

Session 2: Precision Frameworks for Patient Identification and Stratification

Precision Medicine in Neuroscience: Tools, Translation, and Implementation
March 4-5, 2026



Stanford
M E D I C I N E

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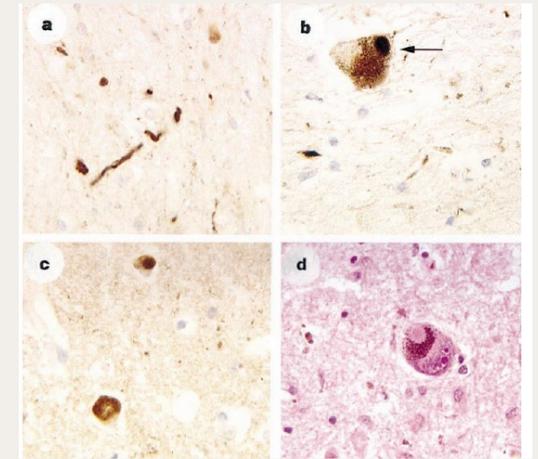
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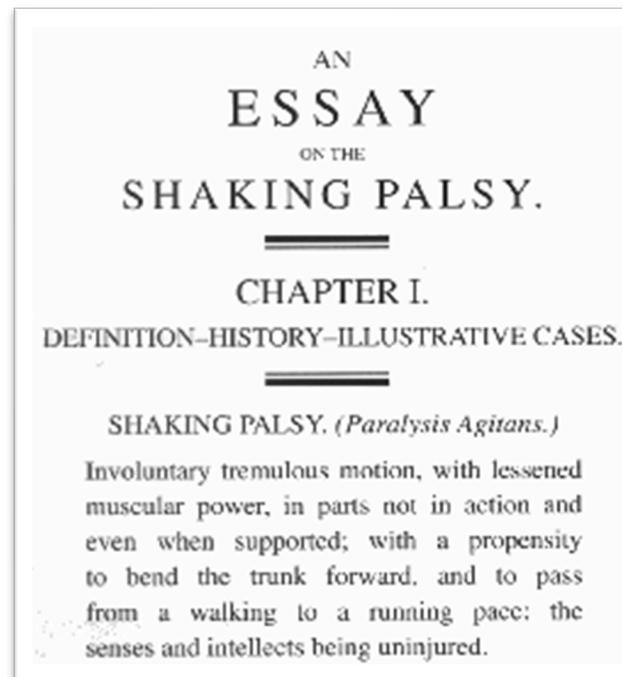
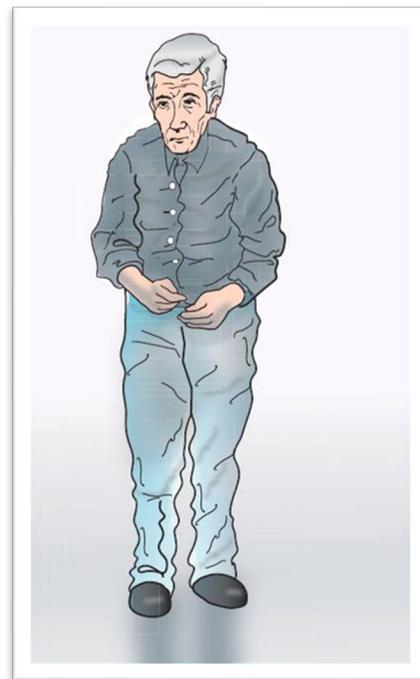
Disclosures

- Consulting for Novartis, Lilly, BioArctic, Biohaven, Curasen, Neuron23 and MapLight
- Scientific advisory board for Curasen and Amprion
- Grants from NIH/NIDDK U01 DK140939; 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.
- Co-author on the NSD-ISS manuscript

Problem: Accurately diagnosing neurodegenerative diseases during a patient's life is very difficult.

