The changing landscape of Parkinson's disease

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Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University

Overview

- Review of currently available treatments for Parkinson’s, including complex therapies
- Discuss ongoing clinical trials of disease-modifying agents and preliminary results
- Discuss recent developments in Parkinson’s biomarkers and introduce new concept of biological definition of the disease

Conflict of interest

None

Other disclosures

Advisory Boards: Britannia, Boston Scientific, Benevolent AI, Roche, Abbvie.

Honoraria: Britannia, Abbvie, GE Healthcare, Boston Scientific.

Grants: Independent Research Fund Denmark, Danish Parkinson's disease Association, Parkinson's UK, Center of Excellence in Neurodegeneration (CoEN) network award, GE Healthcare Grant, Multiple System Atrophy Trust, Weston Brain Institute, EU Joint Program Neurodegenerative Disease Research (JPND), EU Horizon 2020 research, The Michael J. Fox Foundation, F. Hoffmann-La Roche.

Parkinson's

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

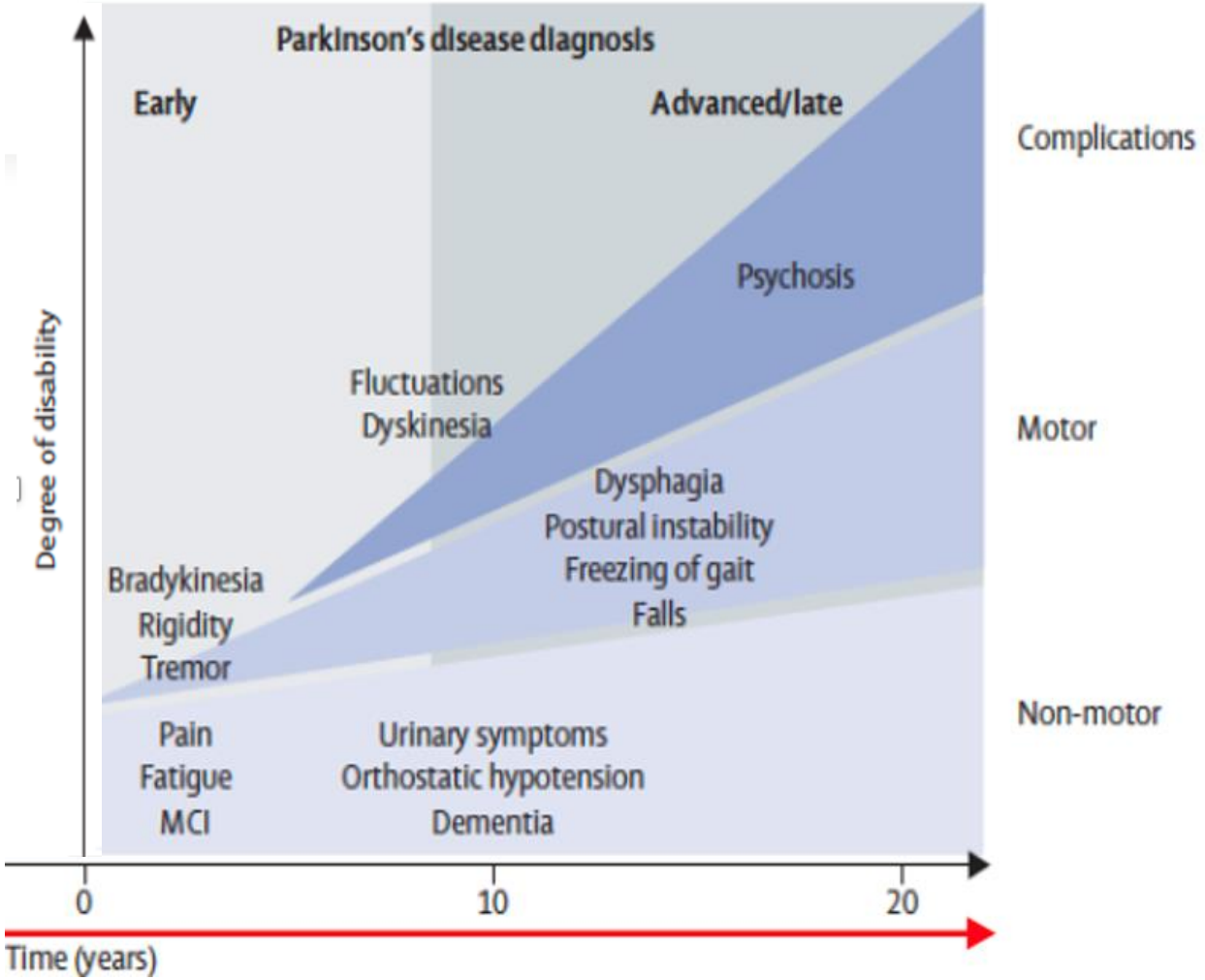
THE term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-

153

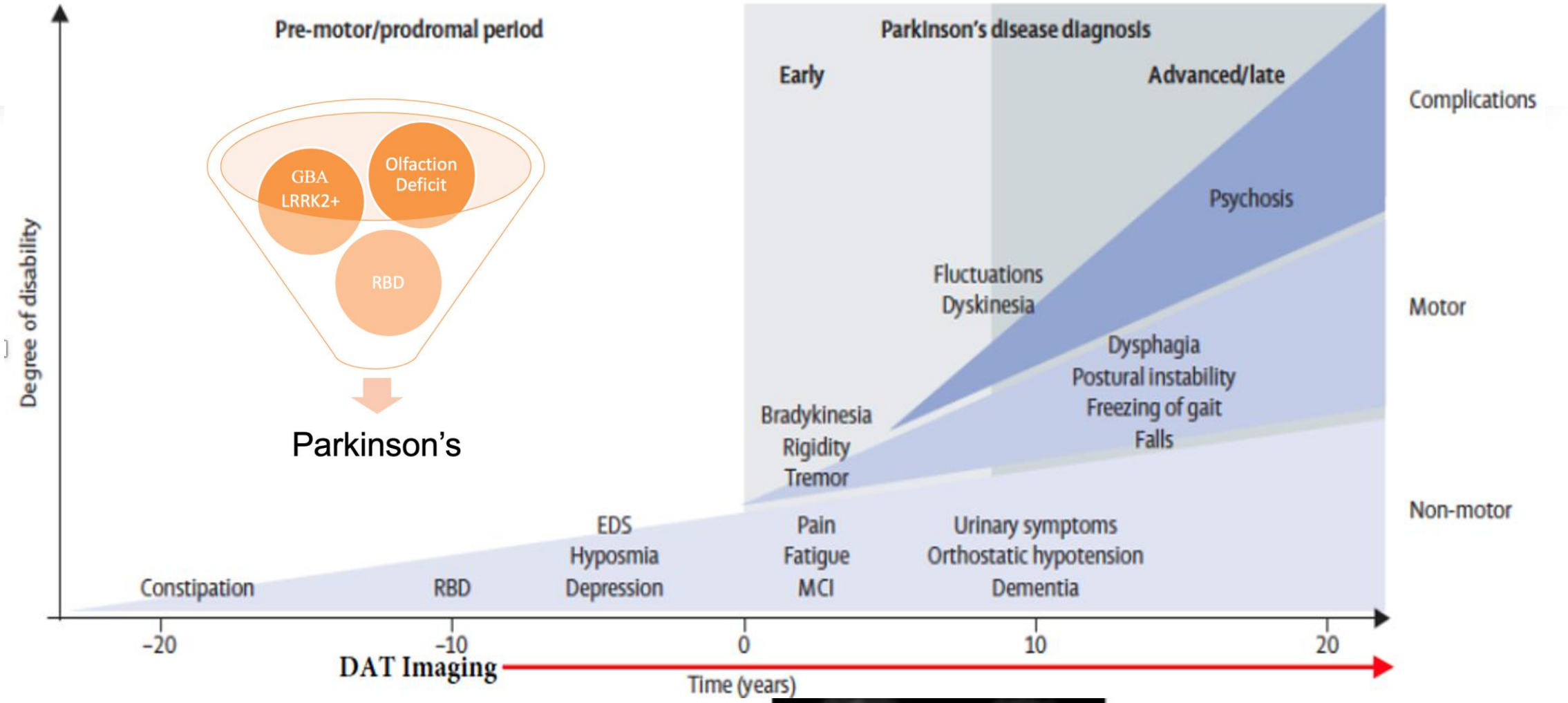
James Parkinson, 1817

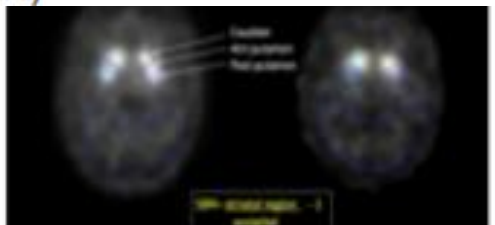
- Progressive neurodegenerative disease
- it occurs everywhere in the world
- 95% of cases begin over age 50
- 1-2% > age 60
- Incidence increases with age
- Men more frequently affected than women (1.5 times)

