

# Advances in Biomarkers of Alpha-Synuclein

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*Stanford University*

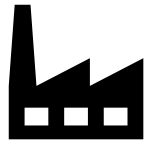
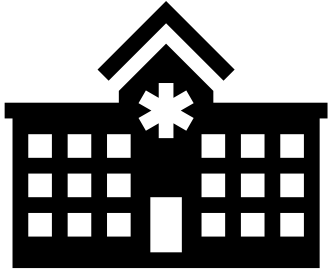
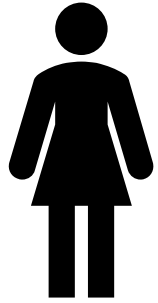


**Stanford**  
MEDICINE

# Disclosures

- Scientific advisory board for Amprion
- Consultancy fees for Curasen, Biohaven and Novartis
- Grants from NIH/NINDS NS115114, NS062684, NS075097, NIH/NIA U19 AG065156, P30 AG066515, The Michael J. Fox Foundation, Lewy Body Dementia Association, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Sue Berghoff LBD Research Fellowship and the Knight Initiative for Brain Resilience.

# Imagine...



Cardiovascular screening

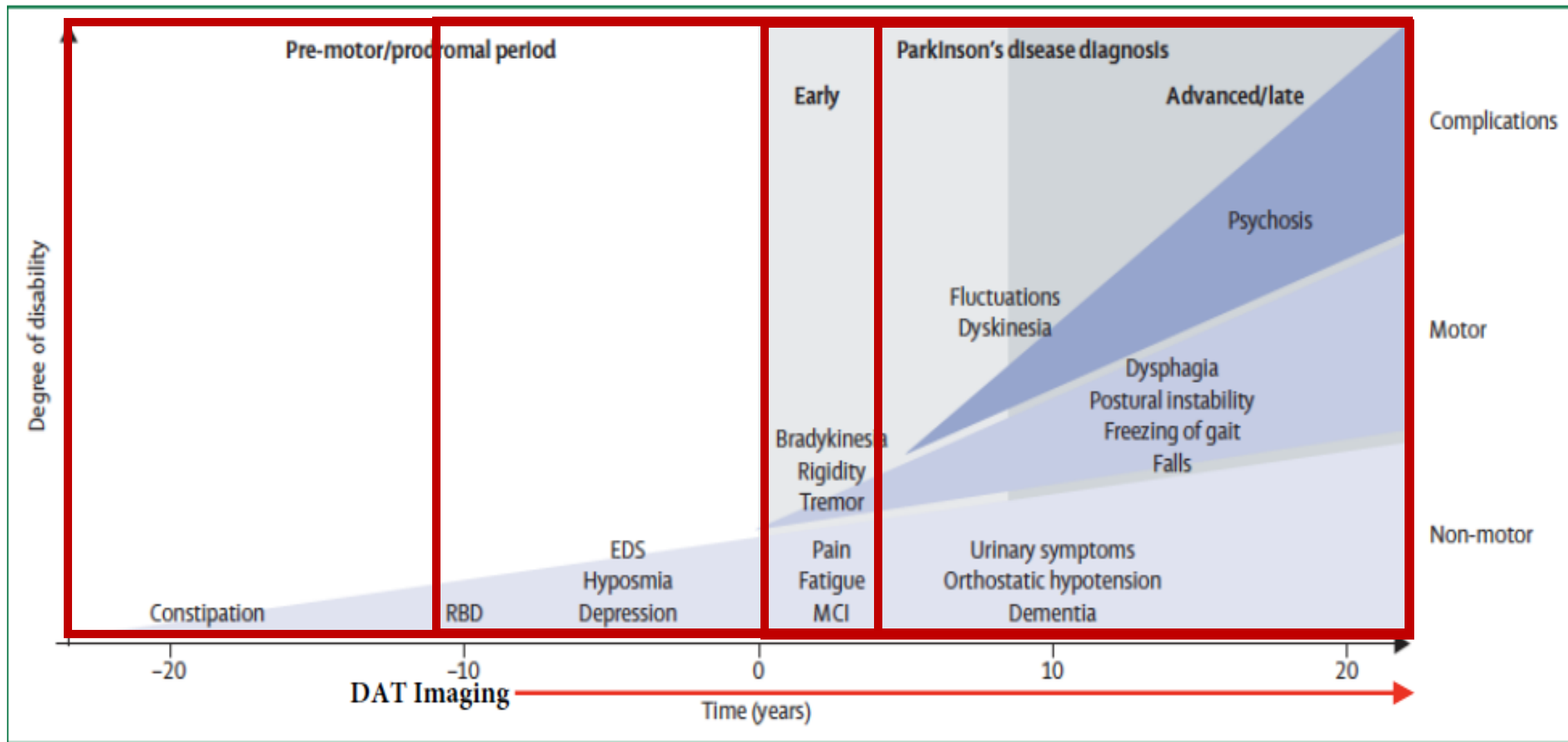


Cancer screening



Neurodegenerative screening

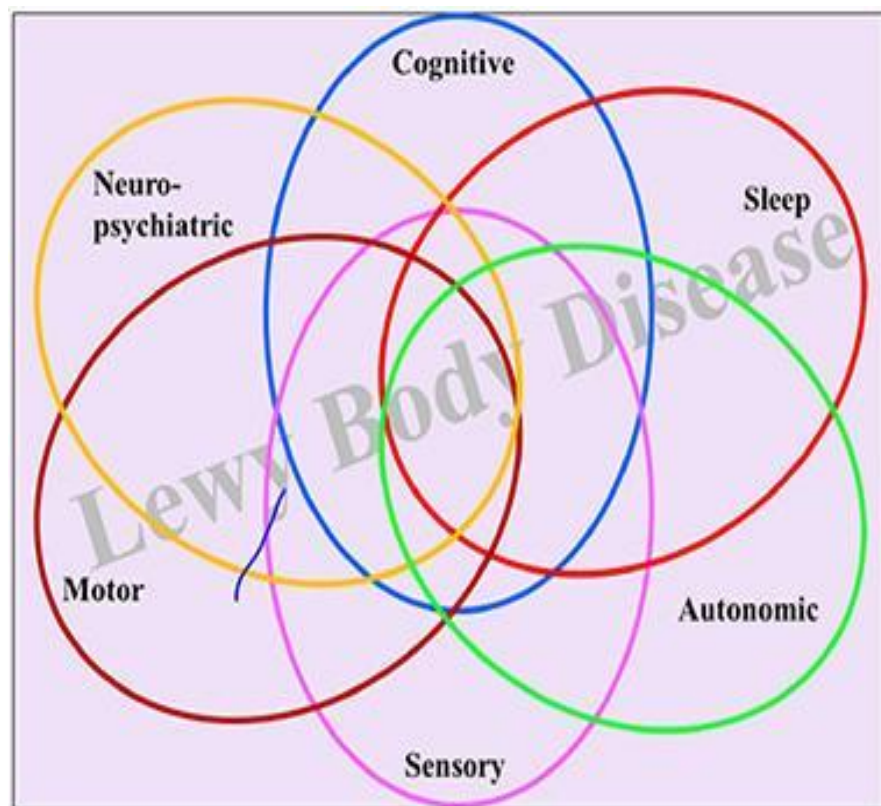
# Time for a paradigm shift – Biologic definition of PD/DLB



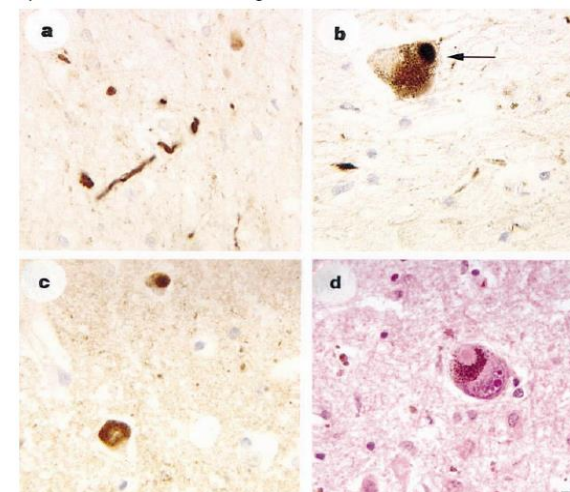
*Kalia LV, Lang AE et al, Lancet 2015*

# Neuronal $\alpha$ -Synuclein Disease (NSD)

## THE BIOLOGY encompasses what is now referred to as clinical PD, clinical DLB and related clinical syndromes



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



Individuals, who at autopsy show evidence of predominantly neuronal aggregated  $\alpha$ -synuclein.