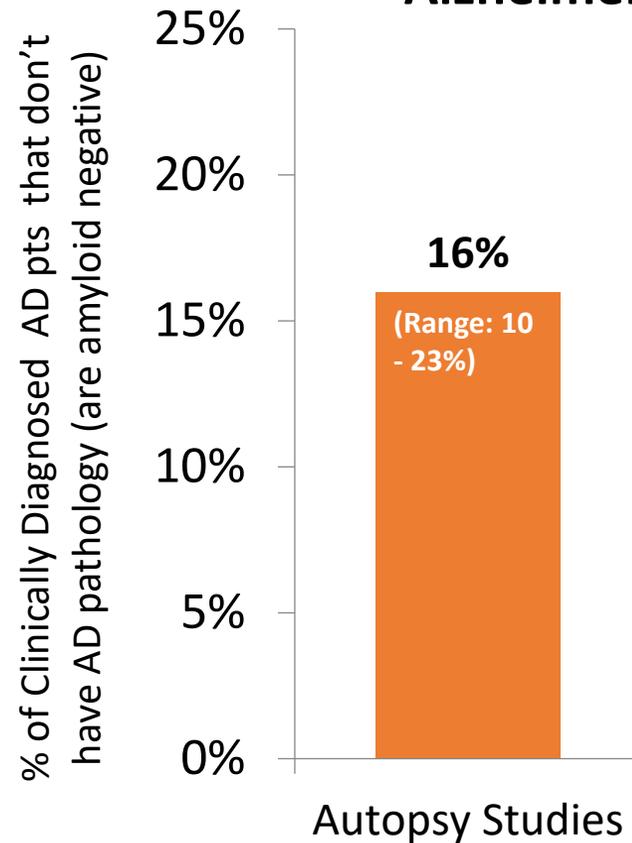


Alpha-synuclein staining aggregates found in neurons at pathology

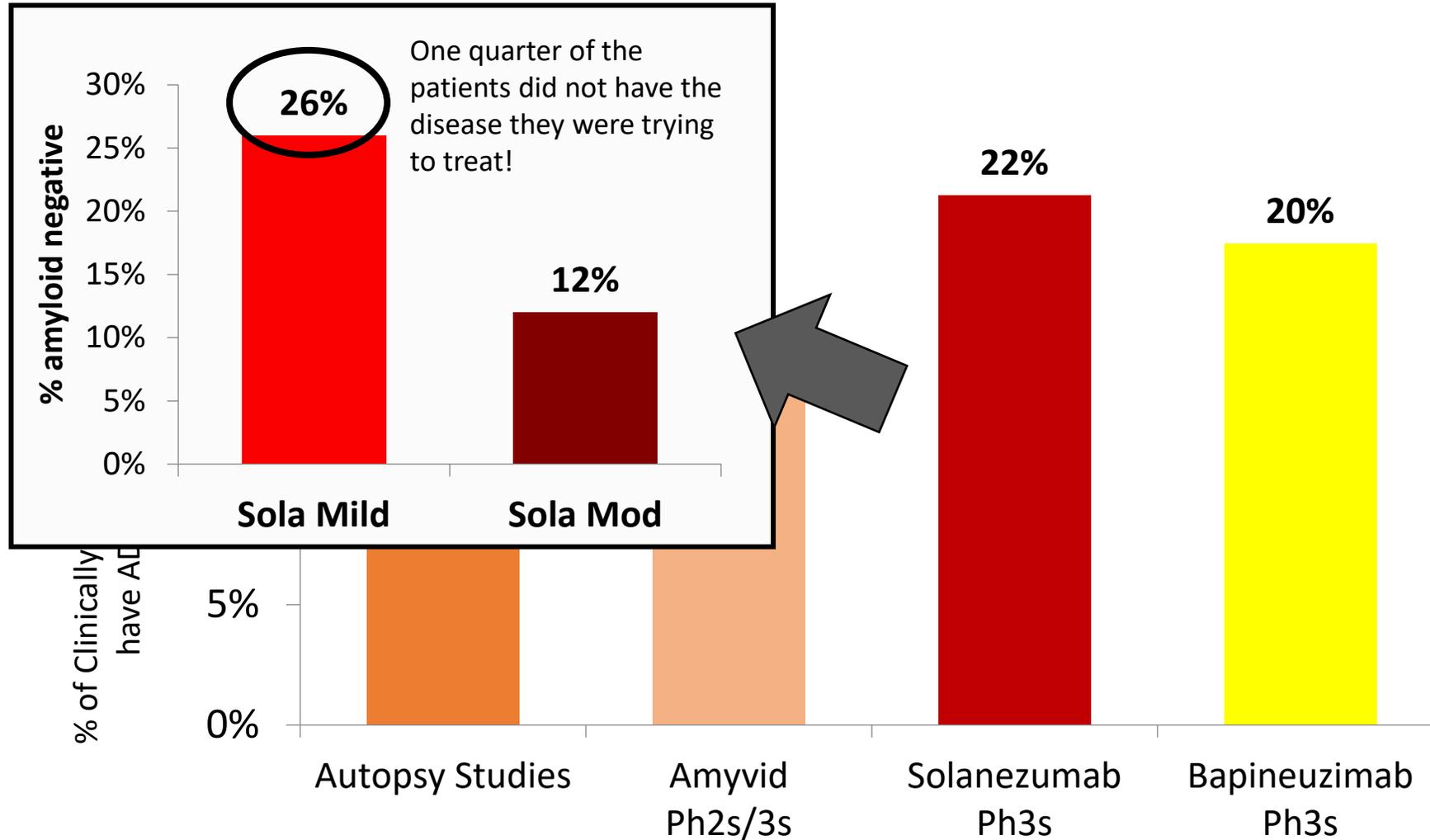


In clinical trials it is important to enroll people who have the disease being targeted: Examples from other diseases.

Many clinically diagnosed “AD patients” don’t have Alzheimer’s disease neuropathology

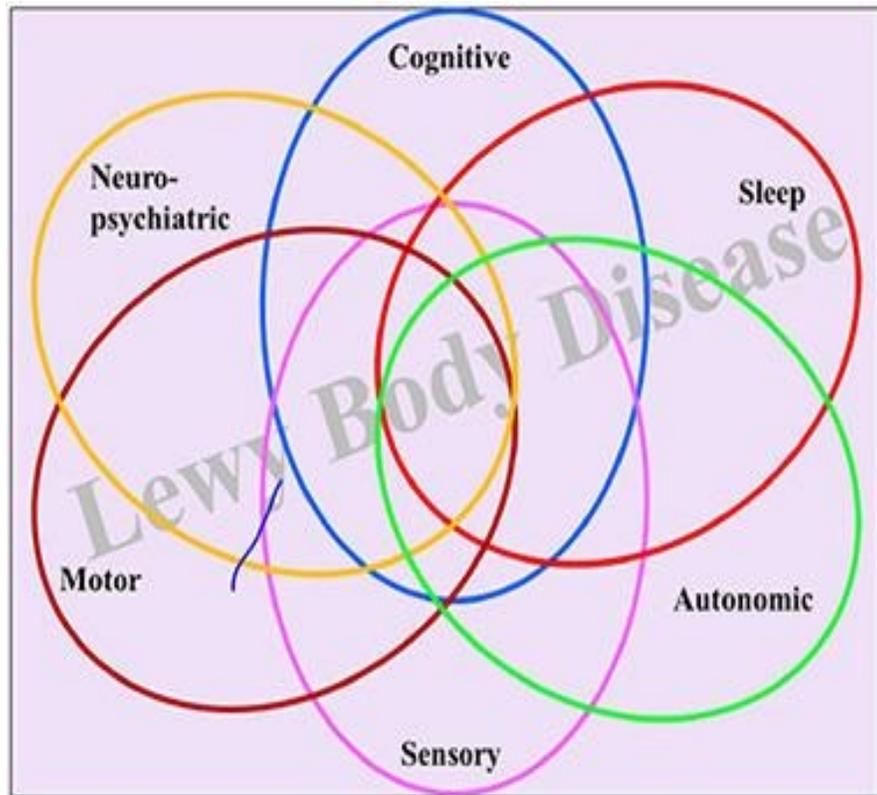


Misdiagnosis of Alzheimer's disease is common – especially in Mild disease



What about Parkinson's disease and dementia with Lewy bodies?

Why is the clinical diagnosis so difficult?

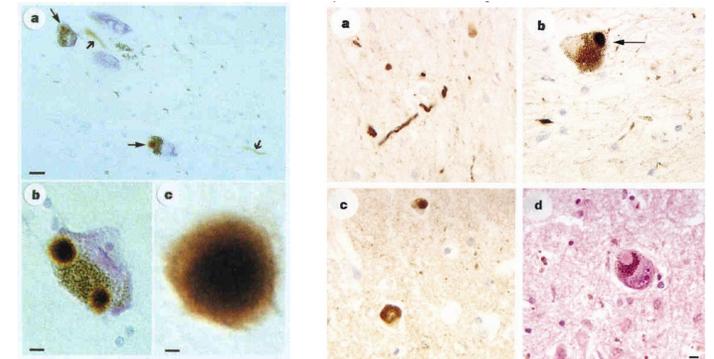


Clinical Terminology conundrum

Parkinson's disease
Dementia with Lewy bodies
Lewy Body Disease
Lewy Body Dementia
PD dementia
Prodromal PD
Prodromal DLB
Isolated RBD
Primary Autonomic Failure

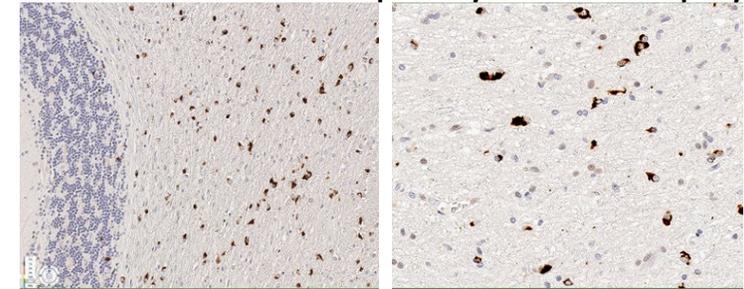
Weintraub D. "What's in a Name? The Time Has Come to Unify Parkinson's Disease and Dementia with Lewy Bodies." *Mov Disord.* 2023