Natural History of Parkinson's



Natural History of Parkinson's

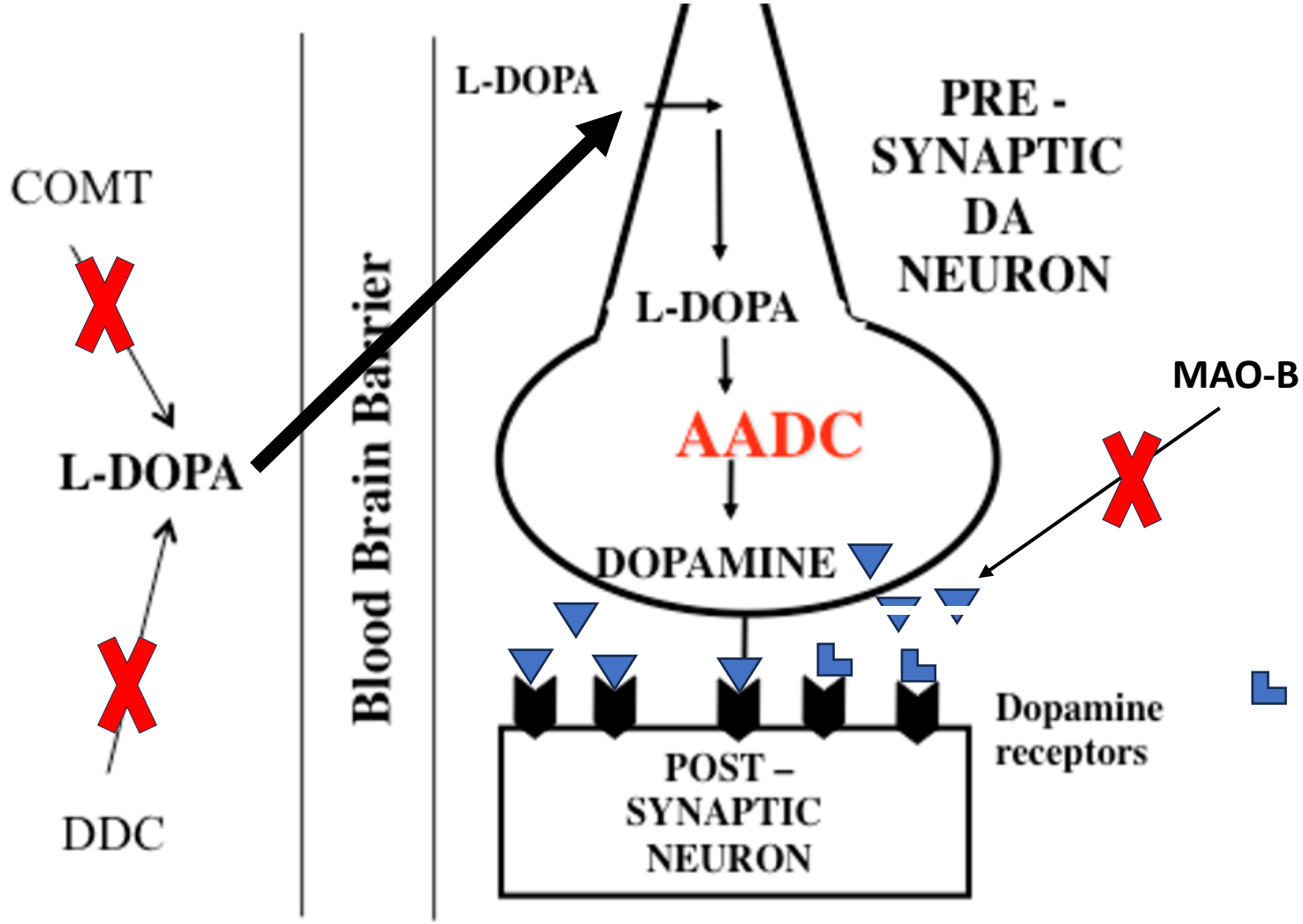




Dopamine Replacement Therapy

COMT inibithors
Entacapone
Opicapone

DDC inibithors
Carbidopa
Benserazide



MAO-B inibithors
Selegiline
Rasagiline
Safinamide

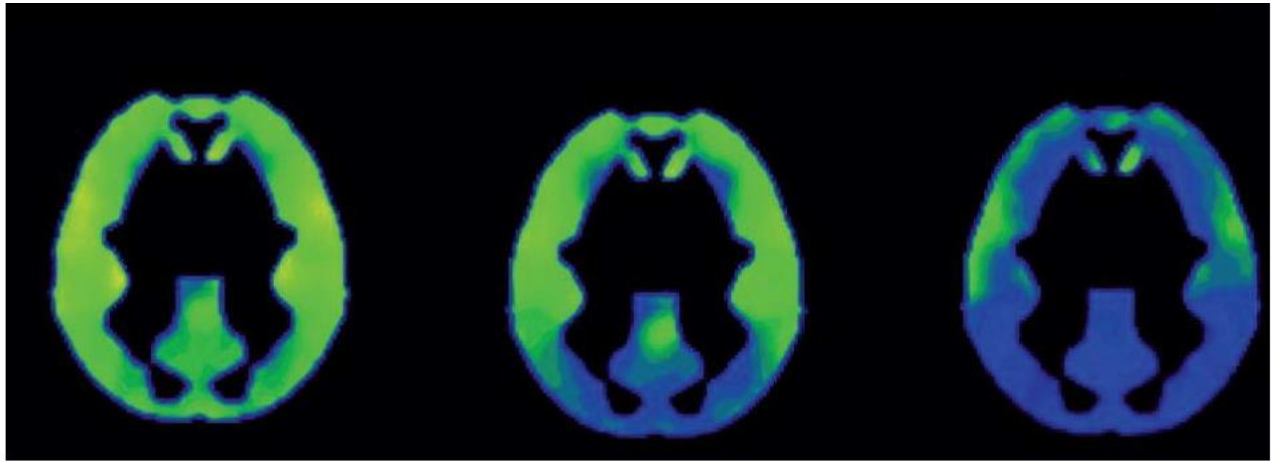
Dopamine agonists
Ropinirole
Pramipexole
Rotigotine
Apomorphine

Non-dopaminergic Therapy

- **Amantadine** for Dyskinesias
- **Anticholinergics** for tremor

Acetylcholine esterase imaging

^{11}C-NM4PA PET

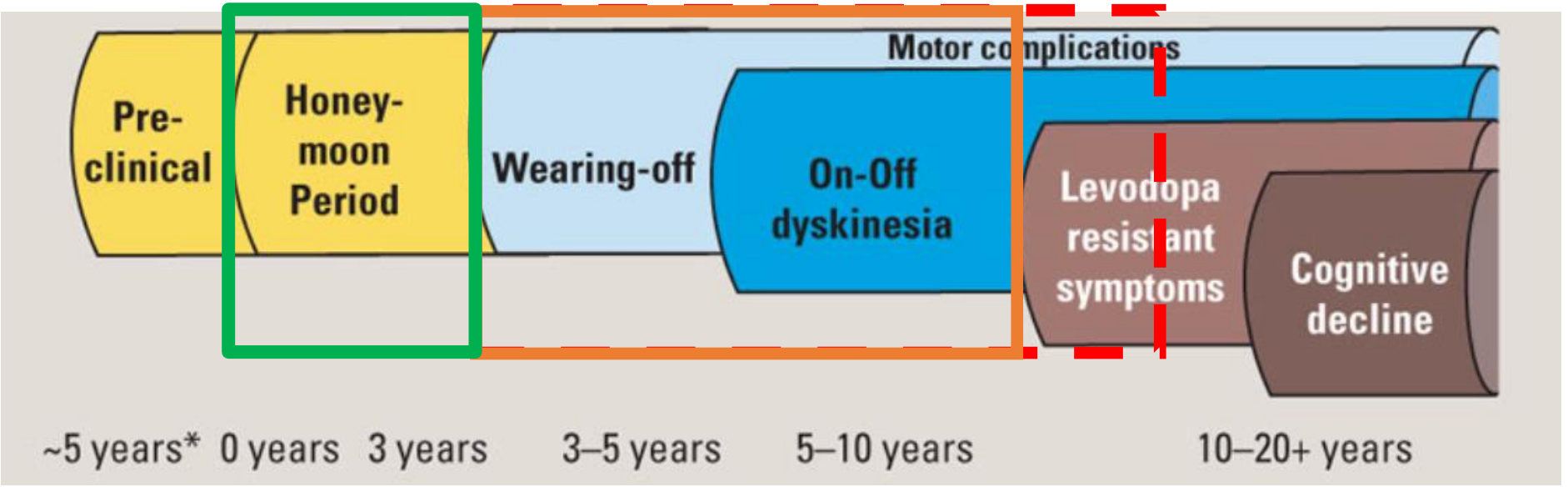


Normal **PD** **PDD** (Dementia)

Also found in RBD patients

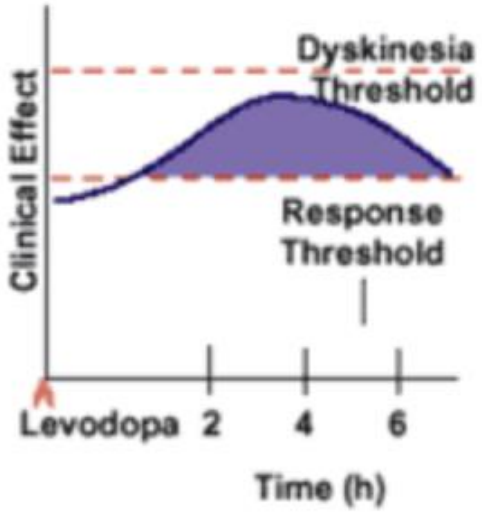
Hilker et al. 2005

Progression of Parkinson's and Therapeutic Response



Changes in Levodopa Response over Time

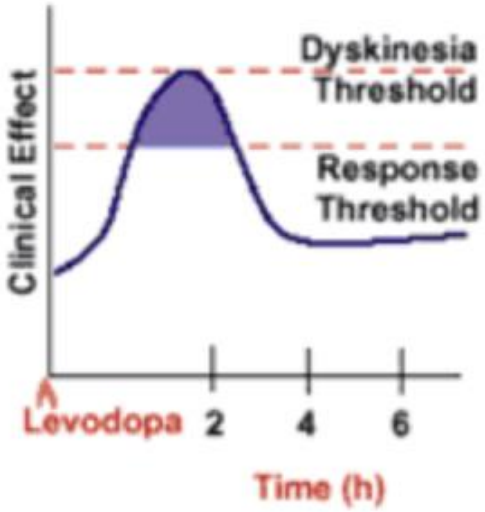
Early PD



Long duration motor response

Low incidence of dyskinesia

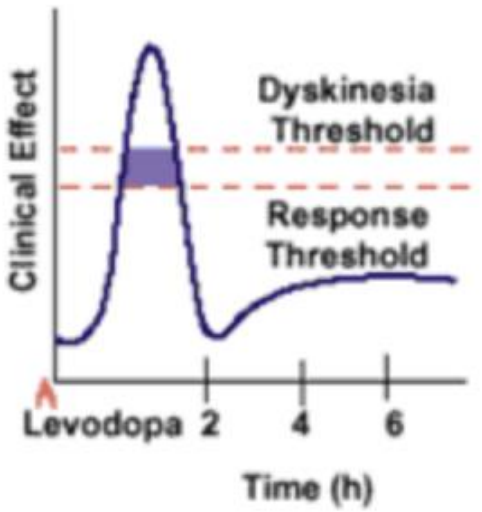
Moderate PD



Shorter duration motor response

Increased incidence of dyskinesia

Advanced PD



Short duration motor response

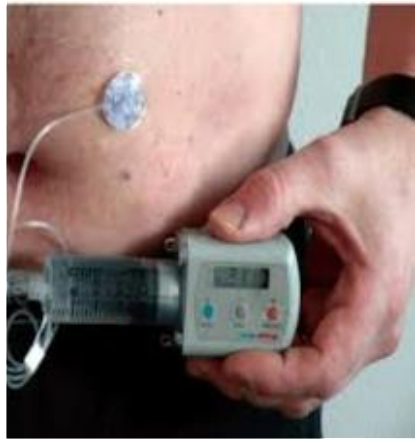
'On'-time consistently associated with dyskinesia

Complex Therapies in PD

Deep Brain Stimulation

Who to choose?