# Synuclein Pathology

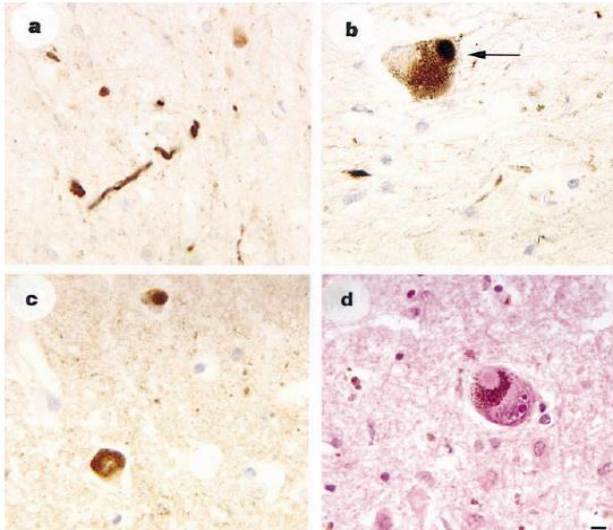


# Synuclein seed amplification assay

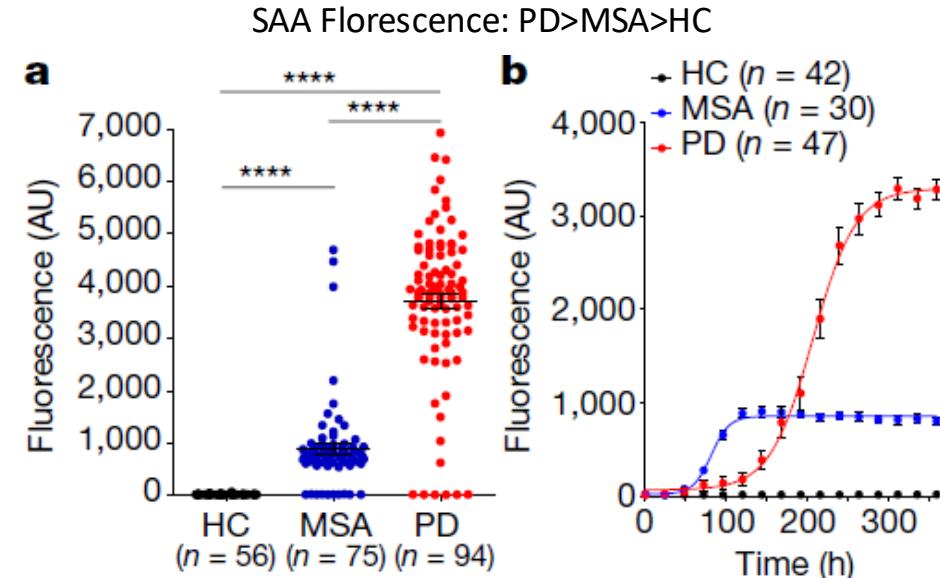
For now!



Lewy (1912) described concentric inclusion bodies especially in the nucleus basalis, the substantia inominata 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%	Grovesman 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% <sup>a</sup>	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.  $\alpha$ -Synuclein Seed Amplification Assays for Diagnosing Synucleinopathies: The Way Forward. Neurology; 2022: 99(5)

# Synuclein Pathology

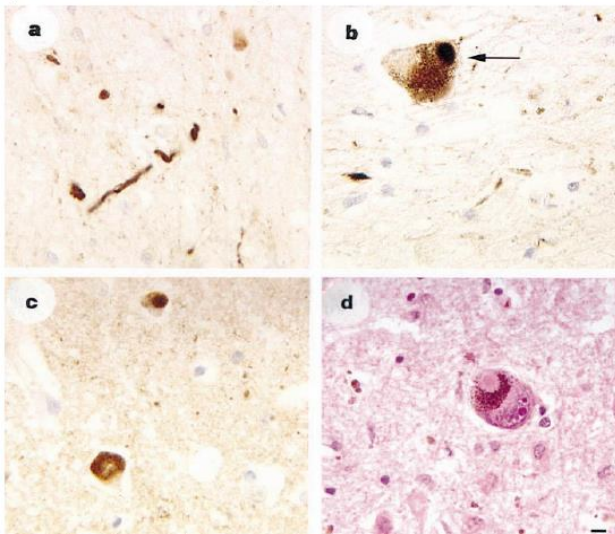


# Synuclein seed amplification assay

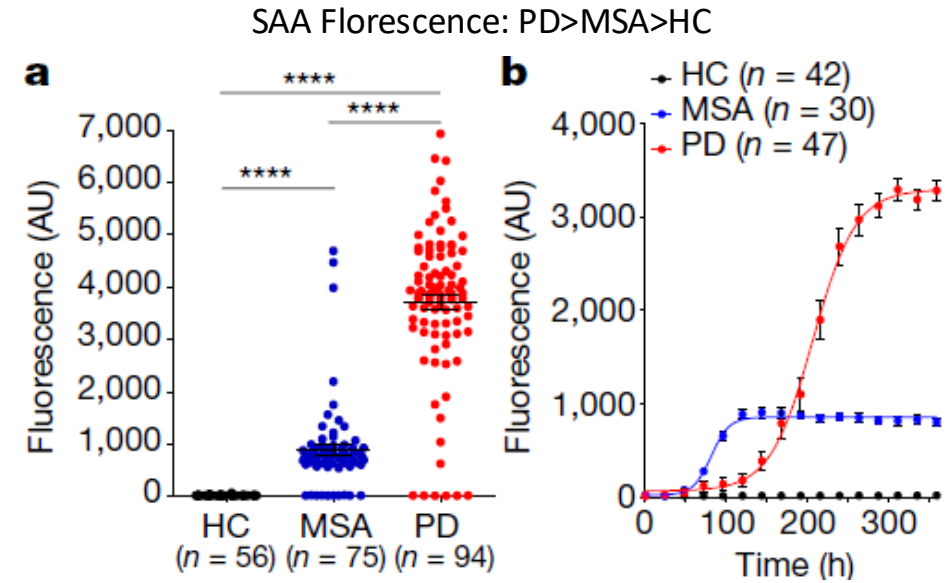
For now!