α Syn positive Lewy Body Pathology



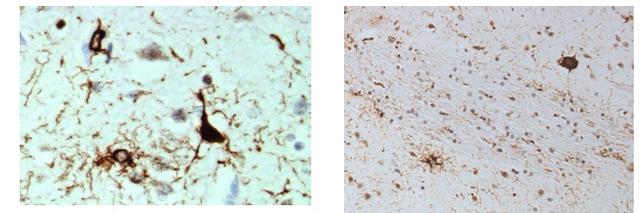
From Spillantini, Schmidt, Lee, Trojanowski, Jakes and Goedert, *Nature* 1997

α Syn positive Glial Cytoplasmic Inclusions in Multiple System Atrophy



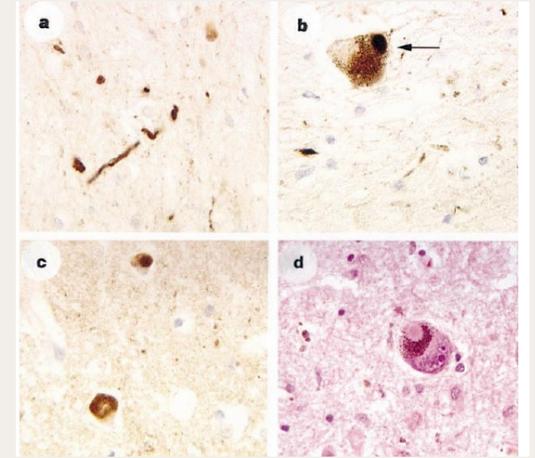
Images from T. Montine

4R-Tau positive pathology in Progressive Supranuclear Palsy and in Corticobasal Degeneration



Images from J.P. Vonsattel

Solution: Shift from using a diagnosis based purely on a clinical syndrome to one based on biological markers of the pathology



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

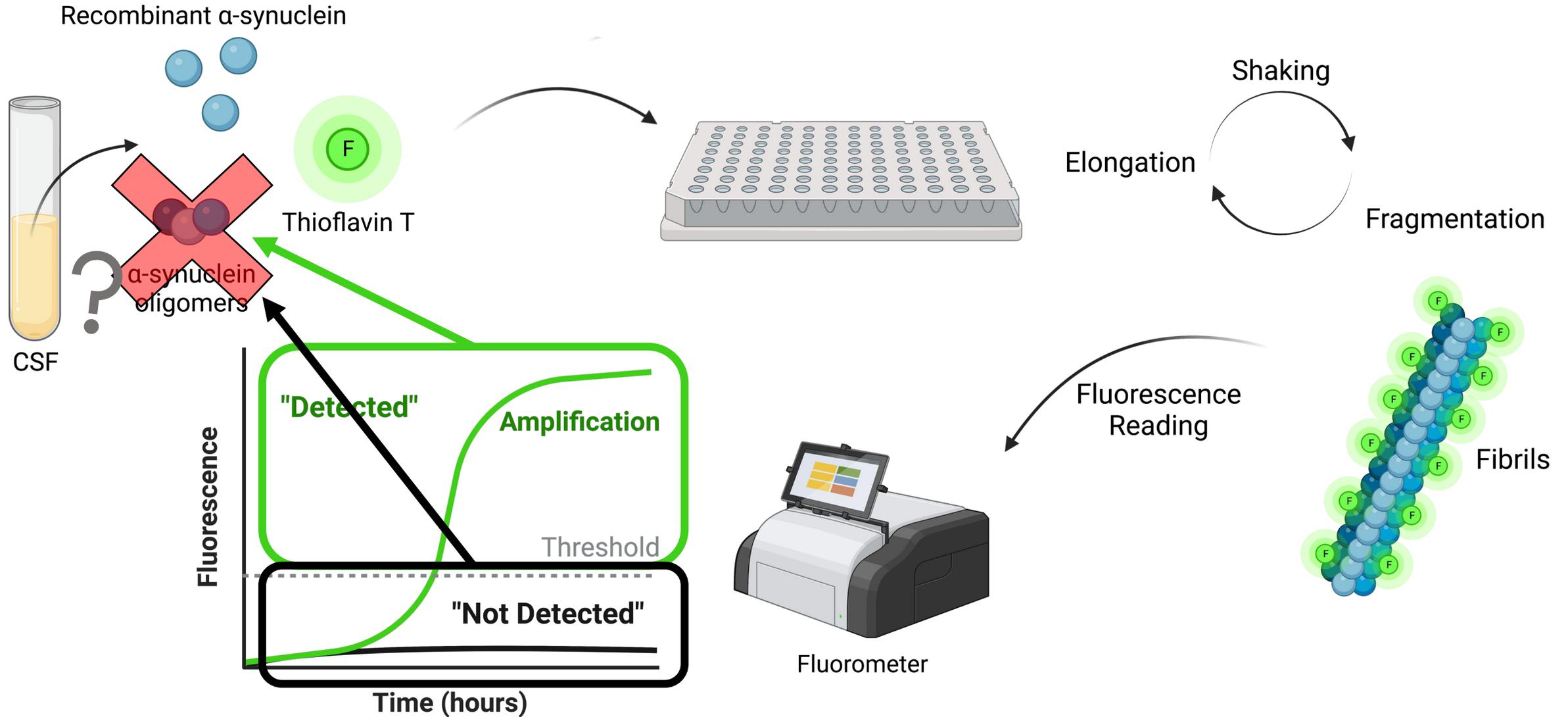
*Tanya Simuni**, *Lana M Chahine**, *Kathleen Poston*, *Michael Brumm*, *Teresa Buracchio*, *Michelle Campbell*, *Sohini Chowdhury*, *Christopher Coffey*, *Luis Concha-Marambio*, *Tien Dam*, *Peter DiBiaso*, *Tatiana Foroud*, *Mark Frasier*, *Caroline Gochanour*, *Danna Jennings*, *Karl Kiebertz*, *Catherine M Kopil*, *Kalpana Merchant*, *Brit Mollenhauer*, *Thomas Montine*, *Kelly Nudelman*, *Gennaro Pagano*, *John Seibyl*, *Todd Sherer*, *Andrew Singleton*, *Diane Stephenson*, *Matthew Stern*, *Claudio Soto*, *Caroline M Tanner*, *Eduardo Tolosa*, *Daniel Weintraub*, *Yuge Xiao*, *Andrew Siderowf*, *Billy Dunn*, *Kenneth Marek* **Lancet Neuro 2024**