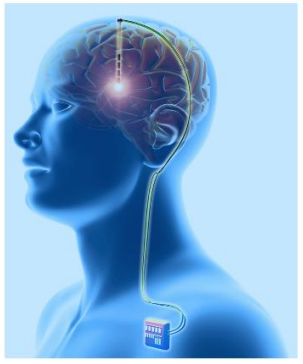
Intestinal Levodopa/Carbidopa Infusion

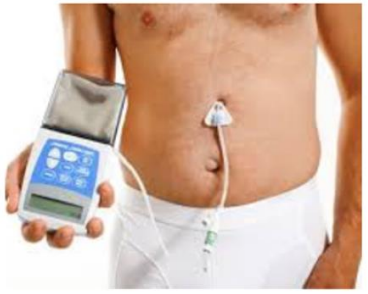


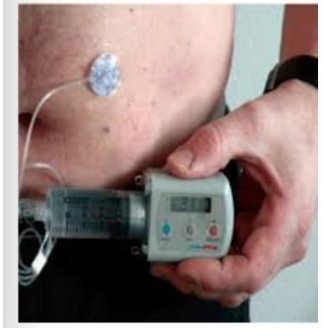
Subcutaneous Apomorphine Infusion

Subcutaneous Foslevodopa/foscarbidopa Infusion

5-2-1 Criteria



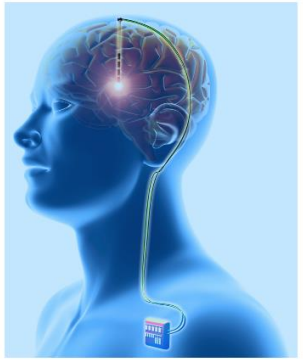


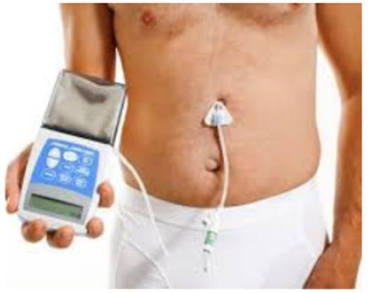


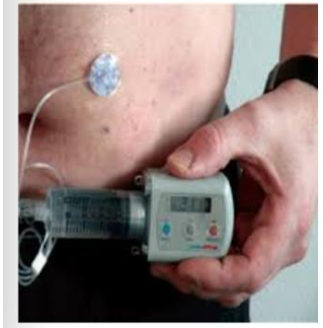
The 5-2-1 criteria have been proposed to determine when a patient's PD has progressed to an advanced state

Aldred et al. 2020

5-2-1 Criteria





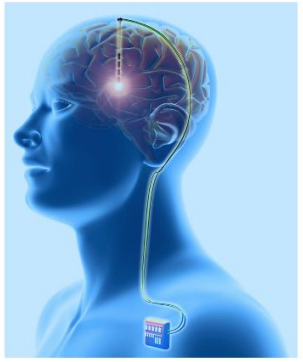


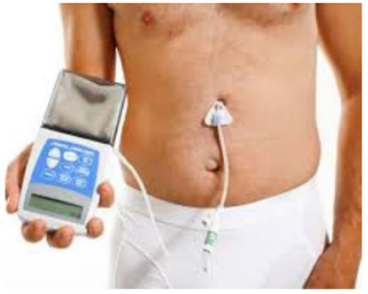
Patients are considered to have advanced PD when they meet at least one of the 5-2-1 criteria:

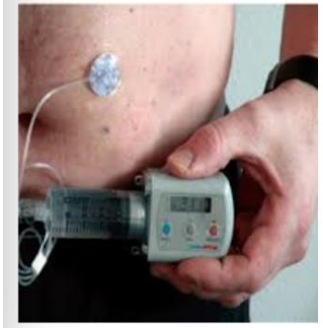
- taking L-Dopa at least five times a day
- having at least 2 hours with “OFF” symptoms during the day
- or having at least 1 hour of troublesome, uncontrolled dyskinesia

Aldred et al. 2020

Absolute Criteria for Considering Referral Complex Therapies







- Parkinson’s for at least 4 years
- Presence of bothersome disease- related symptoms and/or side effects
- Motor improvement with dopaminergic medications
- Absence of other significant medical conditions
- Absence of ongoing severe, medically resistant neuropsychiatric diseases

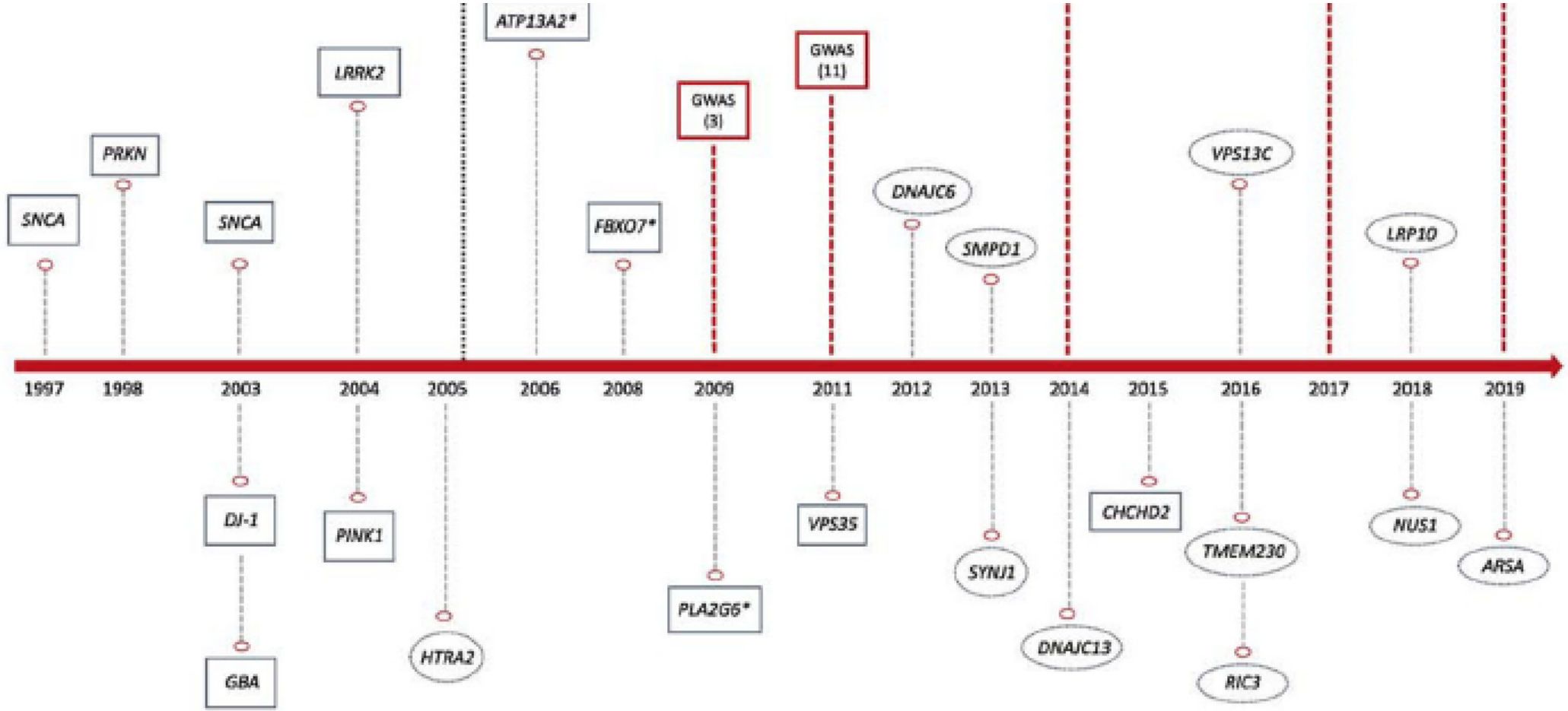
Aetiology of Parkinson's

The aetiology of PD is unknown and a number of possible factors must be considered

It is likely that the cause of PD is multifactorial with contributions from

- aging
- impaired oxidative mechanisms
- exposure to toxins/viruses
- head injuries
- genetic predisposition

The genetics of Parkinson's over Time



Red squares represent genome-wide association studies and number of discovered risk loci in brackets
Green squares represent controversial or not widely validated genes linked to typical Parkinson disease

CAN GBA and LRRK2 PLAY A ROLE ALSO IN NON-MUTATED PD?

doi:10.1093/brain/awt367 Brain 2014: 137; 834–848 | 834

BRAIN
A JOURNAL OF NEUROLOGY

Reduced glucocerebrosidase is associated with increased α-synuclein in sporadic Parkinson's disease

Karen E. Murphy,[1,2] Amanda M. Gysbers,[1] Sarah K. Abbott,[3,4] Nahid Tayebi,[5] Woojin S. Kim,[1,2] Ellen Sidransky,[5] Antony Cooper,[6,7] Brett Garner[3,4] and Glenda M. Halliday[1,2]

Chiasserini *et al. Molecular Neurodegeneration* (2015) 10:15
DOI 10.1186/s13024-015-0010-2

MOLECULAR NEURODEGENERATION

SHORT REPORT Open Access

Selective loss of glucocerebrosidase activity in sporadic Parkinson's disease and dementia with Lewy bodies

Davide Chiasserini[1†], Silvia Paciotti[2†], Paolo Eusebi[1,3], Emanuele Persichetti[2], Anna Tasegian[2], Marzena Kurzawa-Akanbi[4,5], Patrick F Chinnery[4,5], Christopher M Morris[6], Paolo Calabresi[1,7], Lucilla Parnetti[1*] and Tommaso Beccari[2*]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

LRRK2 activation in idiopathic Parkinson's disease

Roberto Di Maio[1,2,3], Eric K. Hoffman[1,2], Emily M. Rocha[1,2], Matthew T. Keeney[1,2], Laurie H. Sanders[1,2,4], Briana R. De Miranda[1,2], Alevtina Zharikov[1,2], Amber Van Laar[1,2], Antonia F. Stepan[5], Thomas A. Lanz[5], Julia K. Kofler[6], Edward A. Burton[1,2,7], Dario R. Alessi[8], Teresa G. Hastings[1,2], J. Timothy Greenamyre[1,2,7]*

NIH U.S. National Library of Medicine

ClinicalTrials.gov

ROPAD - LRRK2 International PD, An international multicenter epidemiological observational study

Newcastle cohort

PD in our Clinics
N = 165

LRRK2
8 (4.85%)

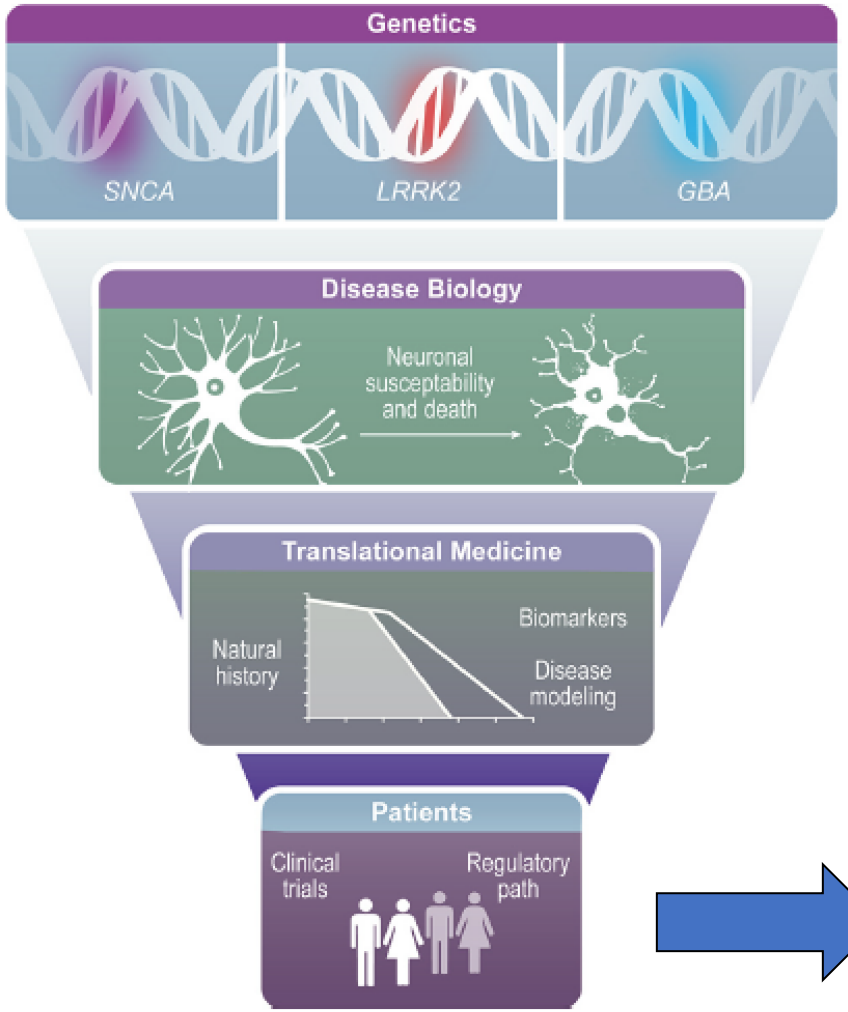
GBA
13 (7.9%)