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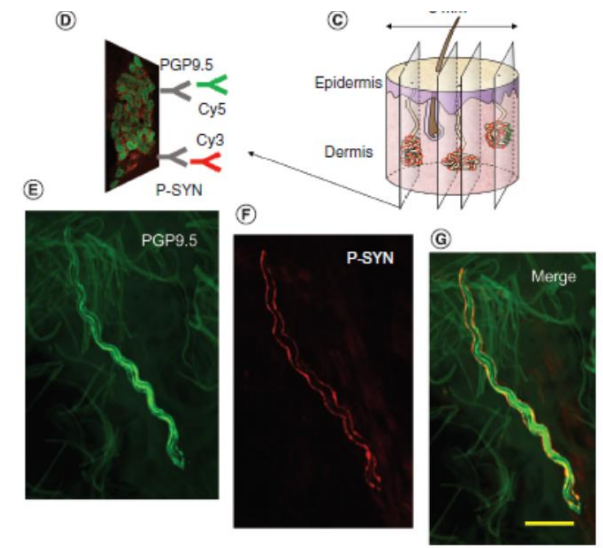


Spillantini, Schmidt, Lee, Trojanowski, Jakes and Goedert, Nature 1997



Shahnawaz et al. Nature, 2020

## Immunofluorescence assay of synuclein in Skin



Gibbons et al 2024  
JAMA Neurology

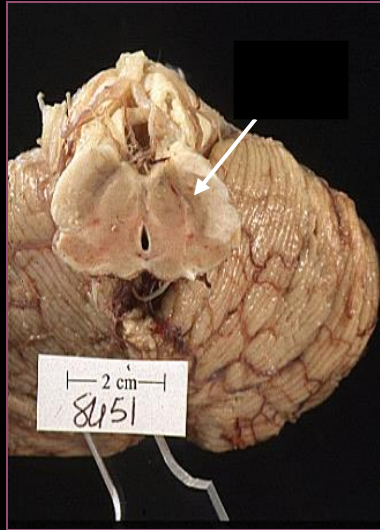
# Dopaminergic Dysfunction



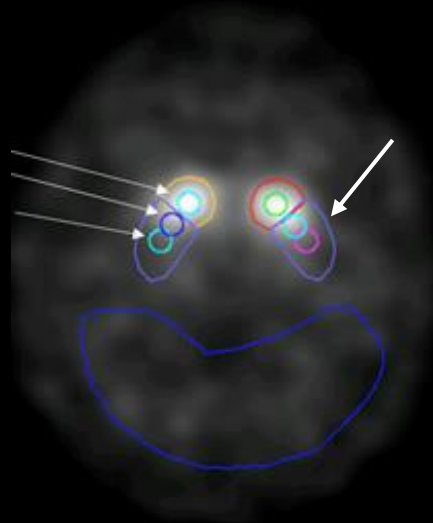
# Dopamine imaging

For  
now!

Severe loss of dopamine  
Neurons (no black stripe)



Severe loss of dopamine  
production



Acta Neuropathologica (2024) 147:52  
<https://doi.org/10.1007/s00401-024-02706-0>

ORIGINAL PAPER



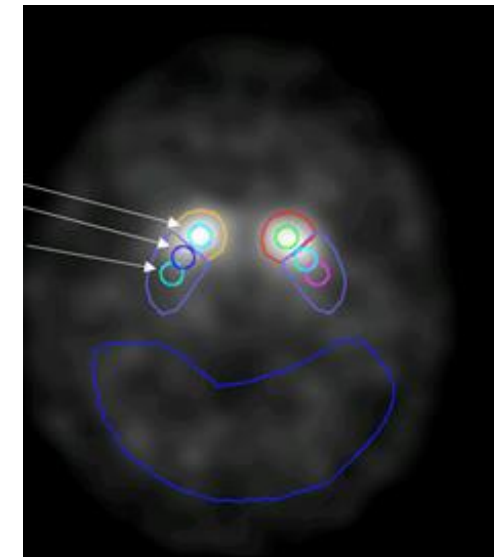
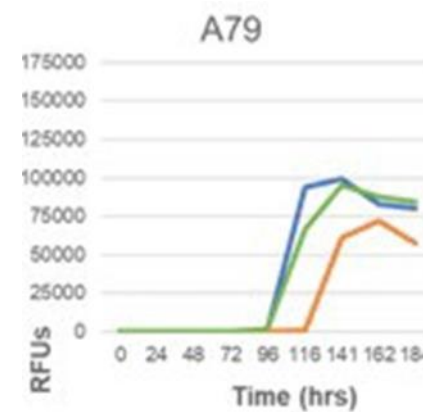
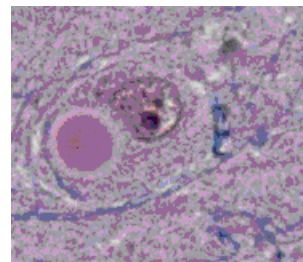
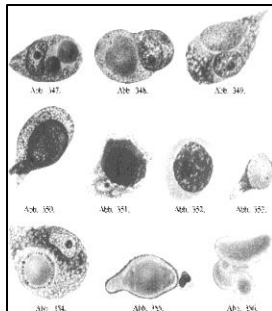
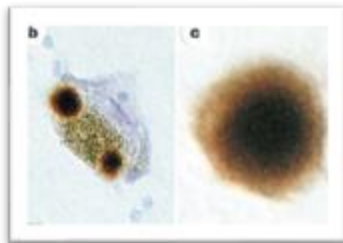
## Comprehensive proteomics of CSF, plasma, and urine identify DDC and other biomarkers of early Parkinson's disease

Jarod Rutledge<sup>1,2</sup> · Benoit Lehallier<sup>2</sup> · Pardis Zarifkar<sup>2,5</sup> · Patricia Moran Losada<sup>2,6</sup> · Marian Shahid-Besanti<sup>2</sup> · Dan Western<sup>3,4</sup> · Priyanka Gorijala<sup>3,4</sup> · Sephira Ryman<sup>2,7</sup> · Maya Yutsis<sup>2</sup> · Gayle K. Deutsch<sup>2</sup> · Elizabeth Mormino<sup>2</sup> · Alexandra Trelle<sup>8</sup> · Anthony D. Wagner<sup>6,8</sup> · Geoffrey A. Kerchner<sup>2,9</sup> · Lu Tian<sup>10</sup> · Carlos Cruchaga<sup>3,4</sup> · Victor W. Henderson<sup>2,11</sup> · Thomas J. Montine<sup>12</sup> · Per Borghammer<sup>13</sup> · Tony Wyss-Coray<sup>2,6,14</sup> · Kathleen L. Poston<sup>2,6,14,15</sup>