A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria

Günter U Högl, *Charles H Adler*, *Daniela Berg*, *Christine Klein*, *Tiago F Outeiro*, *Werner Poewe*, *Ronald Postuma*, *A Jon Stoessl*, *Anthony E Lang* **Lancet Neuro 2024**

Seed Amplification Assay (α Syn-SAA) ~ RT-QulC and PMCA assays

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



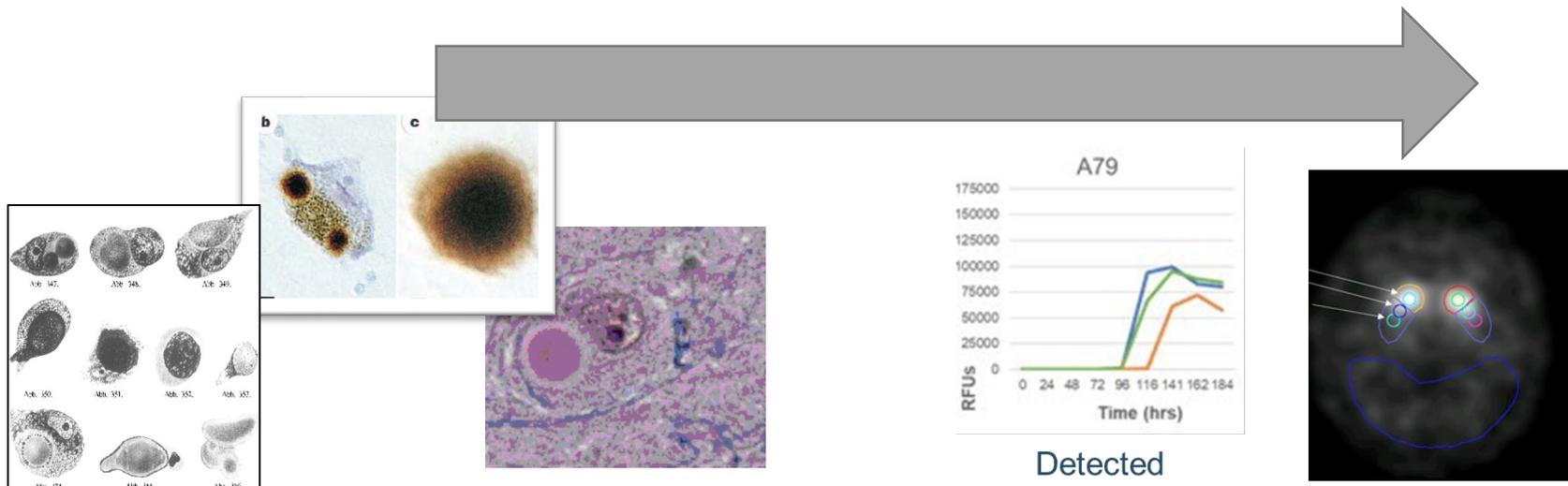


A biological definition of neuronal α -synuclein disease: towards an integrated staging system for research

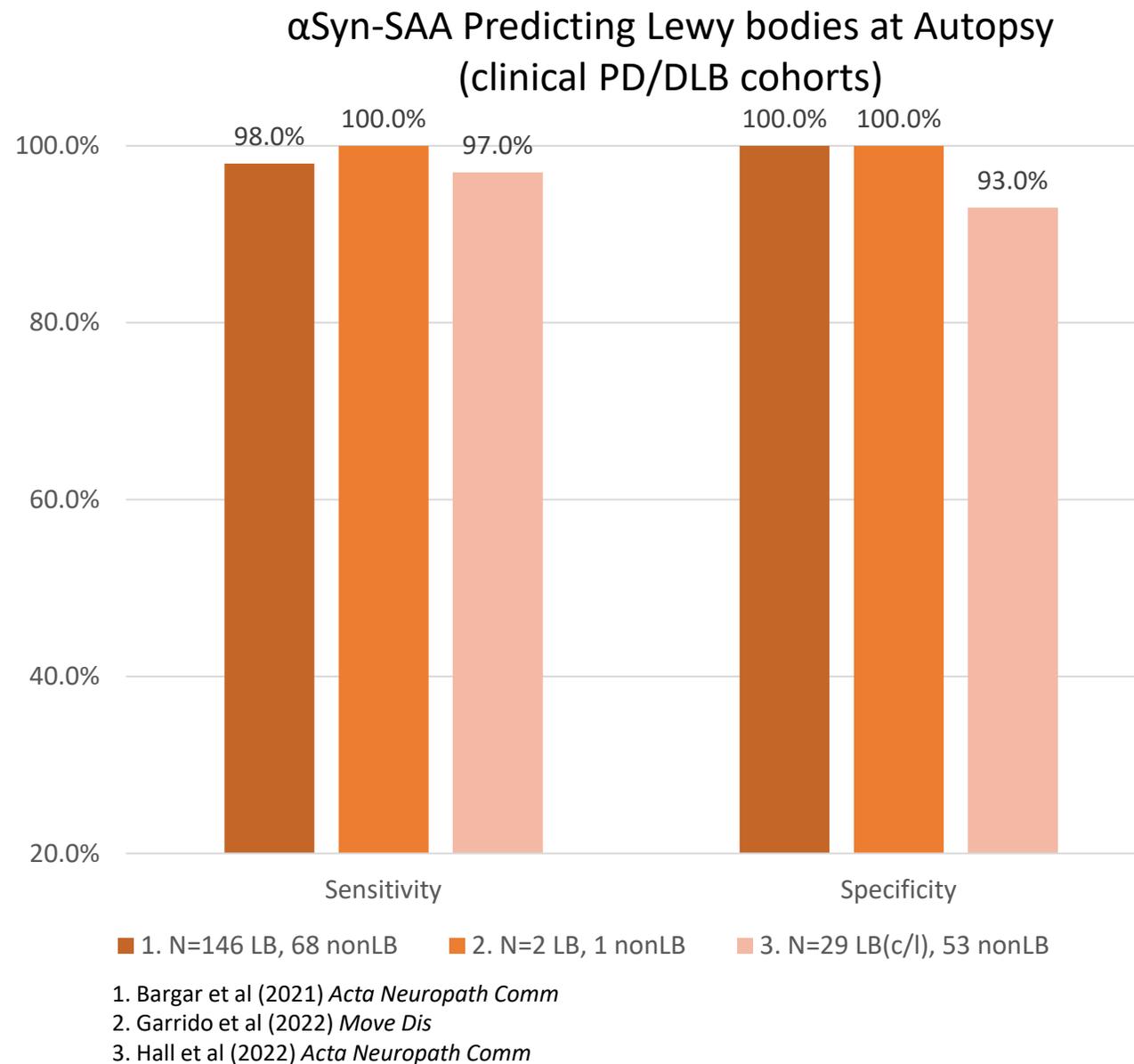
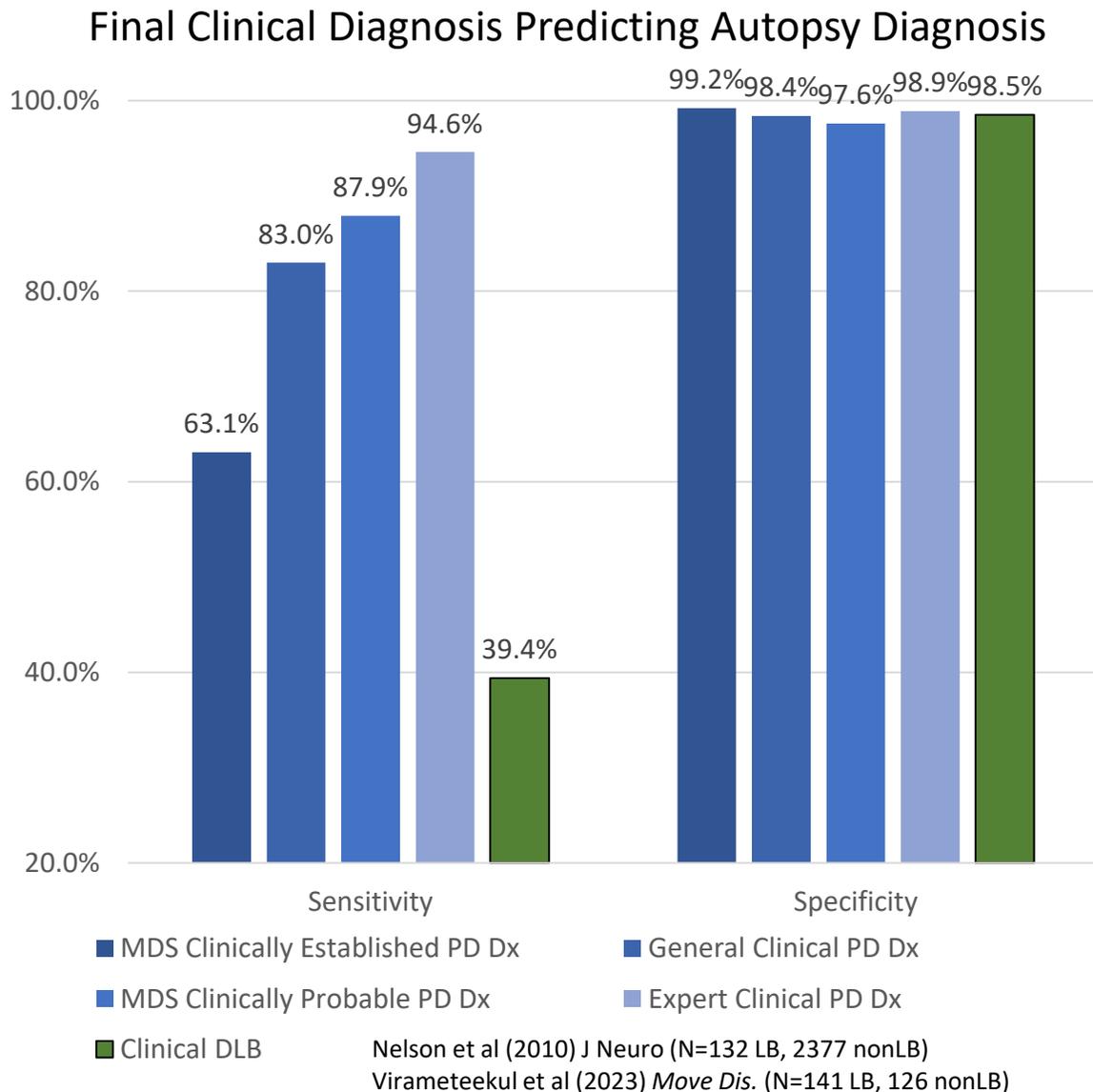
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Lancet Neurol 2024; 23: 178–90