Parkin
4 (2.4%)

Similar phenotype
Similar treatment
No changes of therapy

You do not treat genetic cases in a different way

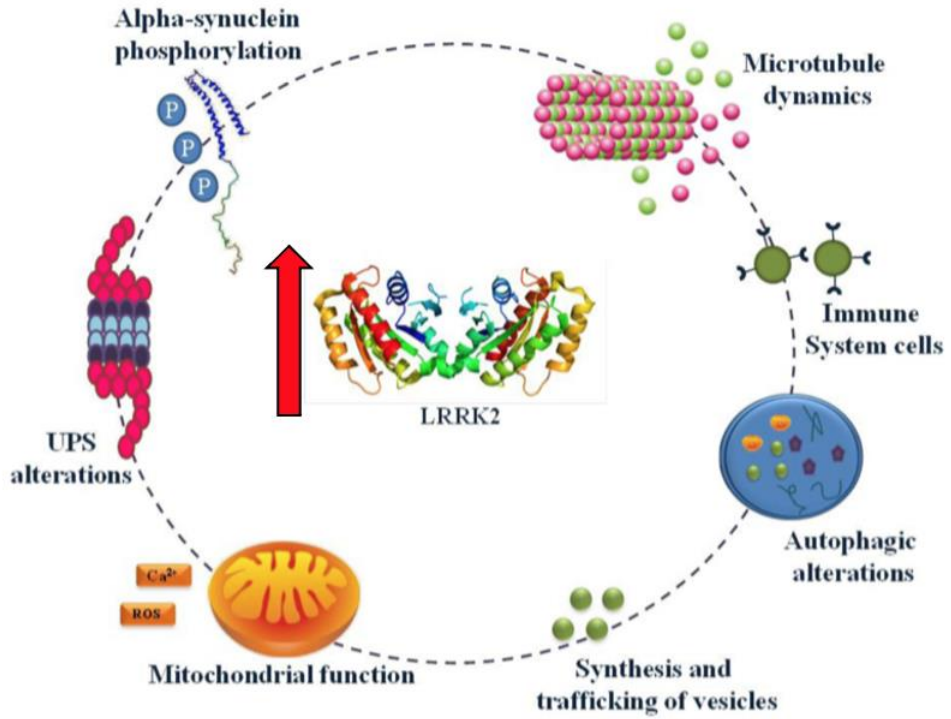
Genetic-based Interventions



Personalised Medicine

Source: Shihabuddin et al .2018

Targeted Therapy in LRRK2-associated Parkinson's



Esteves et at.. 2014

NIH U.S. National Library of Medicine

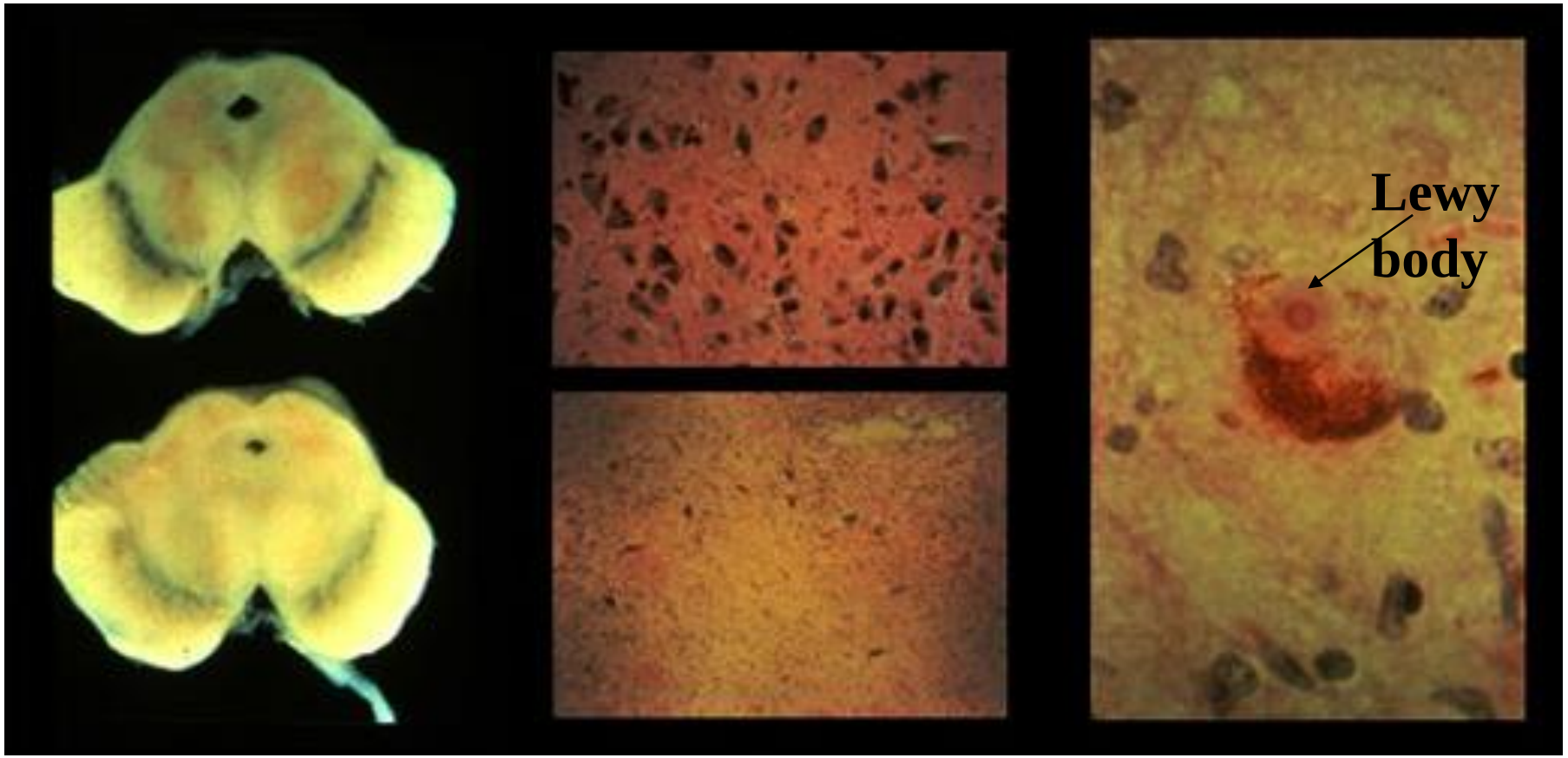
ClinicalTrials.gov

A Study to Assess the Safety of BIIB122 Tablets and if it Can Slow the Worsening of Early-Stage Parkinson's Disease in Participants Between the Ages of 30 and 80 (LUMA)

ClinicalTrials.gov Identifier:
NCT05348785

DNL151 / BIIB122 is a LRRK2 inhibitor co-developed by Denali and Biogen

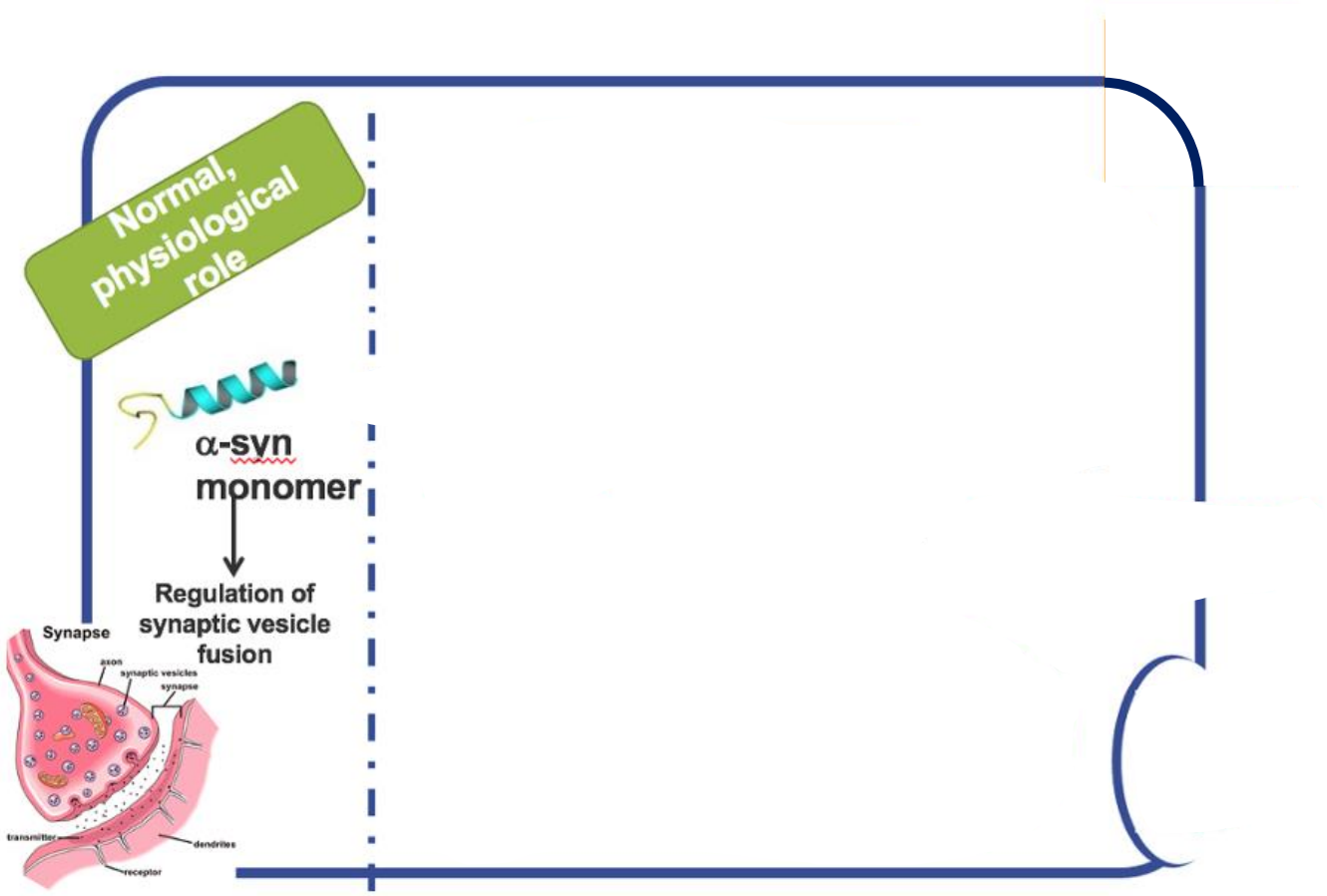
Pathological Changes in PD

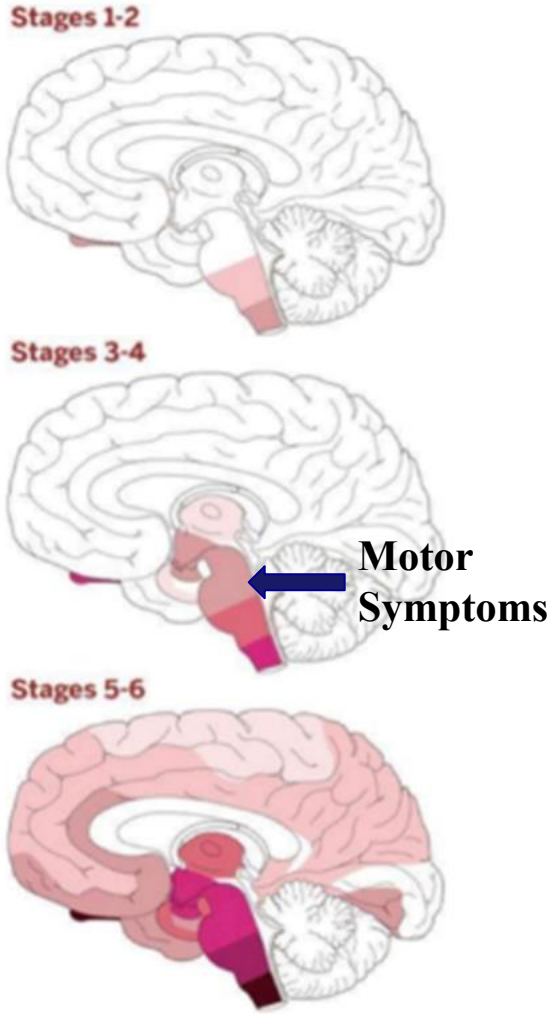


The major component of Lewy bodies and Lewy neurites is an aggregated form of alpha-synuclein

