Perra

3 Vivacqua

4 Chahine

5 Kuzkina

6 Fenyi

Should I get this test done?

Should I get this test done? No.

- For people who already have a diagnosis of PD, the information from the test will not change anything about your current treatment options or care.
- While the results from skin biopsy look promising they are not approved yet, so they are only available through research.
- The additional hassle of the test from CSF after lumbar puncture, and cost of the test (\$1000, and not yet covered by Medicare or any insurance), are not worth it right now.

If I shouldn't do the test, why is it a big deal?

- This finding helps patients today because it has energized many big pharma (and start-up) companies to be interested in drug development for people with PD.
- Pharma companies can be more confident that the people who are enrolled in clinical trials have the underlying biology that is being targeted by their drug.

If I have this test, and the result is negative,
what does that mean?

If I have this test, and the result is negative, what does that mean?

1. The test is wrong (false negative)
2. You have Parkinsons, but not the kind caused by neuronal synuclein (Lewy Bodies).
 - A third of people with Parkinsons caused by a LRRK2 gene mutation will not have neuronal synuclein at autopsy (<2% of all people with Parkinsons)
 - You might have a different cause of parkinsonism (multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration)

Should people 'at risk' for Parkinson's or my family members get the test done?

Should people 'at risk' for Parkinson's or my family members get the test done?

- No
- The test has not been well validated yet in people who do not have any symptoms. Researchers are working on this, but right now we don't know if a positive test in a person completely asymptomatic is a 'false positive' or a 'true positive'.
- If we get a positive test in someone without any symptoms and it is a 'true positive', we do not know *when* they will develop symptoms. Researchers are working on answering this question as well.

The Future

- Consider participating in research studies focused on understanding biomarkers that can help us find better treatments for Parkinson's disease.

DID YOU KNOW

- 30% of all clinical trials fail to recruit a single person
- 85% of clinical trials face delays due to limited participation
- Fewer than 10% of Parkinson's patients ever take part in trials, despite overwhelming interest in working with scientists to help speed treatment breakthroughs

The Healthy Brain Aging Study

- NIH funded since 2015
- Goal is to understand mind and memory problems in Parkinson's disease, Alzheimer's disease and Aging
- People with Parkinson's disease who do not have memory problems and who have mild to moderate memory problems.
- People with a diagnosis of dementia with Lewy bodies
- We are also recruiting non-Parkinson's disease participants to understand age-related memory changes.
- 3 days the first year, then 1-2 days/year
- Research coordinator: Veronica Ramirez 650-721-2409 adrcstanford@stanford.edu

PPMI: Parkinsons Progression Biomarker Initiative

<http://www.ppmi-info.org/>

- Recruitment in the Bay Area is at UCSF
<https://clinicaltrials.ucsf.edu/trial/NCT04477785>
- A diagnosis of Parkinson disease for 2 years or less at Screening.
- Not expected to require PD medication with at least 6 months from Baseline.



Parkinson's
Progression
Markers
Initiative



The role of **gut microbes** in the pathogenesis of Parkinson's disease

Study lead:

Bianca Palushaj (neurology resident)

Study PI:

Dr. Ami Bhatt

Bhatt Lab Study Coordinators:

Meena Chakraborty

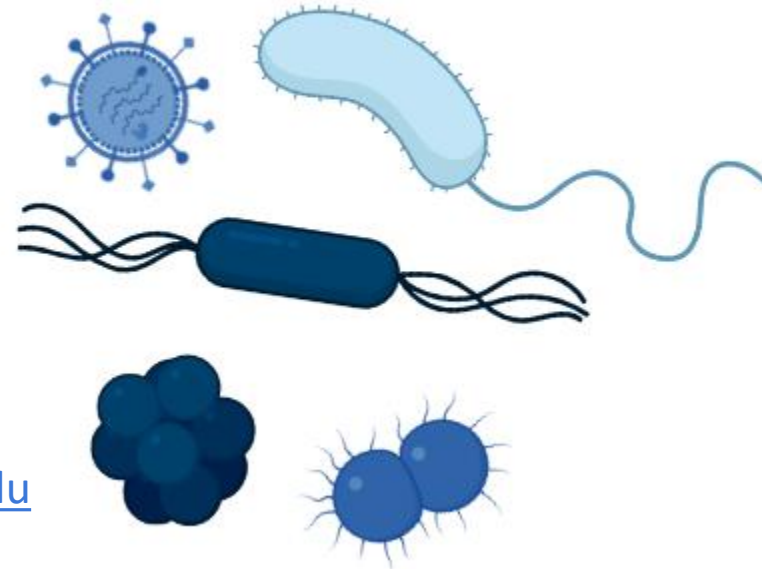
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Erin Brooks

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Stay Up to Date on Research

https://med.stanford.edu/neurology/divisions/md/clinicaltrials.html#parkinson_s

(or google Stanford Parkinson's Clinical Trials)

<https://clinicaltrials.ucsf.edu/parkinsons-disease>

Conclusions

- NSD as a biological definition is based on transformational ability to measure PD/DLB biology in living people
- NSD is strongly data supported and data driven
- Adoption of NSD and the associated integrated staging system (ISS) will enable
 - Selection of patients with early *biologically defined* disease for clinical trials
 - Stage dependent selection of endpoints for clinical trials in these populations
 - Transition to true disease prevention paradigm in therapeutic development
- **NSD-ISS will evolve** as new biomarkers are developed / validated but NSD-ISS provided the framework and construct that can be adapted / expanded