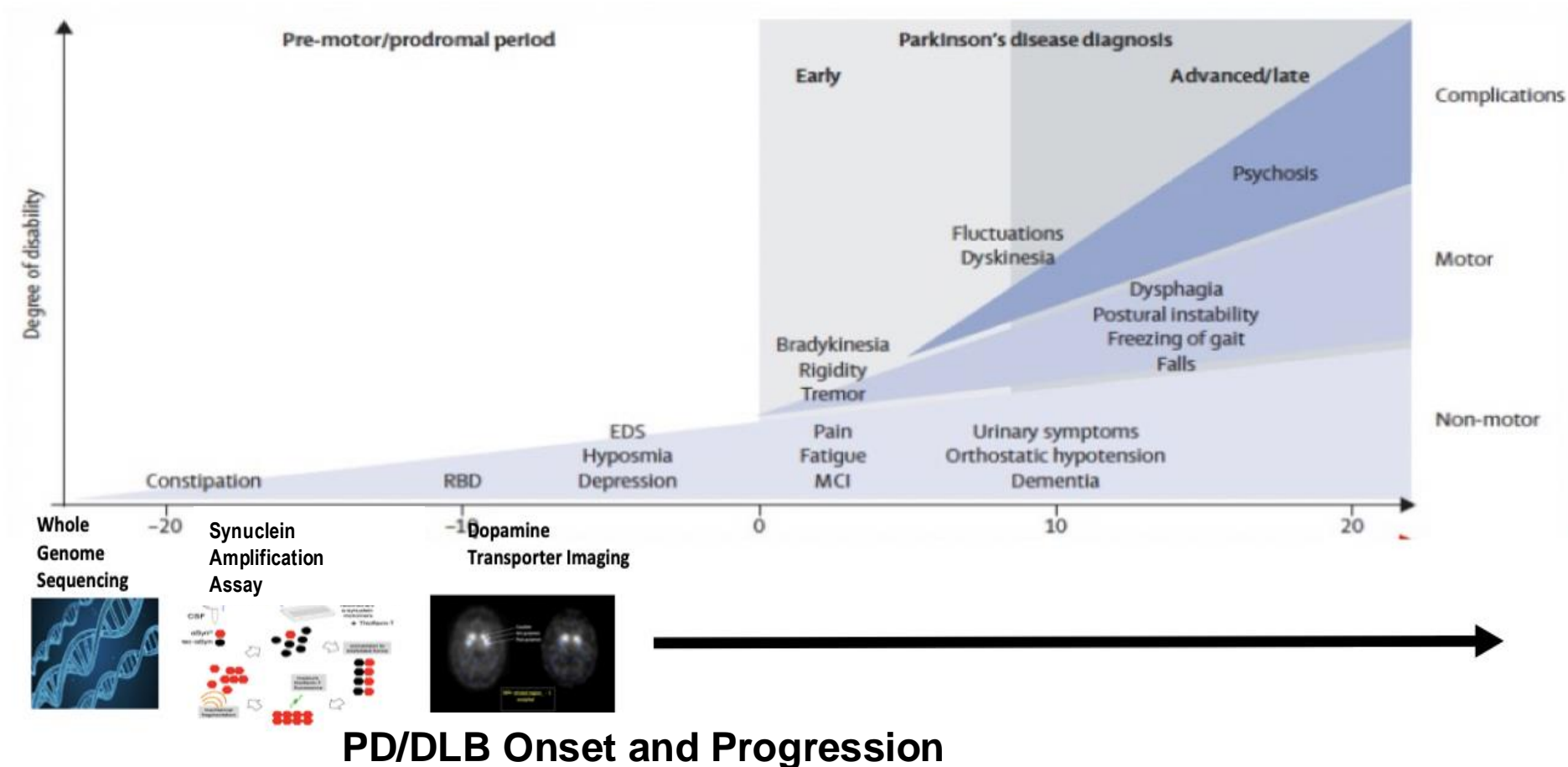


# Biologic Definition of NSD

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



# Iteration will occur as data, knowledge, and technology evolve



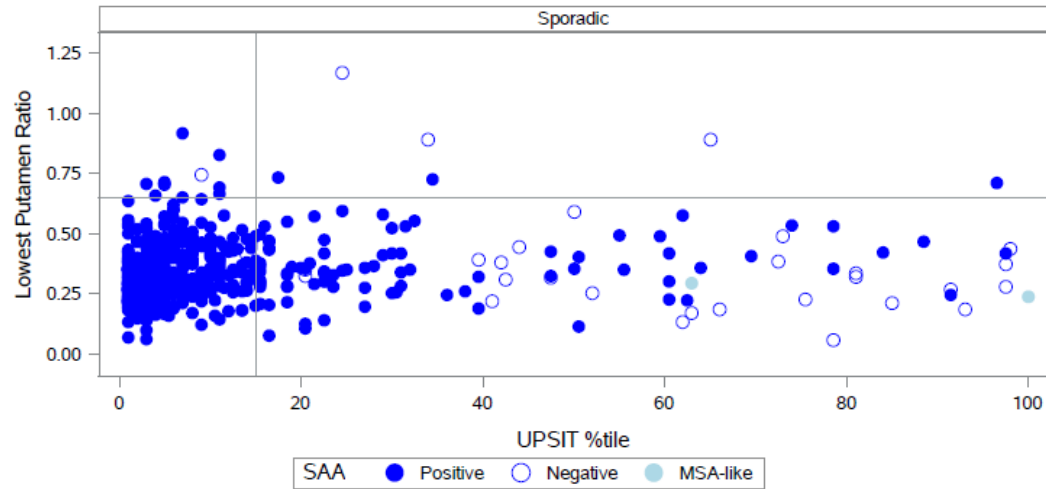
**This is a framework, and this is the first version**



# Parallelism

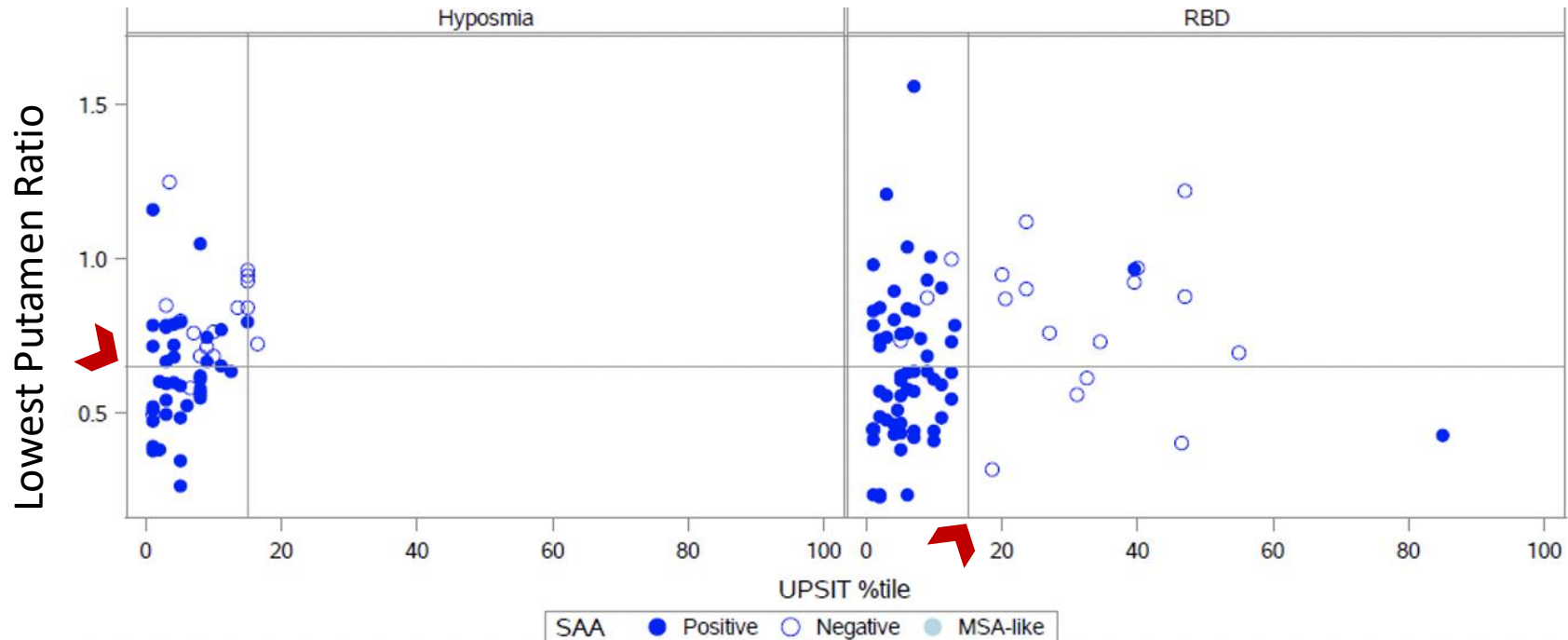
- Most people with clinical symptoms or in clinical research will not have biomarker data to determine if they have NSD or not.
- For now, continuing to use the clinical definitions for diagnosis will be appropriate in most patients, and in people enrolled in clinical trials when biomarker data is not being used.
- Coexistence of NSD and clinical diagnoses in a contextually appropriate way