www.mdvu.org/library/disease/pd/par_path.asp

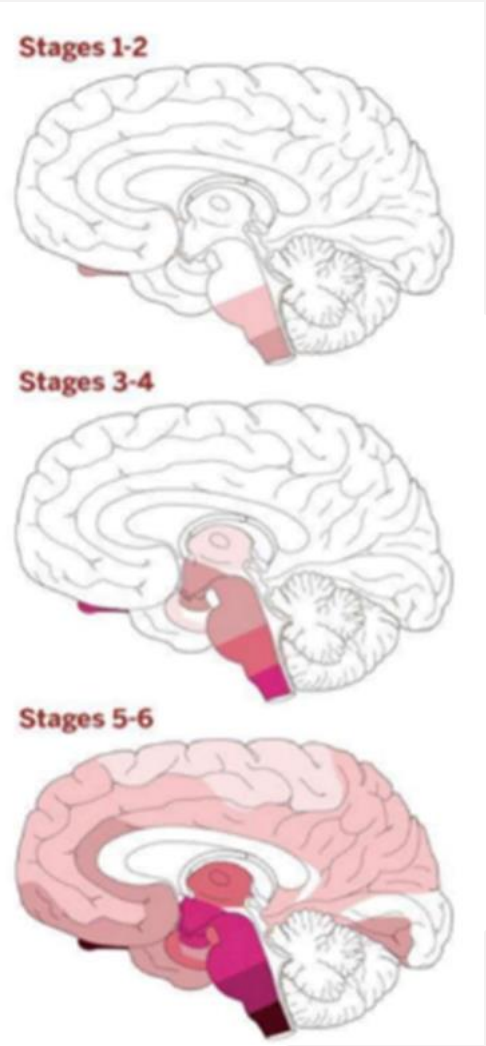
Alpha-Synuclein Misfolding in Parkinson's



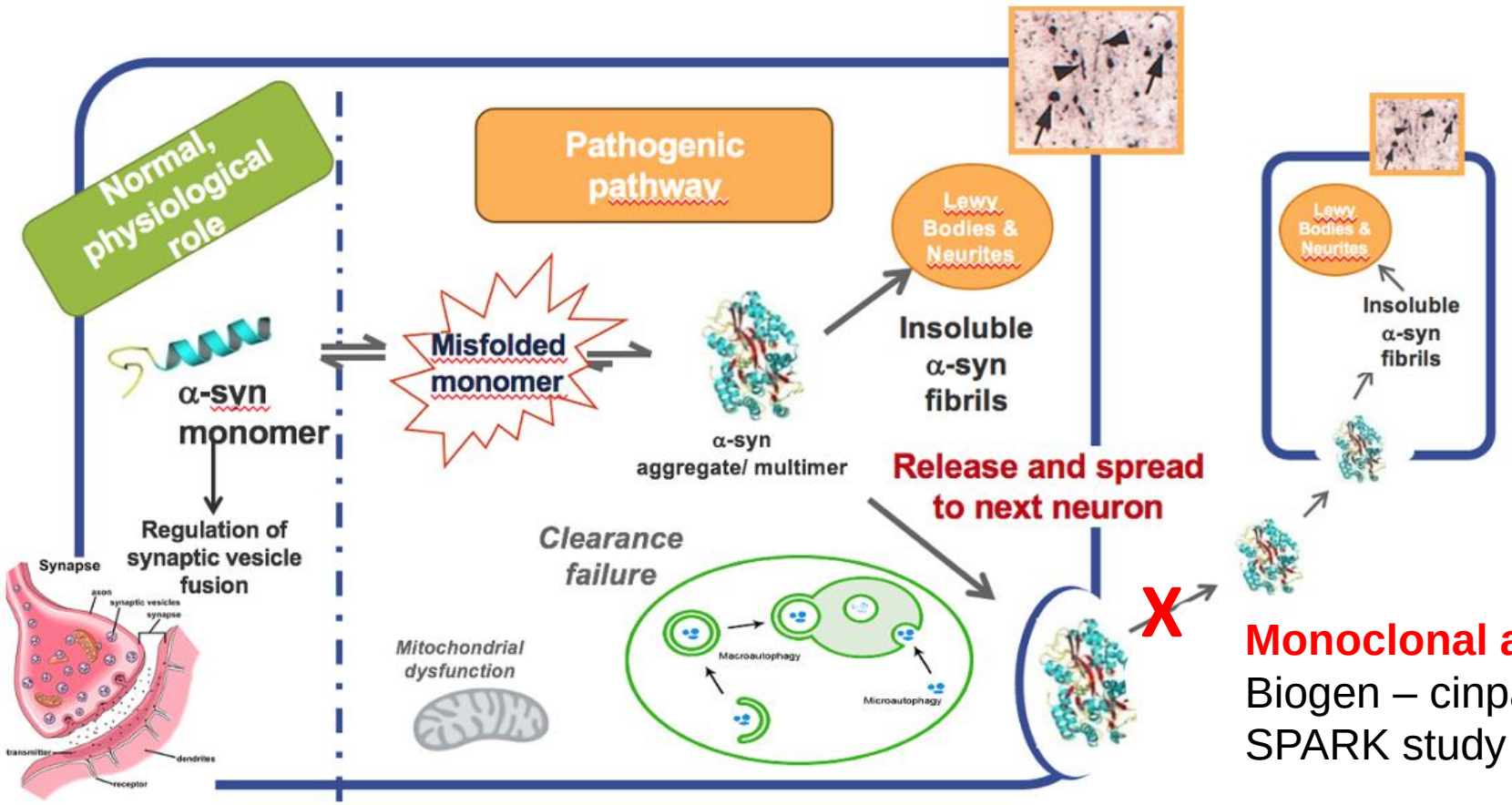


Braak Stages

Clinical Trials of Disease-modifying agents



Alpha-Synuclein Misfolding in Parkinson's



Monoclonal antibodies

Biogen – cinpanemab – SPARK study

Roche - Prasinezumab Pasadena and Padova studies

PASADENA Study

The NEW ENGLAND JOURNAL of MEDICINE

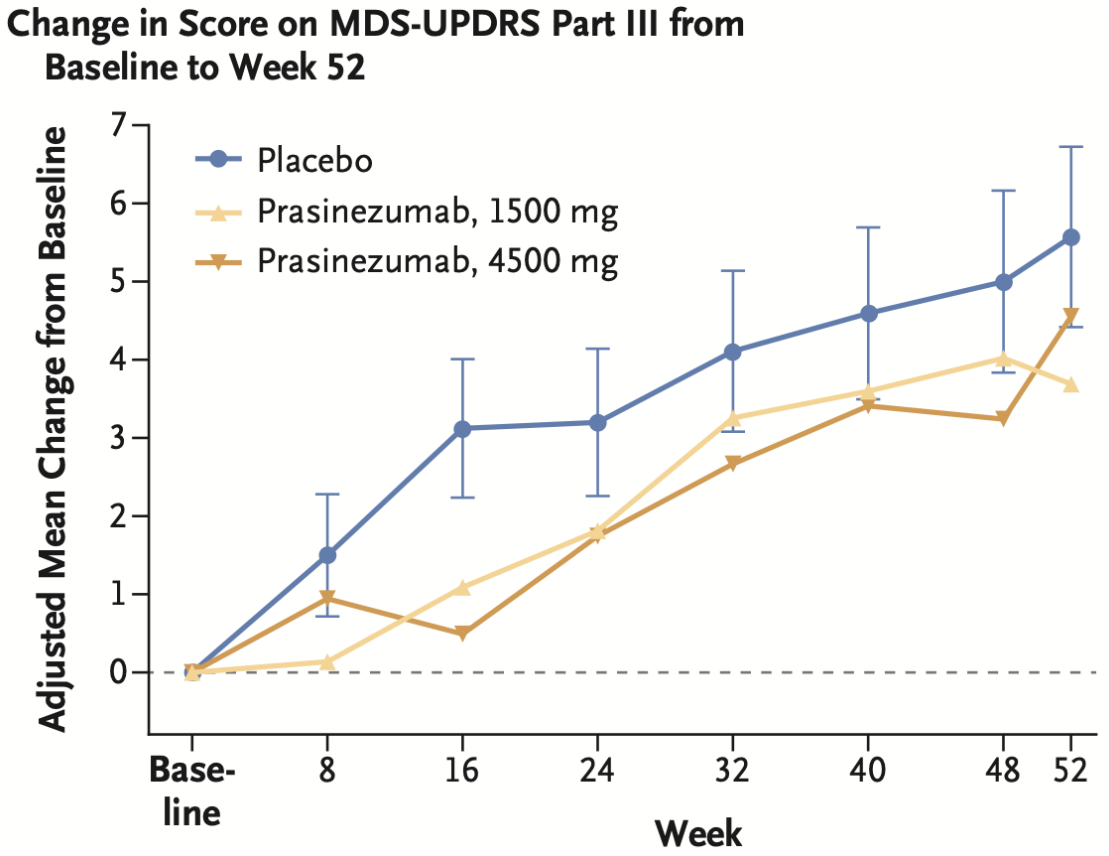
ORIGINAL ARTICLE

Trial of Prasinezumab in Early-Stage Parkinson's Disease

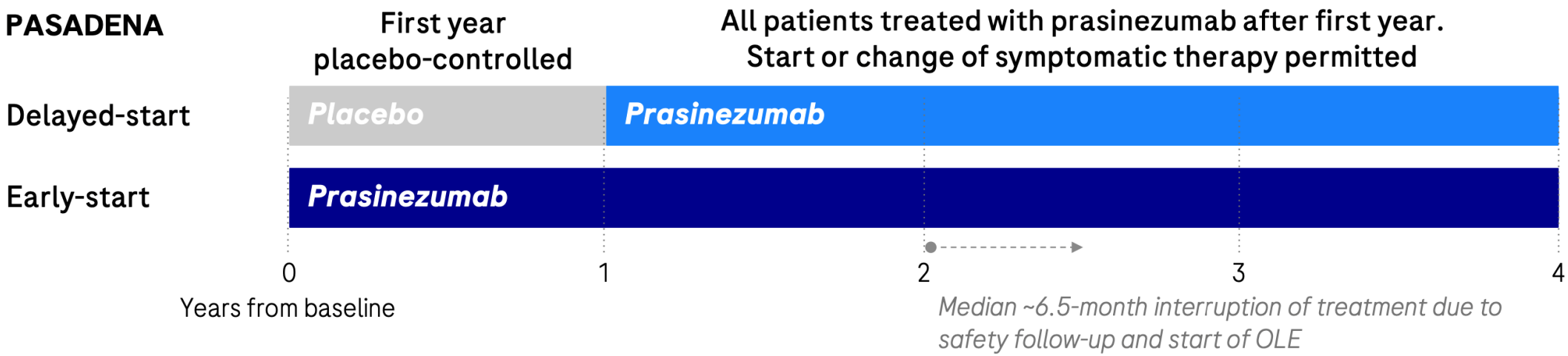
G. Pagano, K.I. Taylor, J. Anzures-Cabrera, M. Marchesi, T. Simuni, K. Marek, R.B. Postuma, N. Pavese, F. Stocchi, J.-P. Azulay, B. Mollenhauer, L. López-Manzanares, D.S. Russell, J.T. Boyd, A.P. Nicholas, M.R. Luquin, R.A. Hauser, T. Gasser, W. Poewe, B. Ricci, A. Boulay, A. Vogt, F.G. Boess, J. Dukart, G. D'Urso, R. Finch, S. Zanigni, A. Monnet, N. Pross, A. Hahn, H. Svoboda, M. Britschgi, F. Lipsmeier, E. Volkova-Volkmar, M. Lindemann, S. Dziadek, Š. Holiga, D. Rukina, T. Kustermann, G.A. Kerchner, P. Fontoura, D. Umbricht, R. Doody, T. Nikolcheva, and A. Bonni, for the PASADENA Investigators and Prasinezumab Study Group*