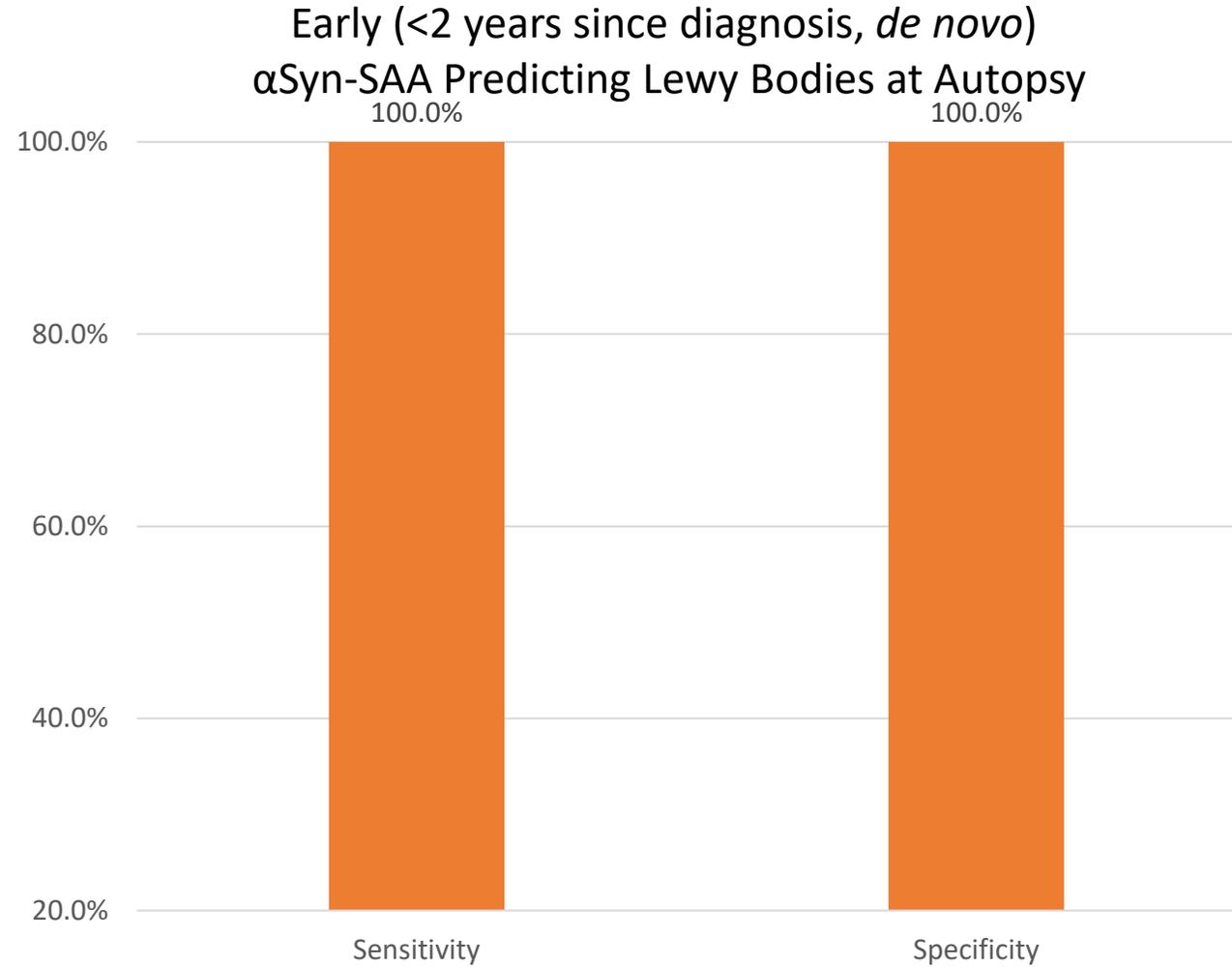
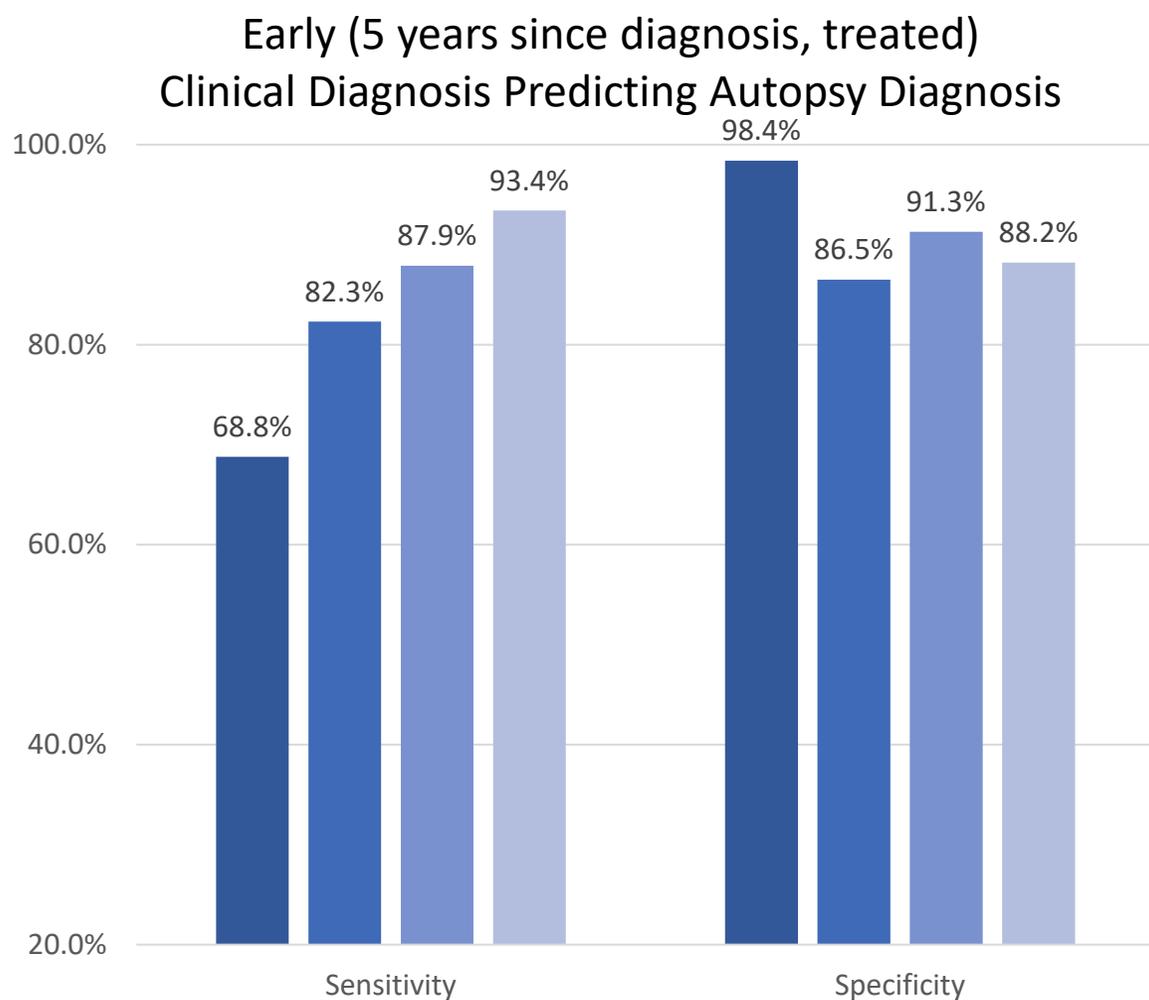
- **Neuronal Synuclein Disease (NSD)** is defined by presence of disease specific (*predominantly*) neuronal α -synuclein pathology and dopaminergic neuronal degeneration
- **Biomarker Context of Use:** Biomarkers that identify people in life who will have a specific pathological findings at autopsy, independent of specific clinical syndrome.