# Majority of people with currently defined PD/ DLB have NSD



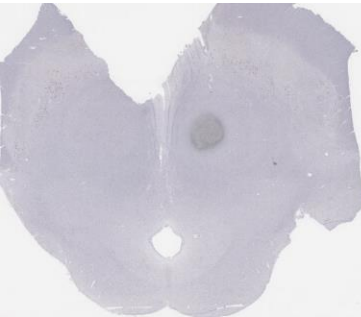
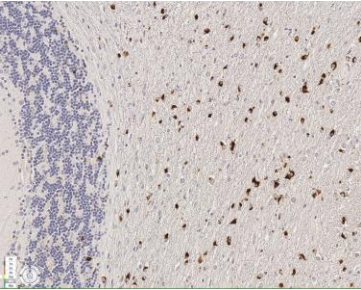
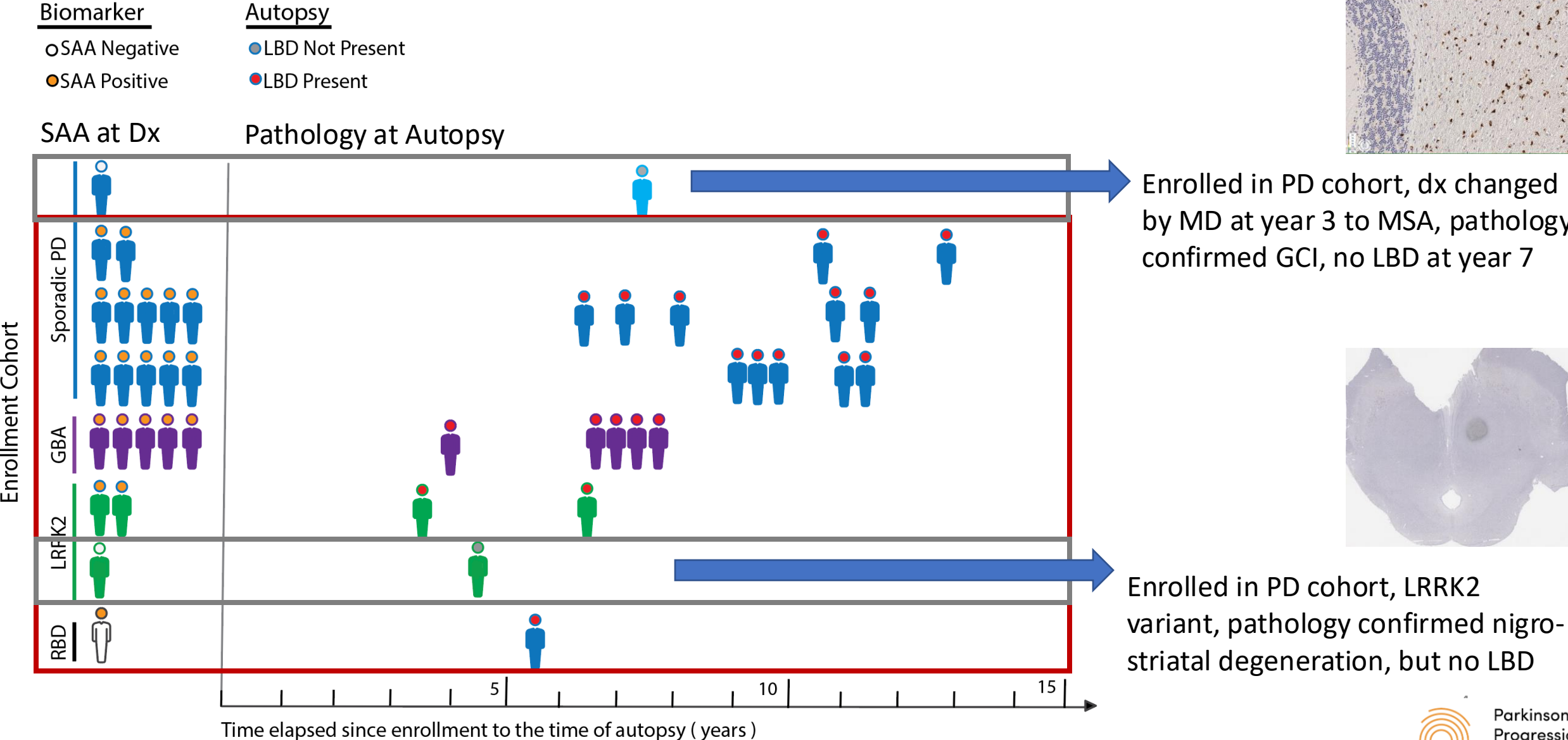
- Sporadic PD - Sensitivity 93%, Specificity 94%
- 97% (548/567) of all PD with UPSIT  $\leq$  15<sup>th</sup> %ile are SAA positive

# A substantial subset of Hyposmic and RBD individuals have NSD



- Most hyposmics and RBD are SAA positive
  - 70% (38/54) hyposmics, 75% (58/77) RBD
- RBD - 93% (56/60) with UPSIT  $\leq$  15<sup>th</sup> %ile are SAA positive
- SAA positive appears to precede DAT deficit in RBD and hypomics prior to the onset of clinical PD.

# In PPMI, $\alpha$ Syn-SAA is 100% concordant with the presence or absence of LBD at autopsy



Images courtesy of T. Montine and S. Bukhari, (unpublished, manuscript in prep)

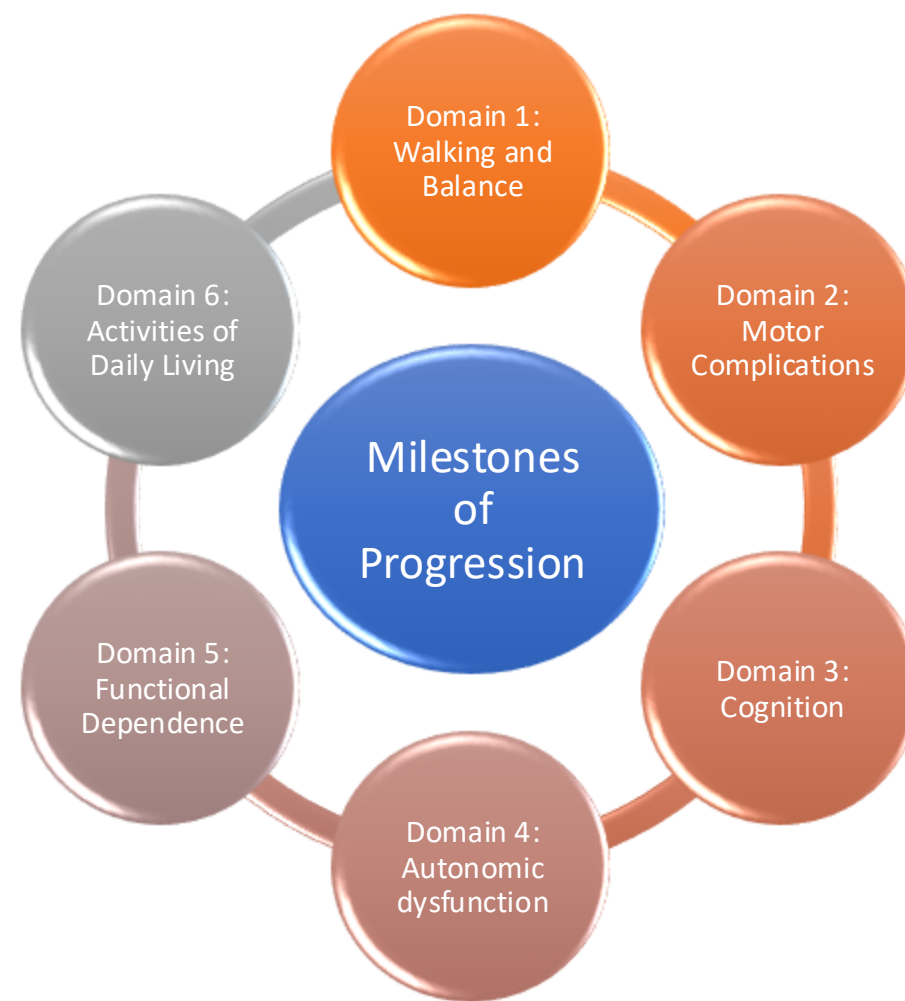
# PPMI participants, enrolled as PD non-genetic cohort (sPD), who are SAA negative at enrollment

**Table 1a. Demographic characteristics of SAA- and SAA+ sporadic PD participants at enrollment.**

Variable	SAA- sPD (N = 78)	SAA+ sPD (N = 872)	p-value*
Age at enrollment, years, median (IQR)	66.7 (61.0–73.3)	63.9 (57.2–70.0)	0.004
Male sex, n (%)	50 (64%)	570 (65%)	0.822
Time since diagnosis at enrollment, median (IQR)	0.5 (0.3–0.7)	0.5 (0.3–1.0)	0.384

Report generated on data submitted as of: 23SEP2024.

\*Comparisons by SAA status used Chi-Square or Fisher's Exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables.