2022

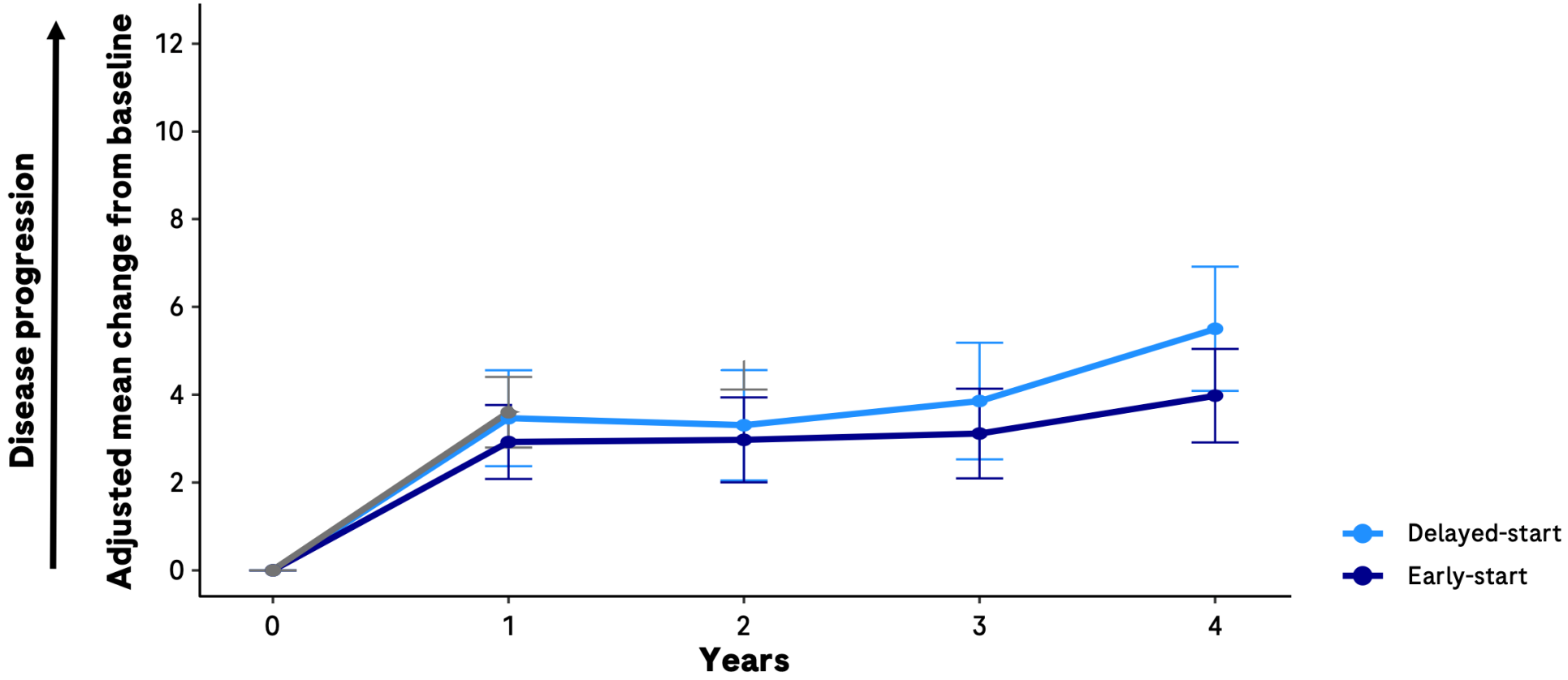
No Change in Sum of Scores on MDS-UPDRS Parts I, II, and III from Baseline to Week 52



The PASADENA Trial



Progression of MDS-UPDRS Part III OFF (motor examination) in Prasinezumab-treated individuals



https://medically.roche.com/content/dam/pdmahub/restricted/neurology/adpd-2024/ADPD-2024-presentation-pagano-PASADENA-long-term-open-label-extension.pdf

PADOVA Study

NIH U.S. National Library of Medicine

ClinicalTrials.gov

A Study to Evaluate the Efficacy and Safety of Intravenous Prasinezumab in Participants With Early Parkinson's Disease (PADOVA)

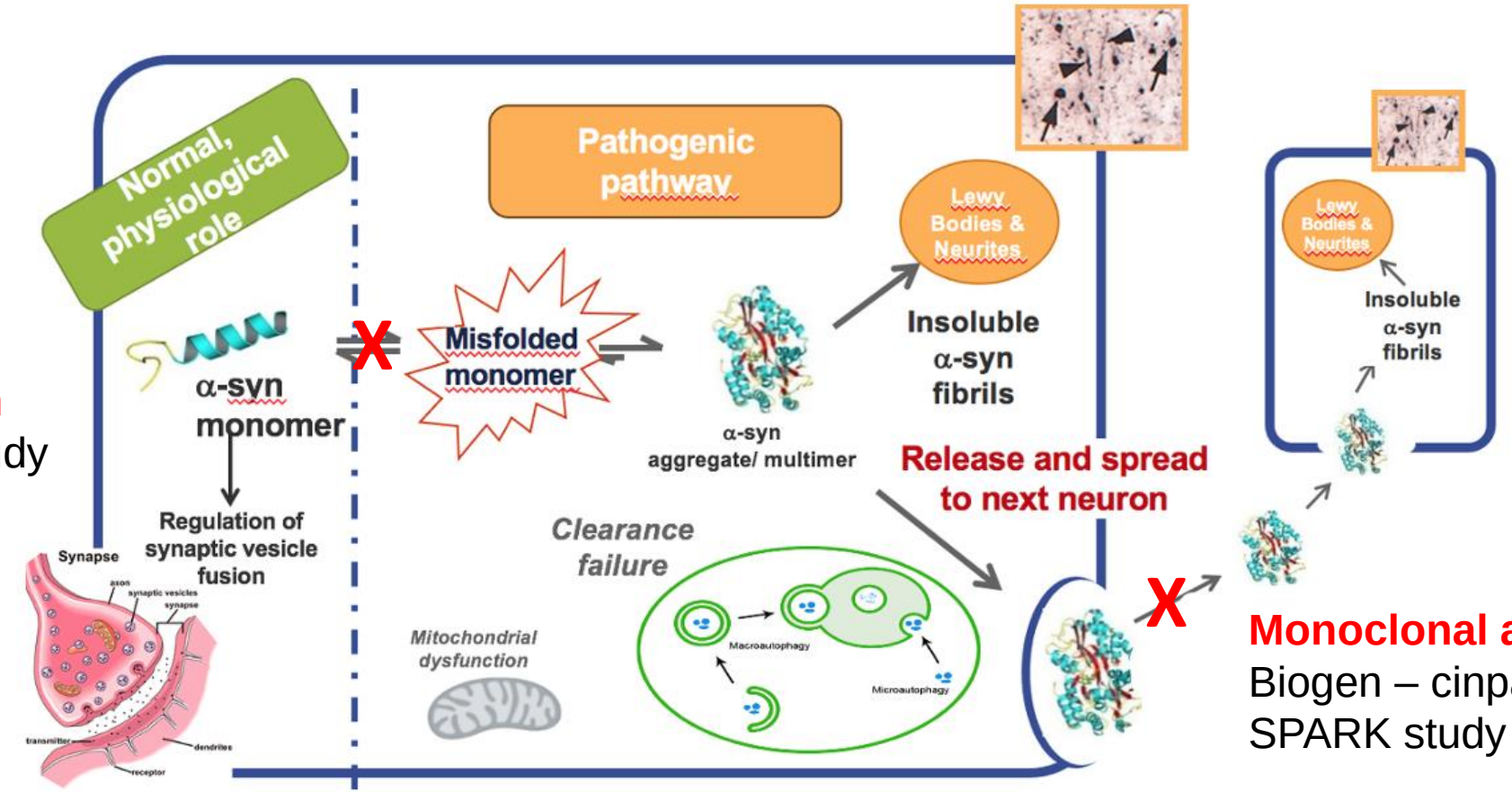
ClinicalTrials.gov Identifier:
NCT04777331

Brief Summary:

This is a multicenter, randomized, double-blind, placebo-controlled study that will evaluate the efficacy and safety of intravenous (IV) prasinezumab versus placebo in participants with Early Parkinson's Disease (PD) who are on stable symptomatic PD medication.

Alpha-Synuclein Misfolding in Parkinson's

UCB0599
Minzasolmin
Orchestra study



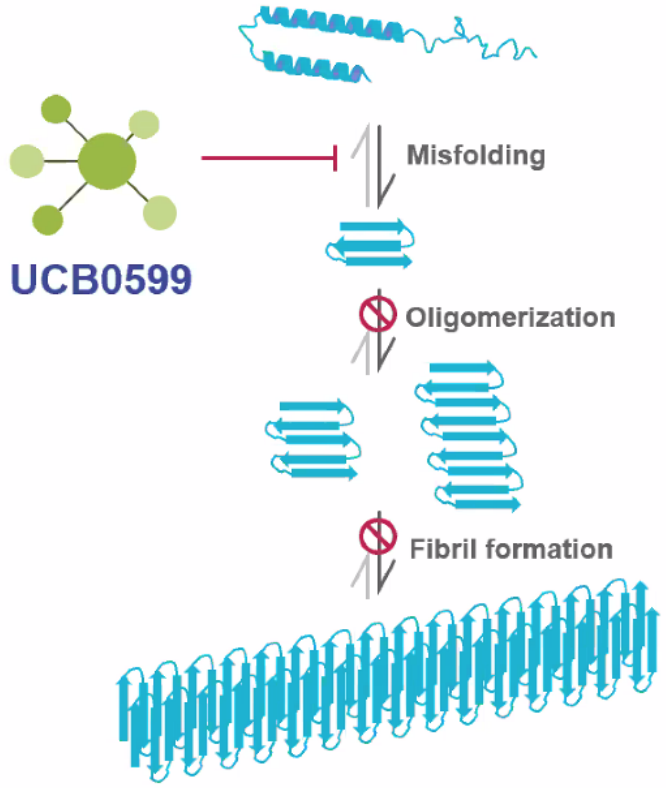
Monoclonal antibodies
Biogen – cinpanemab – SPARK study

Roche - Prasinezumab
Pasadena and Padova studies

Orchestra Study (Minzasolmin vs Placebo)

UCB0599 is an Oral alpha-Synuclein (ASYN) Misfolding Inhibitor

- **ASYN adopts** a **misfolded structure** and **aggregates** into oligomers, which are believed to be the toxic species responsible for the spread of pathology from neuron to neuron in PD progression
- **UCB0599 is an orally administered**, small molecule inhibitor of ASYN misfolding
- **UCB0599 interacts with ASYN early** in the pathological process, **preventing the initial misfolding steps** that lead to fibril formation and consequent progression of PD



Orchestra Study (Minzasolmin vs Placebo)

NIH U.S. National Library of Medicine

ClinicalTrials.gov

A 18-month Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of Oral UCB0599 in Study Participants With Early-stage Parkinson's Disease

ClinicalTrials.gov Identifier:
NCT04658186

Brief Summary:

The purpose of the study is to assess the safety and tolerability of UCB0599 and to demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression over 12 and 18 months in participants diagnosed with early-stage Parkinson's Disease.