α Syn-SAA from CSF late in the disease is *more sensitive* than the clinical diagnosis in predicting Lewy Bodies at autopsy



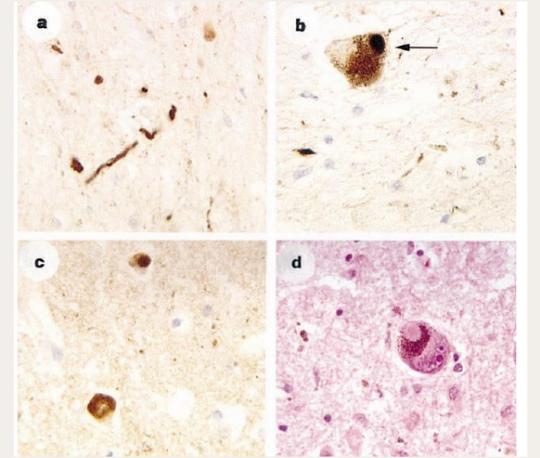
α Syn-SAA early in the disease is *more sensitive* and *more specific* than the clinical diagnosis in predicting Lewy Bodies at autopsy



■ MDS Clinically Established PD Dx ■ General Clinical PD Dx
■ MDS Clinically Probable PD Dx ■ Expert Clinical PD Dx

■ PPMI, N=24 LB, 2 nonLB
 Unpublished data, Poston et al, in prep

Solution: Shift from using a diagnosis based purely on a clinical syndrome to one based on biological markers of the pathology



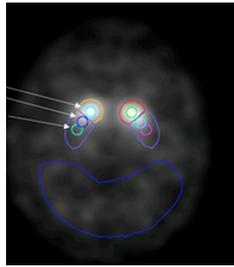
- A biological definition predicts pathological diagnosis better than the best clinical definition.