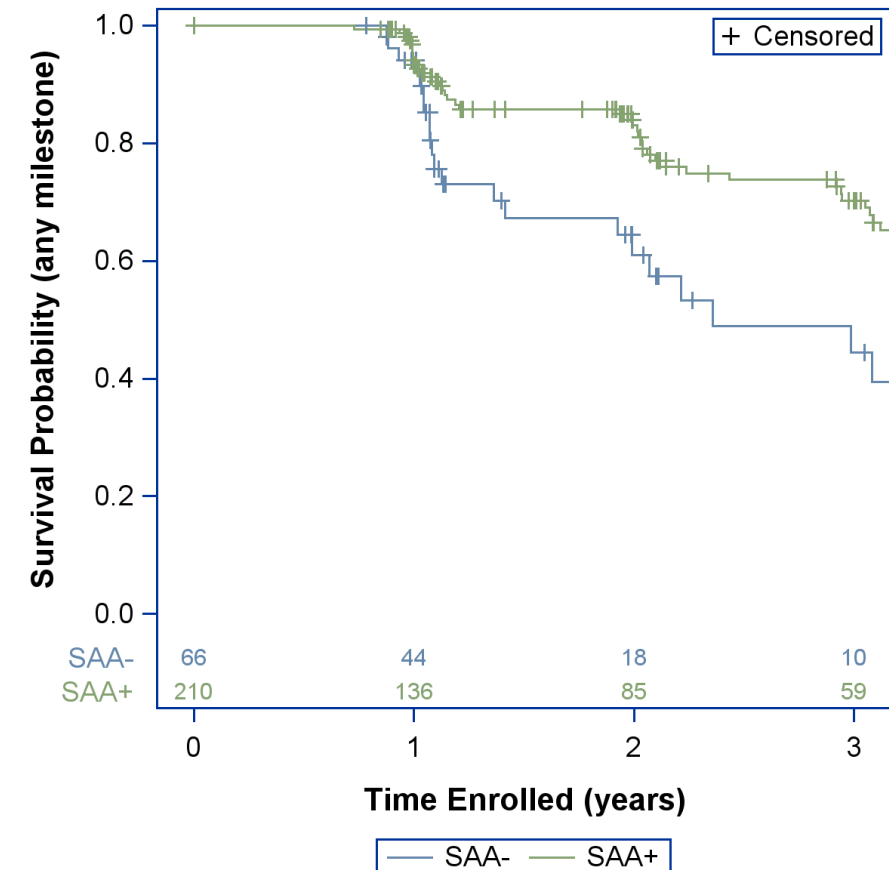
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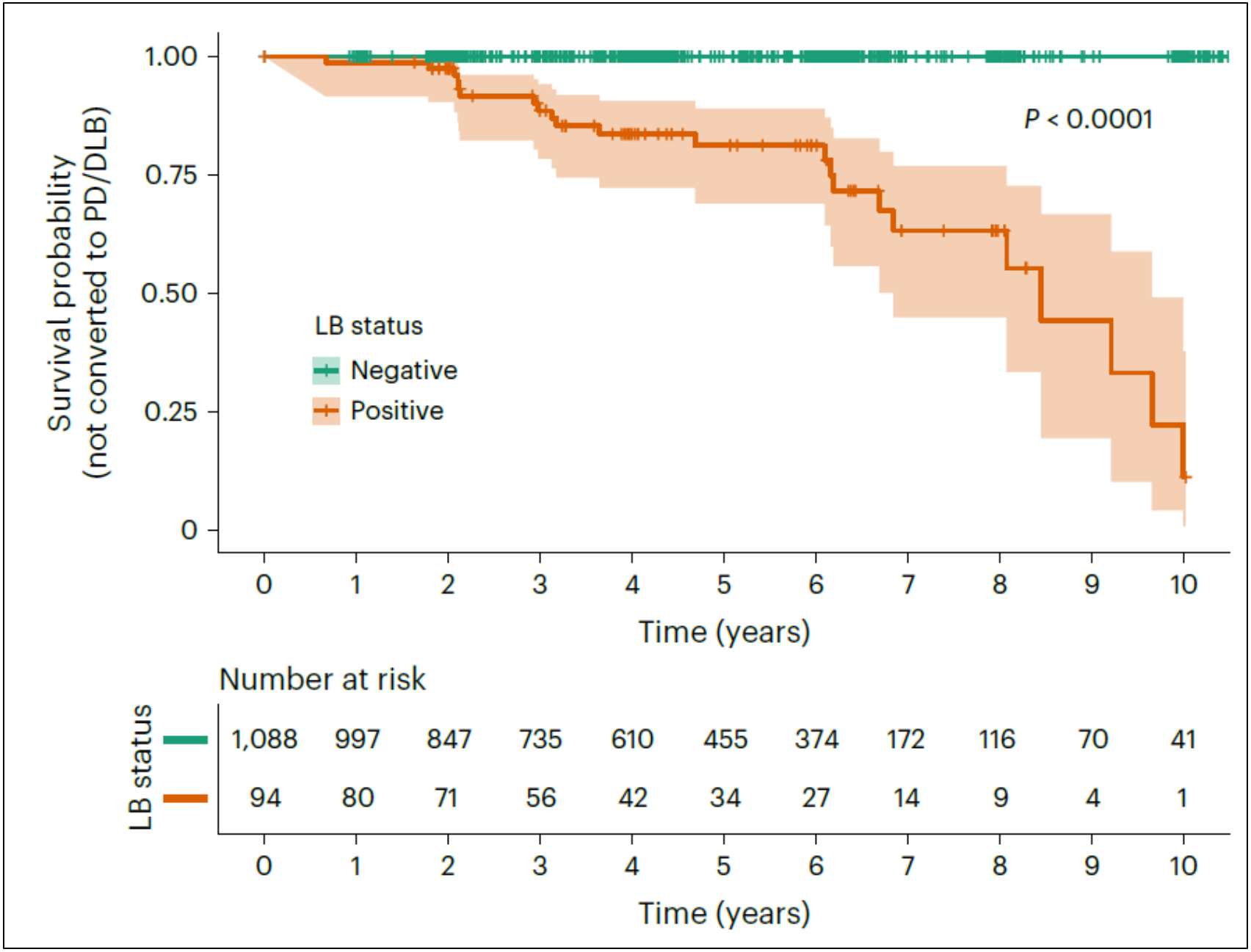
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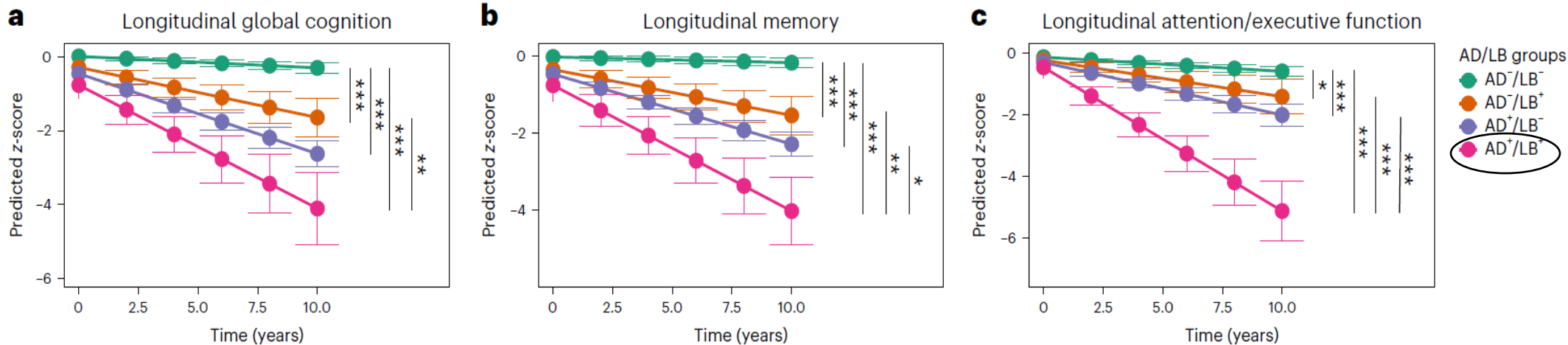
**Cognitively and neurologically unimpaired participants from the BioFINDER-1 & BioFINDER-2 studies.**