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

Why We Exist | Understanding Parkinson's | For Researchers | Take Action

Research News

Breaking News: Parkinson's Disease Biomarker Found

April 13, 2023

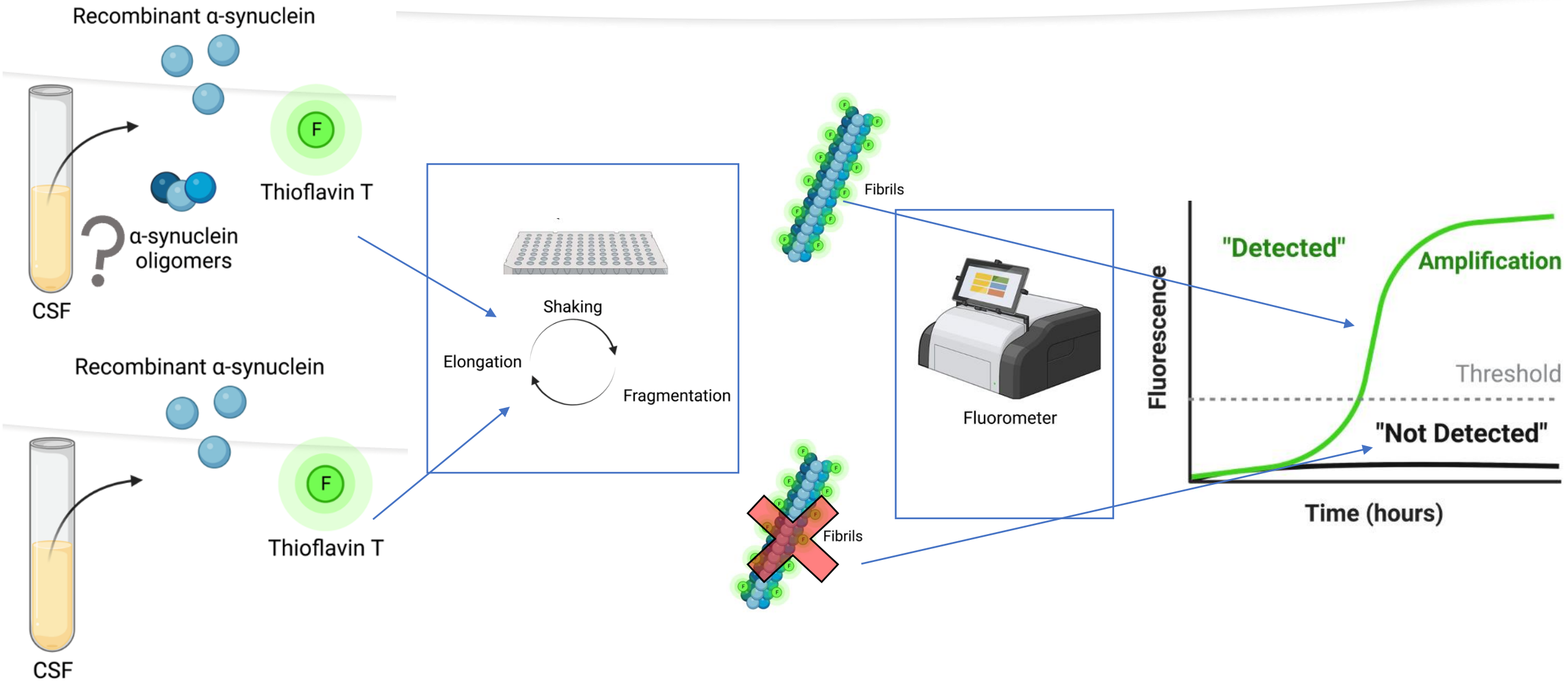
A recently developed highly accurate biological test called the α-synuclein seeding amplification assay (αSyn-SAA) is capable of objectively and reliably detecting the presence of abnormal alpha-synuclein in the cerebrospinal fluid in people with PD