Parkinson's Progression Markers Initiative



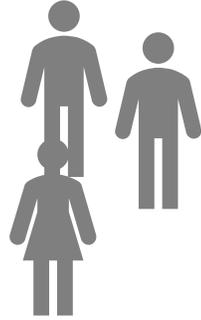
487 untreated with a diagnosis of PD < 2 years



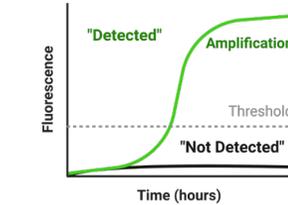
64 SWEDD (scans without evidence of dopaminergic deficit)



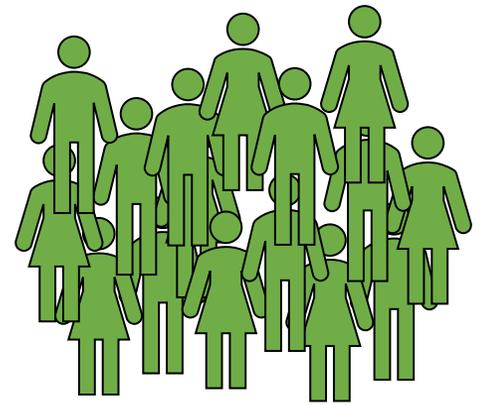
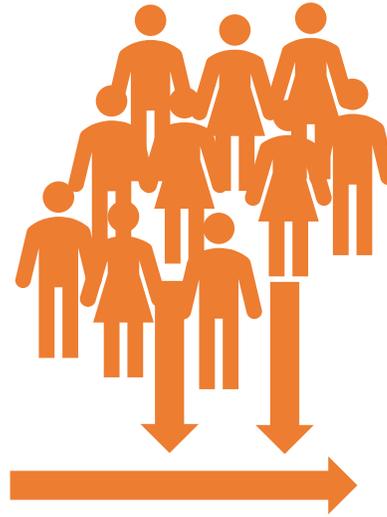
423 untreated with a diagnosis of PD < 2 years, and DAT deficit on visual read



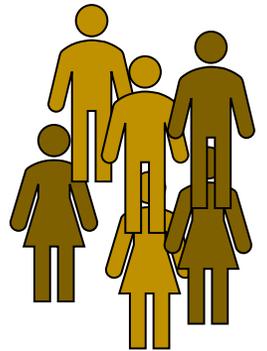
79 SAA- sPD



935 untreated with a diagnosis of PD < 2 years, and DAT deficit on visual read



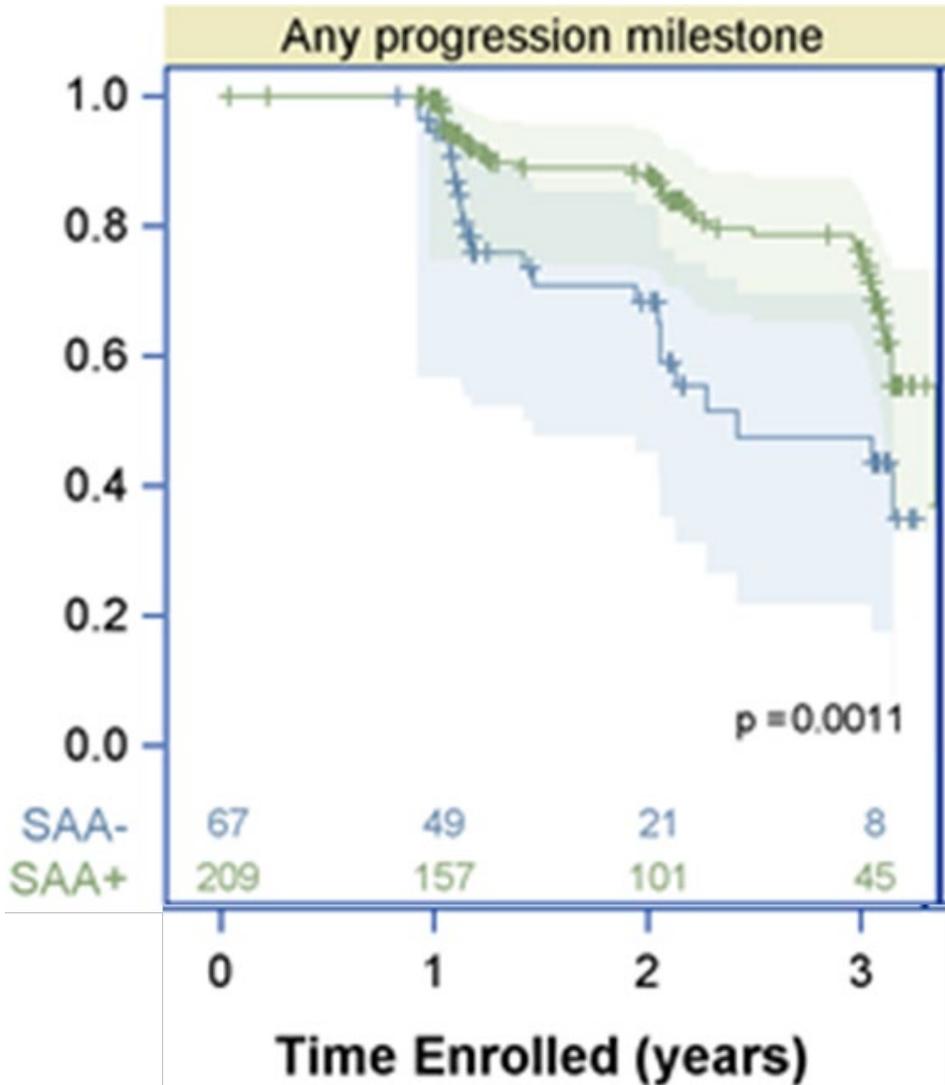
856 SAA+ sPD



PPMI data: sporadic PD (sPD, no known LRRK2, GBA, SNCA mutations), <2 years since PD diagnosis, *de novo* at time of CSF, confirmed abnormal DAT by visual read. 79 SAA- and 856 SAA+

Table 1: Demographic and baseline characteristics of matched SAA- and SAA+ sporadic PD participants

Variable	SAA- sPD (N = 79 ^a)	SAA+ sPD (N = 237)	p-value ^b
Age at enrollment, years, median (IQR)	66.7 (61.3–73.3)	67.4 (62.1–72.5)	0.959
Male sex, n (%)	50 (63%)	150 (63%)	1.000

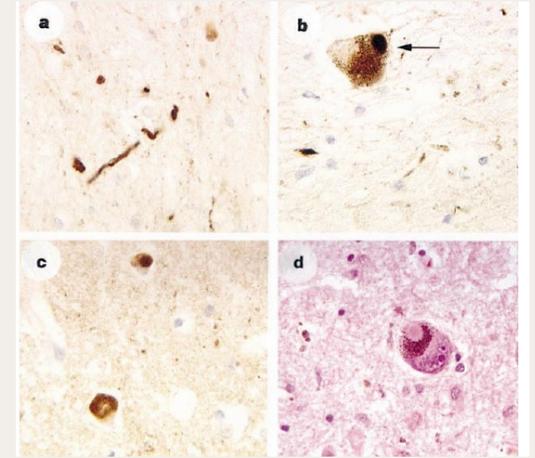


Faster progression over 3 years in sPD SAA- compared to sPD SAA+

14.3% of the SAA- enrolled in the sPD cohort had a change in diagnosis during longitudinal follow-up (most commonly to MSA).

