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

Tanya Simuni*, Lana M Chahine*, Kathleen Poston, Michael Brumm, Teresa Buracchio, Michelle Campbell, Sohini Chowdhury, Christopher Coffey, Luis Concha-Marambio, Tien Dam, Peter DiBiaso, Tatiana Foroud, Mark Frasier, Caroline Gochanour, Danna Jennings, Karl Kieburz, Catherine M Kopil, Kalpana Merchant, Brit Mollenhauer, Thomas Montine, Kelly Nudelman, Gennaro Pagano, John Seibyl, Todd Sherer, Andrew Singleton, Diane Stephenson, Matthew Stem, Claudio Soto, Caroline M Tanner, Eduardo Tolosa, Daniel Weintraub, Yuge Xiao, Andrew Siderowf, Billy Dunn, Kenneth Marek

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 S15 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 diagnosis of neuronal α-synuclein (α-syn) in human beings during life. Neuronal α-synuclein disease is defined by the presence of pathological α-syn species detected in vivo (S; the first biological anchor) regardless of the specific clinical syndrome. On the basis of this definition, we propose that individuals with pathologica...
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High level timeline

PD prevention symposium (MGH). Billy Dunn’s first presentation of the staging concept. October 2022

CPP Neuroscience symposium. November 2022

PD staging working group. January 2023

NSD-ISS draft manuscript prep

NSD-ISS Lancet submission. July 21, 2023

PD-ISS roundtable and webinar April 2023

NSD-ISS draft manuscript public posting June 2023
Cardinal clinical features of Parkinson's disease

- Bradykinesia (slow, low amplitude movement)
- Rigidity (increased muscle tone to passive movement)
- Tremor (primarily in the resting position)
Clinical parkinsonism

Secondary (Drug induced, Vascular, Toxic, Infectious)

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

Parkinson’s disease (PD)
How do we know it’s actually Parkinson’s disease?
Alpha (α) - synuclein

Year: 1912

Year: 1998
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.
Clinical parkinsonism

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

Secondary (Drug induced, Vascular, Toxic, Infectious)

Parkinson’s disease (PD)
Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD)
What is the status of assessing \(\alpha\)-synuclein pathology in living people?

- Traditional ELISA-based assays trying to detect \(\alpha\)-synuclein in people living with Parkinson’s disease has had limitations.
- The new biomarker addresses these limitations and can finally detect \(\alpha\)-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-QuIC and PMCA assays

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

Recombinant α-synuclein

α-synuclein oligomers

Thioflavin T

CSF

Fluorescence vs Time (hours)

Threshold

"Detected"

"Not Detected"

Fluorometer

Fibrils

Shaking

Elongation

Fragmentation

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

**Accuracy of SAA for PD vs HC**

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

Dopaminergic Dysfunction

Severe loss of dopamine neurons (no black stripe)

Dopamine imaging

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.
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

- Loss of smell
- Constipation
- **RBD/Insomnia**
- Sexual problems
- Pain syndromes
- Hypophonia

**Mild to moderate memory problems**
- Depression
- Apathy
- Anxiety
- Urinary urgency
- Excessive sweating
- Excessive salivation
- Dysarthria
- Dysphagia

**Dementia and Psychosis**
- Severe orthostatic hypotension
- Urinary incontinence
- Severe dysphagia and choking

- Can precede diagnosis
- Later in disease
- Earlier in disease
### Diagnostic Criteria for Parkinson’s Disease

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first essential criterion to participation, which is defined as hallucinosis, in combination with at least 1 and often 2 or more, is that of a set of non-phenomenal entities such as echolalia and peripheral hallucinations. The Disorders of Movement and Recognition are criteria for PD.</td>
<td></td>
</tr>
<tr>
<td>1. Absence of a substantial number of features of the MDS-4, including all features of the non-phenomenal entities such as echolalia and peripheral hallucinations.</td>
<td></td>
</tr>
<tr>
<td>2. Absence of a substantial number of features of the MDS-4, including all features of the non-phenomenal entities such as echolalia and peripheral hallucinations.</td>
<td></td>
</tr>
<tr>
<td>3. No substantial number of features of the MDS-4, including all features of the non-phenomenal entities such as echolalia and peripheral hallucinations.</td>
<td></td>
</tr>
</tbody>
</table>

### Diagnostic Criteria for Dementia with Lewy Bodies

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Revised** criteria for the clinical diagnosis of probable and possible Dementia with Lewy bodies (DLB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functioning, or usual social activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent and occur early.</td>
<td></td>
</tr>
</tbody>
</table>

#### 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 precipitate cognitive decline.

#### Supportive clinical features

- Severe sensitivity to antipsychotic agents: postural instability, repeated falls, psychosis, or other extrapyramidal symptoms, or extrapyramidal symptoms.
- Excessive confusion, delirium, or hallucinosis.
- Echolalia, peripheral hallucinations, respiratory difficulties, ataxia, dysautonomia, hypotonicity, hyperkinesia, hypokinetic posturing in other mediational disorders, and parkinsonian features.

#### Indicative biomarkers

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
- Abnormal flow uptake on SPECT-MIBG myocardial scintigraphy.
- Polysomnographic confirmation of REM sleep without atonia.