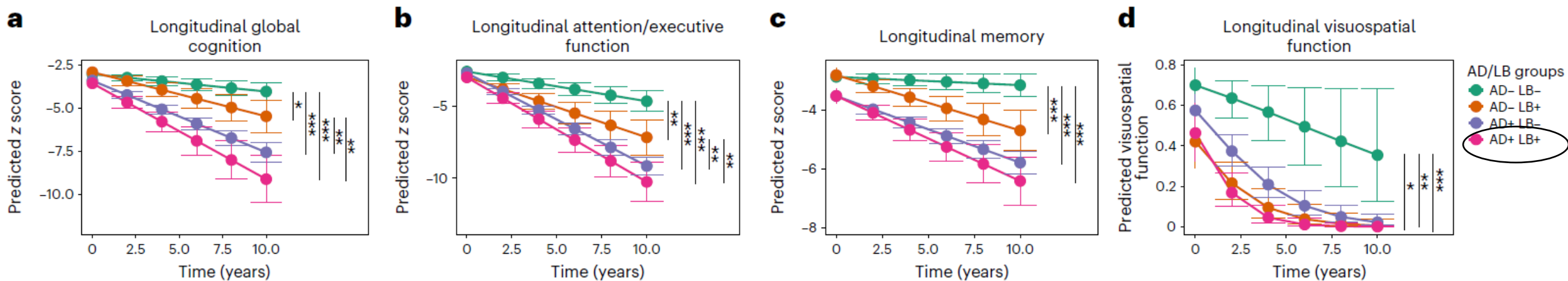
Palmqvist S et al "Cognitive effects of Lewy body pathology in clinically unimpaired individuals." *Nat Med.* 2023  
 Quadalti C et al "Clinical effects of Lewy body pathology in cognitively impaired individuals." *Nat Med.* 2023

# Mixed Pathology in BioFINDER-1 & BioFINDER-2.

## Cognitively and neurologically unimpaired participants



## Cognitively impaired participants

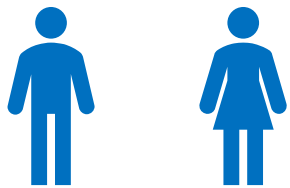


Palmqvist S et al "Cognitive effects of Lewy body pathology in clinically unimpaired individuals." *Nat Med.* 2023

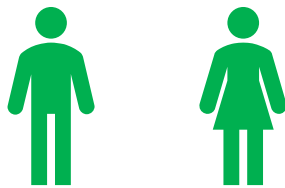
Quadalti C et al "Clinical effects of Lewy body pathology in cognitively impaired individuals." *Nat Med.* 2023

# NSD-ISS (Simplified)

		A-Syn (S)	DA Dysfunction (D)	Clinical Signs, Symptoms, Functional Impairment	
				Clinical Signs and Symptoms	Functional Impairment
Genetic risk ( L vs H)					
R <sup>L</sup>	G+ low risk	-	-	-	-
R <sup>H</sup>	G + high risk	-	-	-	-
NSD stage	NSD				
0	G+ (SNCA)	-	-	-	-
1A/B		+	-/+	-	-
2A/B		+	-/+	+	-
3		+	+	+	SLIGHT
4		+	+	+	MILD
5		+	+	+	MODERATE
6		+	+	+	SEVERE



LB pathology only

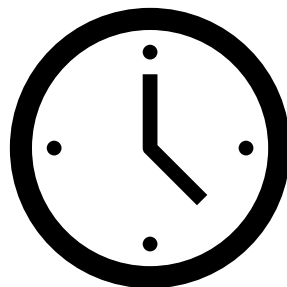
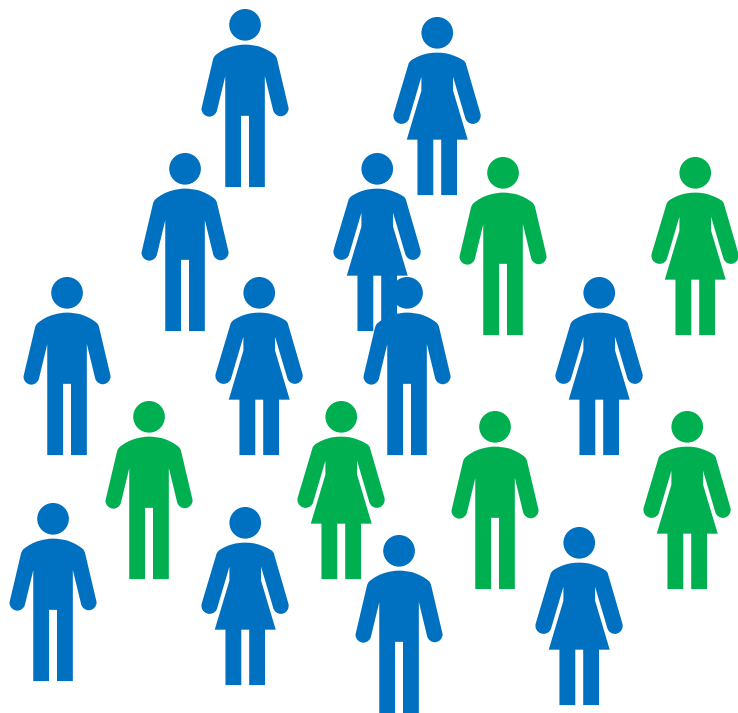