<1% of the SAA+ had a change

Solution: Shift from using a diagnosis based purely on a clinical syndrome to one based on biological markers of the pathology



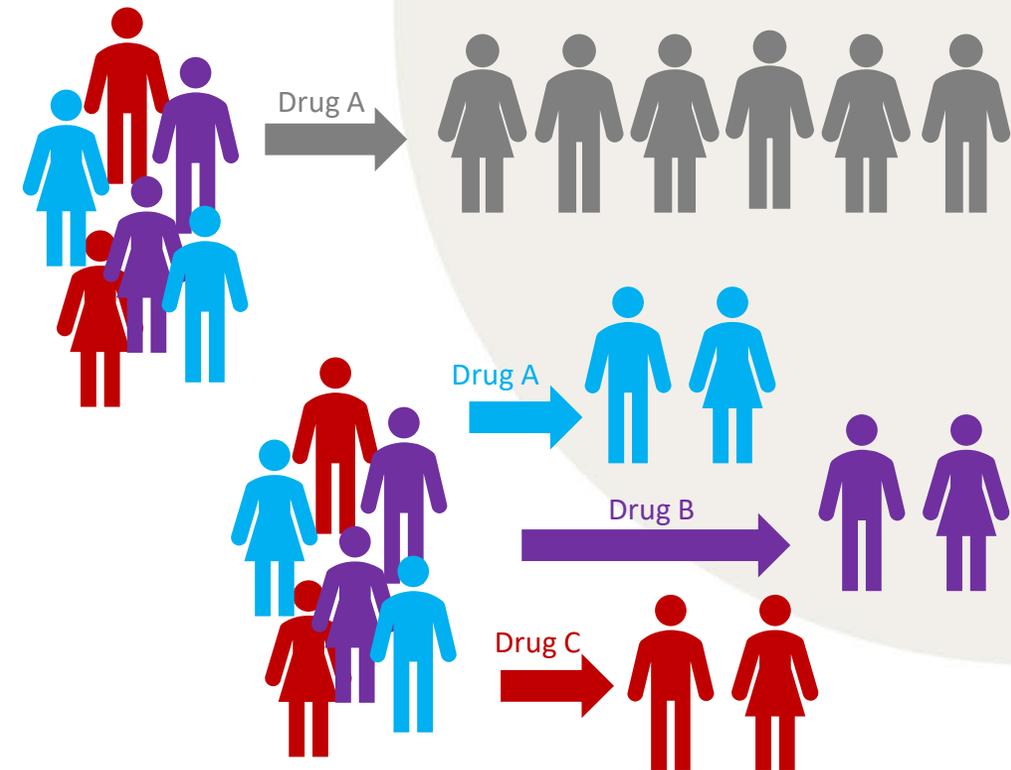
- A biological definition can be applied to newly symptomatic people for more precise enrollment into clinical trials.

Get the right therapy, to the right person, at the right time



Biomarker-based definitions

- Identify biologie(s)
- Identify significant co-pathologie(s)
- Predict rate of progression
- Biological activity of drug



Gall's Law: a principle often used in systems design

1. Start with a simple, functional system

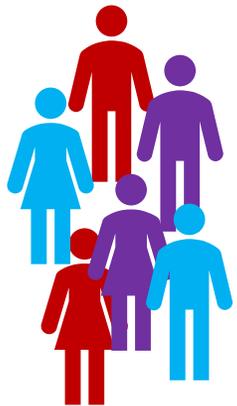
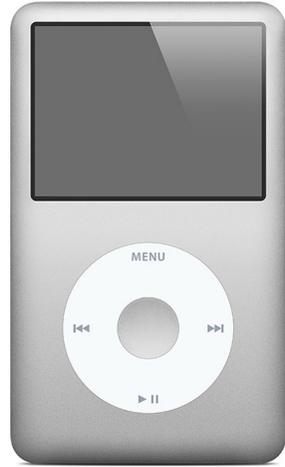
- Begin by creating a minimal, working version of the system that addresses the core requirements.

2. Iteratively expand and refine:

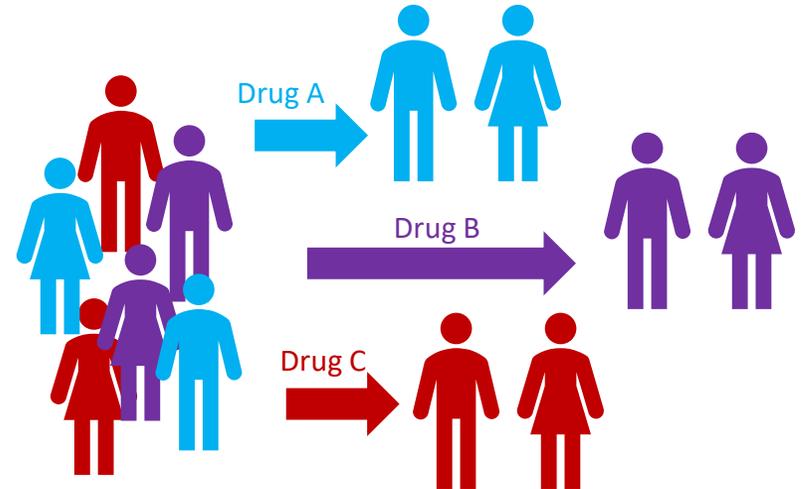
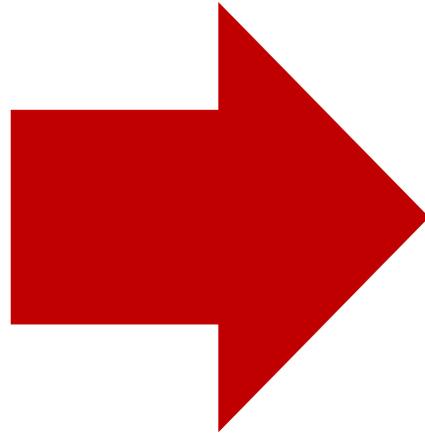
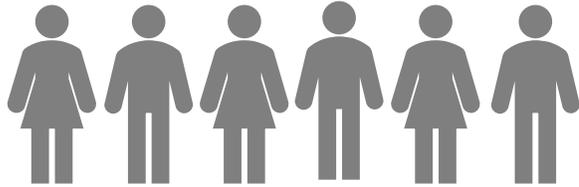
- Gradually add complexity and features, testing and refining the system at each stage based on real-world use and feedback.

3. Embrace the evolutionary process:

- Allow the system to evolve organically over time, guided by the challenges and opportunities it encounters in its environment.



Drug A






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