#### Supportive biomarkers

- Relative preservation of medial temporal lobe structures on CTA MRI scans.
- Generalized slowing on SPECT/CT or functional imaging scan with reduced occipital activity in the skelateral spin.
- Prominent posterior slow activity on EEG with periodic fluctuations in the theta/alpha range.

#### Probable DLB can be diagnosed if:

- The core or more clinical features of DLB are present, with or without the presence of indicative biomarkers.
- Only one core clinical feature is present, but with one or more indicative biomarkers.

#### Possible DLB can be diagnosed if:

- Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or evidence of another clinical syndrome.
- B or more indicative biomarkers are present but there are no core clinical features.

#### DLB is less likely if:

- In the presence of any other physical illness or brain disorder including cardiovascular 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 presentations or further investigations.
- In the absence of any of the core clinical features of DLB, or in a patient with a non-demented Parkinsonian disease who is receiving symptomatic therapy.
- In the presence of any other physical illness or brain disorder including cardiovascular 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 presentations or further investigations.
- In the absence of any of the core clinical features of DLB, or in a patient with a non-demented Parkinsonian disease who is receiving symptomatic therapy.
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
<table>
<thead>
<tr>
<th>Reality</th>
<th>Disease Positive (Parkinsons)</th>
<th>Disease Negative (Not Parkinsons)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test Positive (Detected)</td>
<td><strong>True Positive</strong></td>
<td>False Positive</td>
</tr>
<tr>
<td>Test Negative (Not Detected)</td>
<td>False Negative</td>
<td><strong>True Negative</strong></td>
</tr>
</tbody>
</table>
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

Stage 0: Fully penetrant SNCA variant

Stage 1A/B: Biomarkers of pathology and dopaminergic dysfunction

Stage 2 A/B: Clinical signs and symptoms

Stages 3-6: Functional impairment

Stage 3: Slight
Stage 4: Mild
Stage 5: Moderate
Stage 6: Severe

Anchors:

- Genetic risk variants – low (RL) vs. high (RH) age adjusted risk
- Fully penetrant genetic variant (SNCA)
- Asyn pathology
- Dopamine dysfunction/degeneration
- Clinical signs or symptoms (non motor/motor)
- No functional impairment

Anchors:

- Emergence and worsening of functional impairment
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 Population

<table>
<thead>
<tr>
<th>N=4000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1100 PPMI current participants</td>
</tr>
<tr>
<td>700 PD</td>
</tr>
<tr>
<td>100 HC</td>
</tr>
<tr>
<td>300 Prodromal</td>
</tr>
<tr>
<td>1000 newly enrolled at clinical site</td>
</tr>
<tr>
<td>900 PD</td>
</tr>
<tr>
<td>100 HC</td>
</tr>
<tr>
<td>2000 Prodromal PD – Enrolled through staged risk paradigm</td>
</tr>
</tbody>
</table>

Subjects followed for 5 to 13 years

### Assessments/Clinical Data Collection

- Motor assessments
- Neuropsychiatric/Neurobehavioral testing
- Autonomic, olfaction, sleep
- DaTSCAN, MRI – imaging sub-studies
- Digital data
- Online PROs

### Biologic Collection

- 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

### Shared Data & Biosamples

- Open-source data
- > 10 M data downloads
- Biosamples available; 200+ sample requests via BRC
- Ancillary study opportunity
- Subjects followed for 5 to 18 years

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

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

Andrew Siderowf, Luis Correa-Manzano, David-Rick Lufton, Carly M. Farris, Yihua Ma, Pasuki Attanarajah, Fatimah Ansawi, Roy N. Alcalay, Lane M. Chatterjee, Tatiana Fonov, Douglas Geleris, Karl Kieburtz, Kalpana Merchant, Erin Mullenberg, Kathleen L. Poston, Xiuqin Sebji, Tanya Simuni, Caroline M. Tanner, David Wurtz, Aleksandra Vladimirova, Seung-Ho Cho, Ryan Korth, Sherry Willard-Garcia, Christopher S. Coffey, Mark Fraser, Luis M. A. Oliveira, Samantha Hutton, Todd Shree, Kenneth Mank, Claudia Soto, on behalf of the Parkinson's Progression Markers Initiative

_Lancet Neurol. 2019; 18: 402-17_
SAA in PPMI participants with Clinical symptoms present
(newly diagnosed PD)

Siderowf et al Lancet Neuro 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 \( \alpha \)-synuclein Lewy body pathology at autopsy

- 2 participants were SAA negative in the CSF at the time of diagnosis and neither of them had \( \alpha \)-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

<table>
<thead>
<tr>
<th></th>
<th>CSF SAA</th>
<th>Skin SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>78%</td>
<td>86%</td>
</tr>
<tr>
<td>Specificity</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>96%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Donadio et al. In Vivo Diagnosis of Synucleinopathies: A Comparative Study of Skin Biopsy and RT-QuIC. Neurology. 2021. 18;96(20)
Accuracy of asyn SAA in peripheral specimens for PD Dx

- Olfactory Mucosa: 55%²
- Submandibular Gland: 52%⁴
- CSF: 90%¹
- Saliva: 70%³
- Skin from the neck: 78%⁵
- Colon: 47%⁶

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.
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
PhD Candidate
mchakra@stanford.edu

Erin Brooks
Research Assistant
efbrooks@stanford.edu
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
  o Selection of patients with early biologically defined disease for clinical trials
  o Stage dependent selection of endpoints for clinical trials in these populations
  o 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