LB & AD mixed pathology

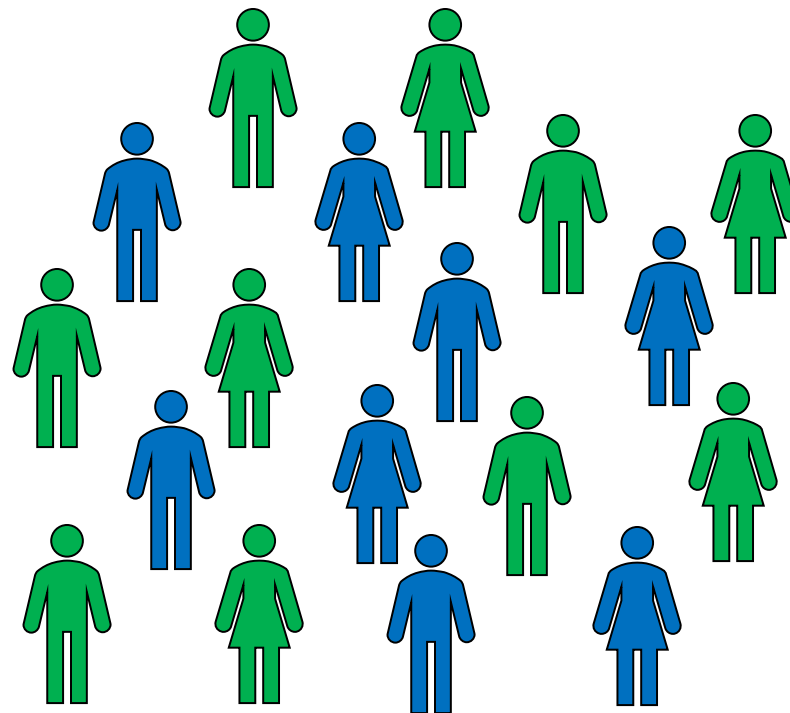


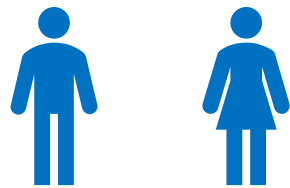
AD pathology only

Clinical PDD

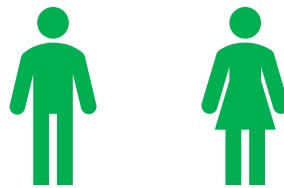


Clinical DLB





LB pathology only

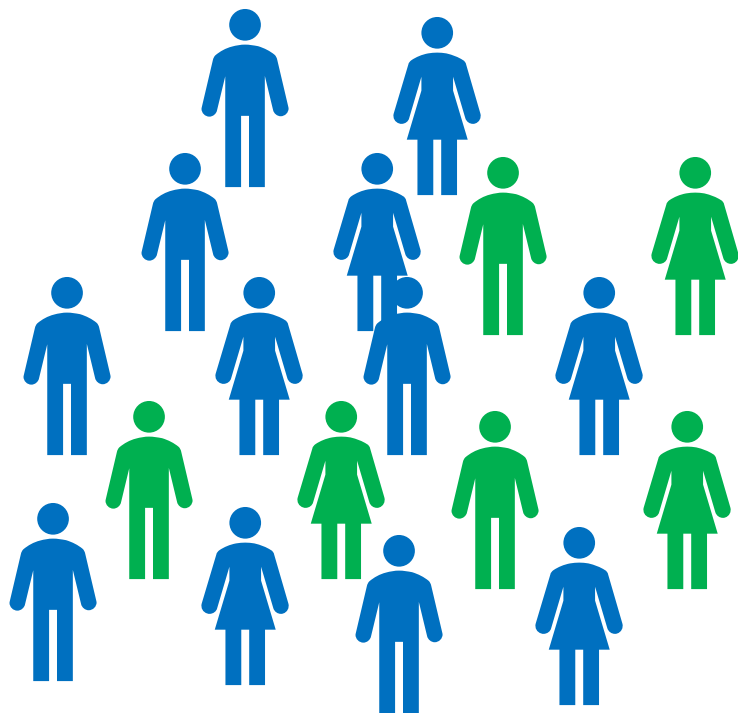


LB & AD mixed pathology

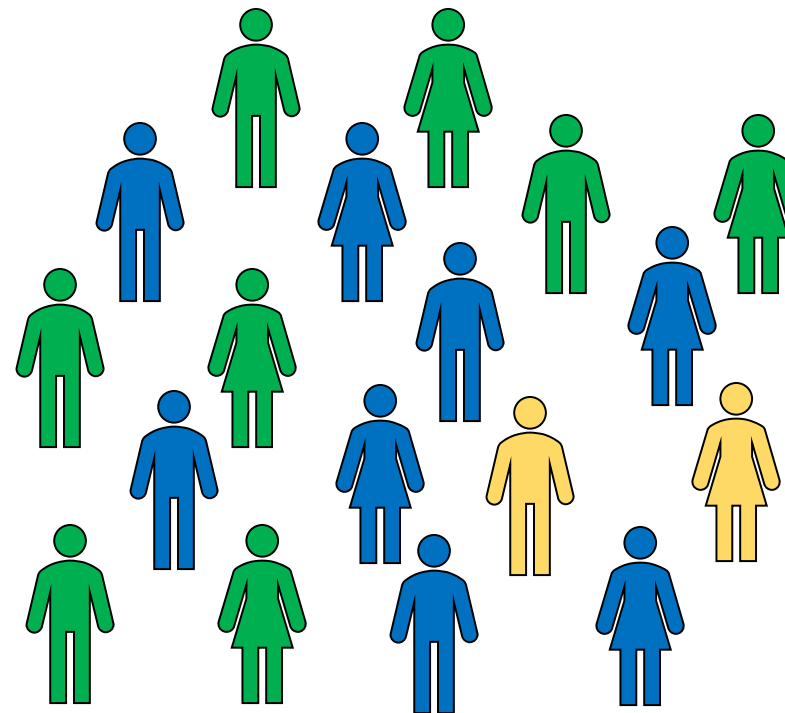


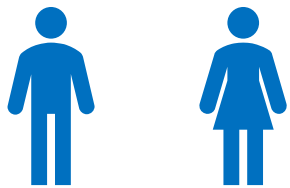
AD pathology only

Clinical PDD

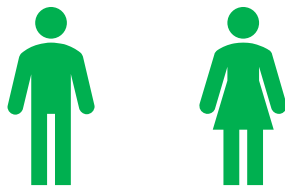


Clinical DLB





LB pathology only

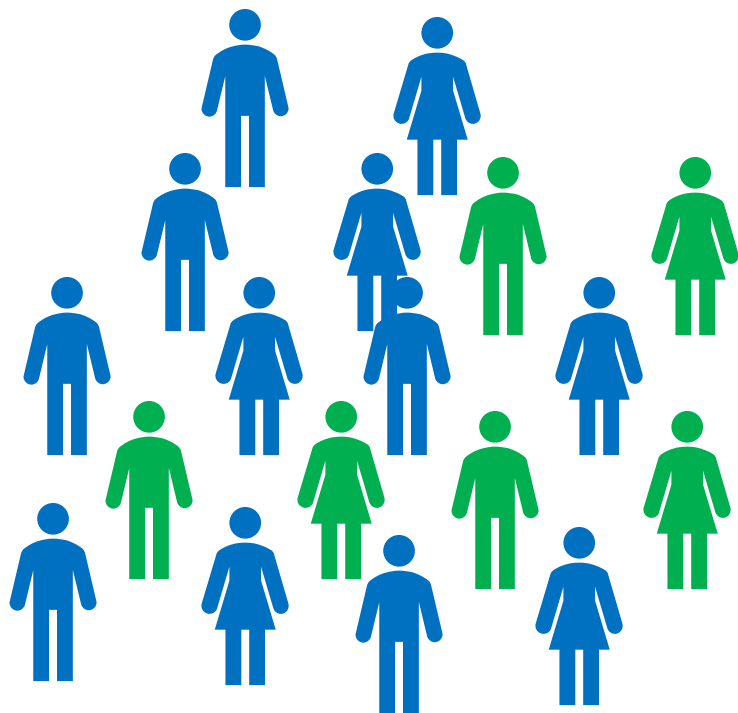


LB & AD mixed pathology



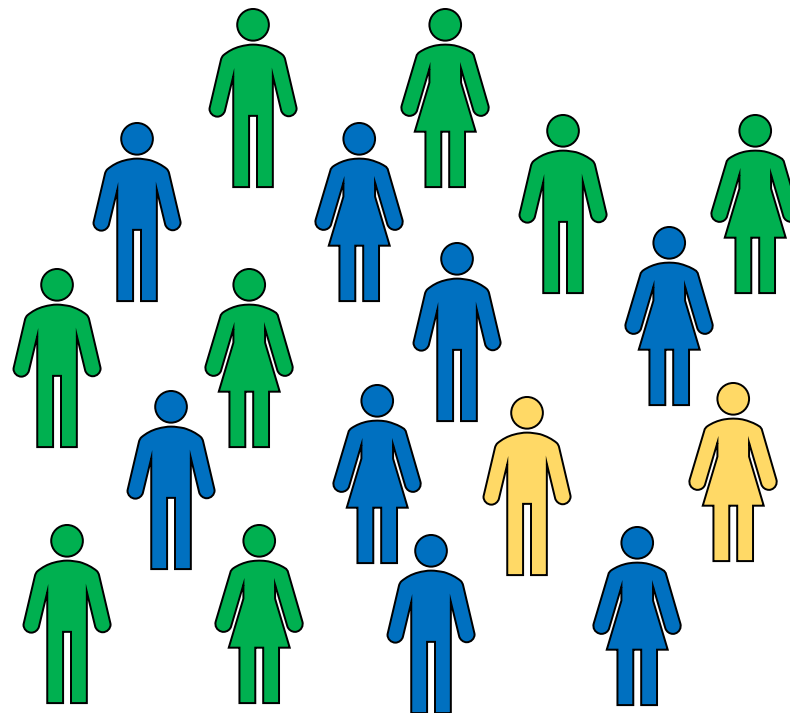
AD pathology only

Clinical PDD



LB biomarkers only

Clinical DLB



LB & AD mixed biomarkers

AD biomarkers only

# Simplified Integrated Staging System common to HD, AD, and NSD.