Parkinson's Progression Markers Initiative

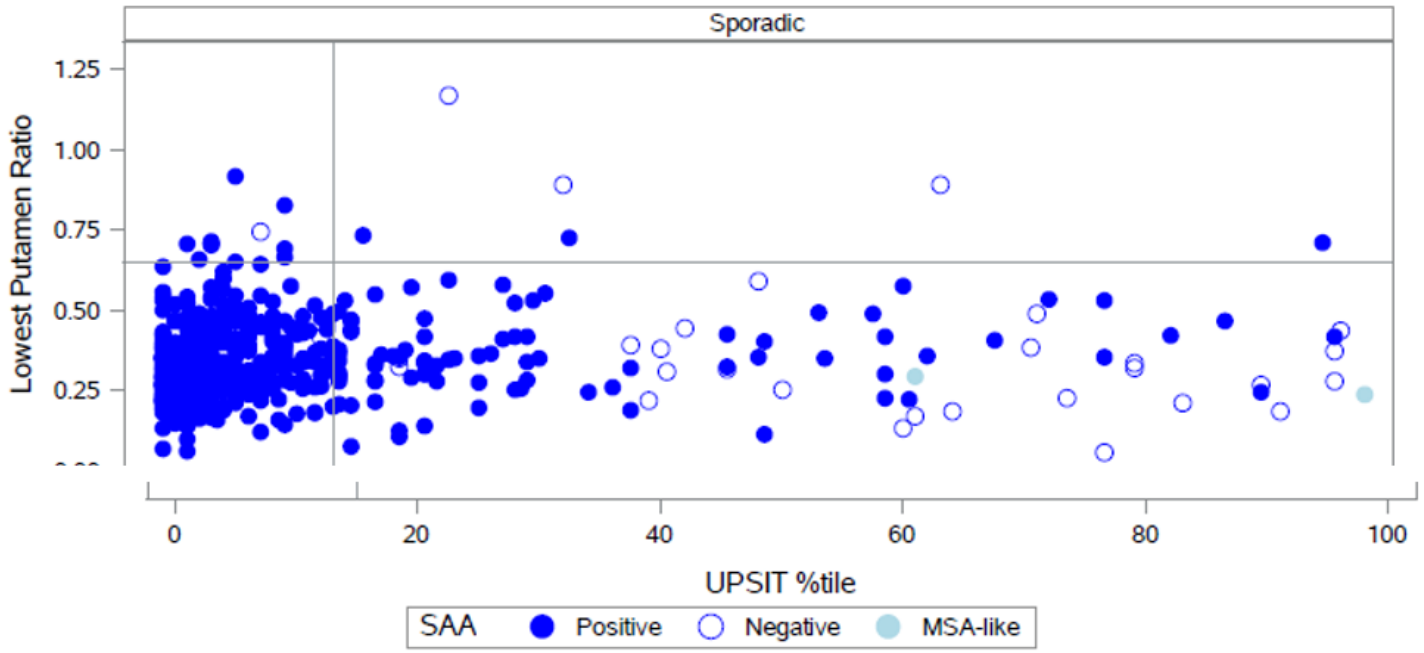
Siderowf A et al, Lancet Neurol. 2023

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

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



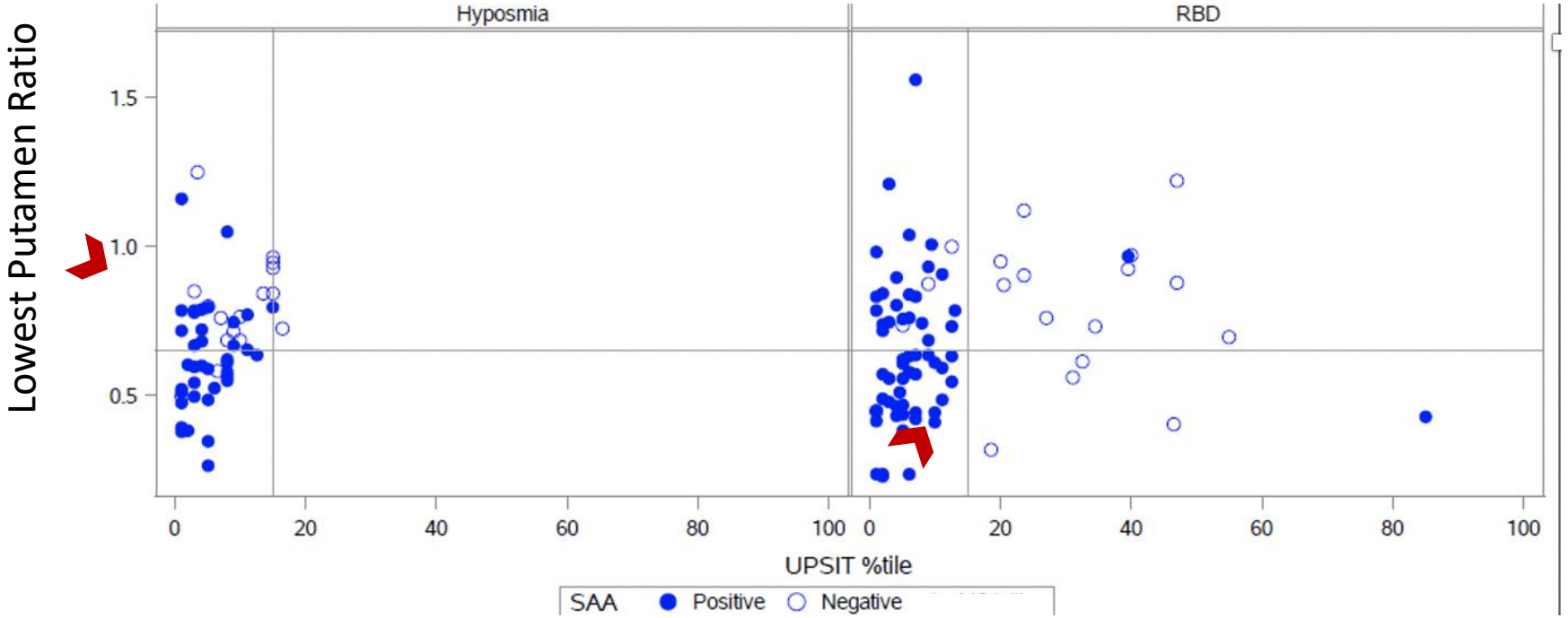
Defined PD/ DLB individuals



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

Siderowf A et al, Lancet Neurol. 2023

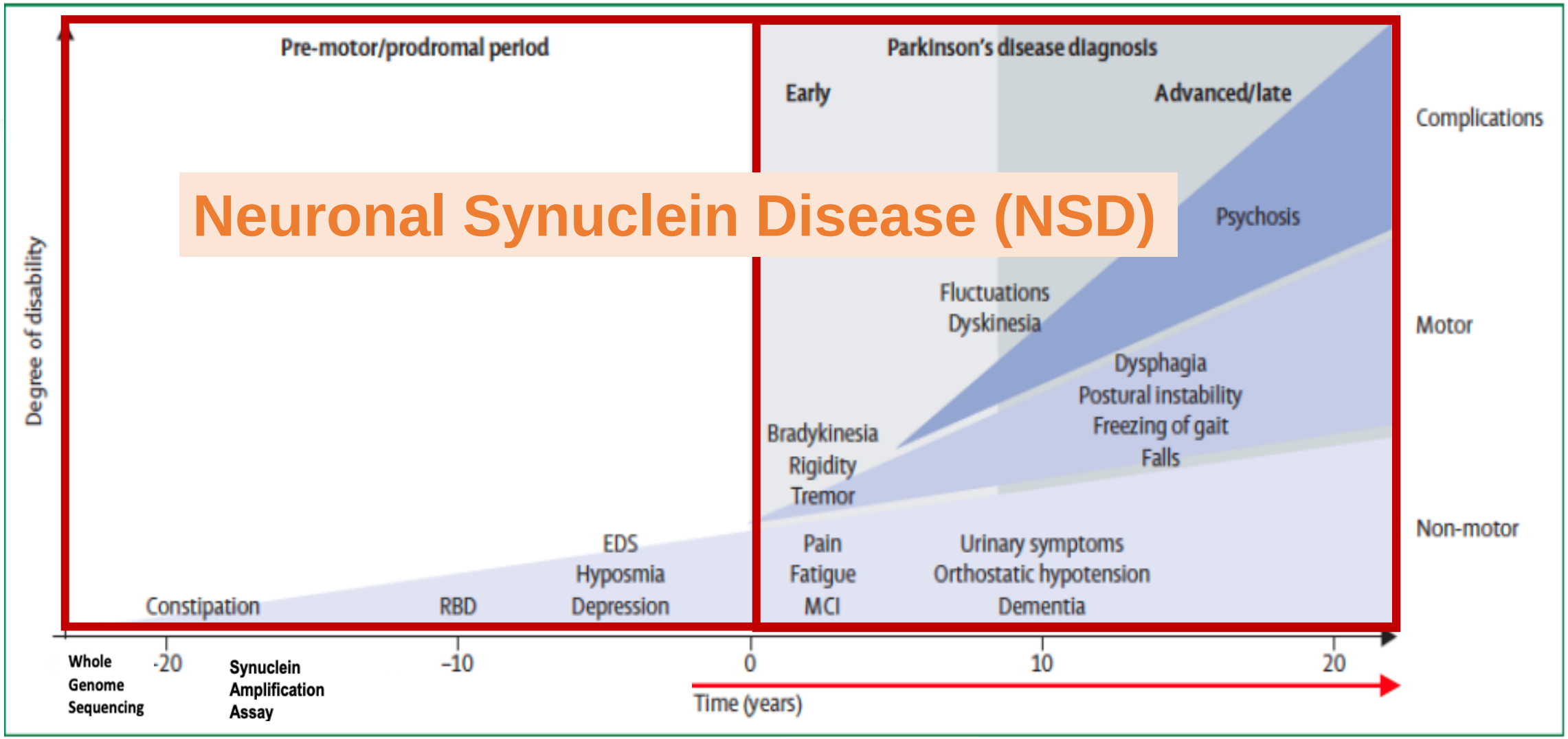
Hyposmic and RBD individuals

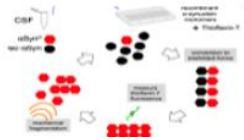


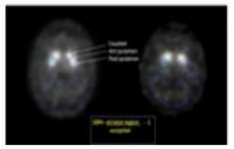
- Most hyposmics and RBD are SAA positive
  - 70% (38/54) hyposmics, 75% (58/77) RDB
- RBD - 93% (56/60) with UPSIT <= 15th %ile are SAA positive
- SAA positive appears to precede DAT deficit in RBD and hypomics prior to the onset of clinical PD

Siderowf A et al, Lancet Neurol. 2023

Biological Definition of Parkinson's







Parkinson's Progression Markers Initiative

Position Paper

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 seed 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

Conclusions

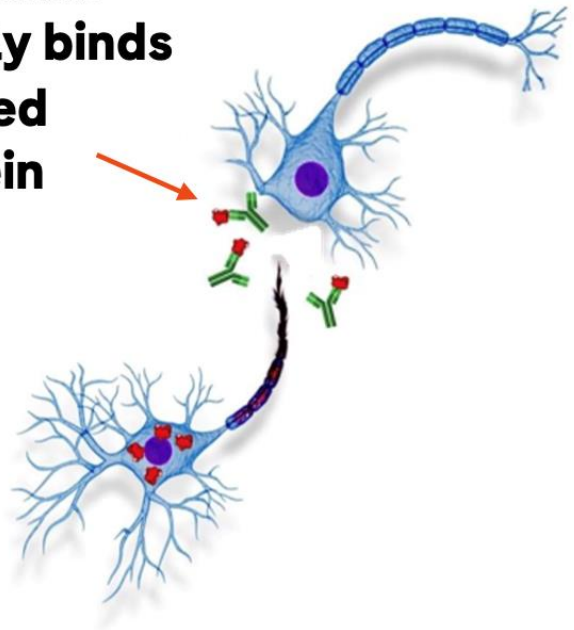
- Disease modifying drugs are currently been investigate with promising preliminary results
- Abnormal alpha-synuclein can now be detected in people with PD and individuals at risk of PD
- NSD applies to all those who have biomarker evidence of synucleinopathy, not only those with clinical symptoms

Thank you!

The PASADENA Trial

Prasinezumab's mode of action

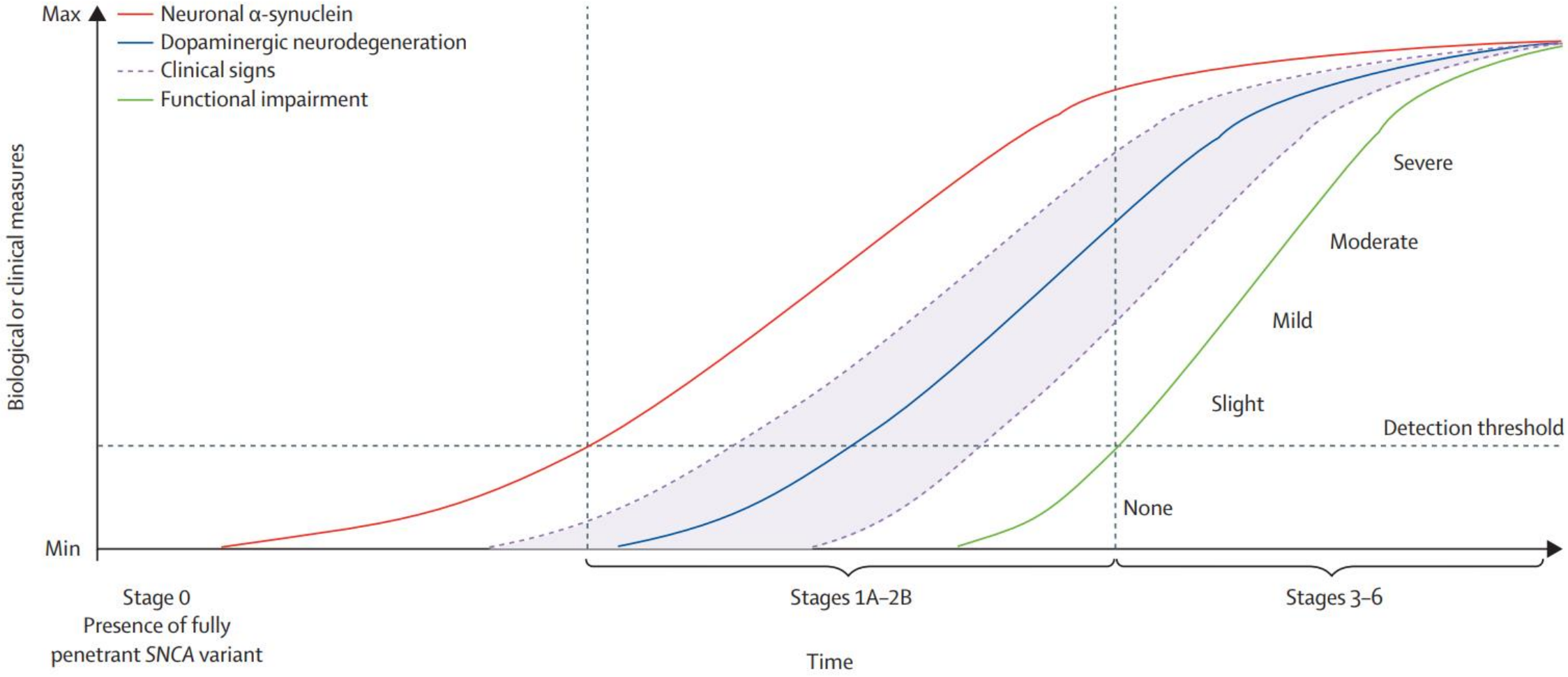
Prasinezumab selectively binds aggregated α-synuclein



Proposed effects:

- Reducing neuronal toxicity
- Preventing cell-to-cell transfer of pathogenic α-synuclein aggregates
- Slowing disease progression

Hypothetical model of dynamic biomarkers of the neuronal α-synuclein disease-integrated staging system (NSD-ISS)



Note: Shapes and slopes of the curves and their temporal relationship are qualitative and hypothetical

The proposed neuronal α-synuclein disease integrated staging system

		Neuronal α-synuclein biomarker (S)	Dopamine dysfunction biomarker (D)	Clinical signs and symptoms attributable to neuronal α-synuclein disease	Functional impairment attributable to neuronal α-synuclein disease
Genetic risk					
R^L	(G) Genetic risk variants–low age-adjusted risk	Absent	Absent	No clinical signs or symptoms	No functional impairment
R^H	(G) Genetic risk variants–high age-adjusted risk	Absent	Absent	No clinical signs or symptoms	No functional impairment
Stage definition					
0	Fully penetrant *SNCA* variant (G+)	S–	D–	No clinical signs or symptoms	No functional impairment
1A	Characteristic pathological changes, but no evidence of clinical signs or symptoms	S+	D–	No clinical signs or symptoms	No functional impairment
1B	Characteristic pathological changes plus dopaminergic dysfunction, but no evidence of clinical signs or symptoms	S+	D+	No clinical signs or symptoms	No functional impairment
2A	Characteristic pathological changes and subtle detectable clinical signs and symptoms, but no functional impairment	S+	D–	Subtle clinical signs or symptoms that can be motor or non-motor: hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety	No functional impairment
2B	Characteristic pathological changes plus dopaminergic dysfunction and subtle detectable clinical signs and symptoms, but no functional impairment	S+	D+	Subtle clinical signs or symptoms that can be motor or non-motor: hyposmia, RBD, cognitive impairment, constipation, dysautonomia, depression, and anxiety	No functional impairment
3	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing slight functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a slight degree of functional impairment	Slight: functional impairment with minimal impact on activities of daily living
4	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing mild functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a mild degree of functional impairment	Mild: functional impairment severe enough to cause some impairment in activities of faily living, but those related to personal care are intact, such as bathing, dressing, walking, using the toilet, and eating
5	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing moderate functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a moderate degree of functional impairment	Moderate: functional impairment severe enough to require assistance with activities of daily living
6	Characteristic pathological changes plus dopaminergic dysfunction and clinical signs and symptoms causing severe functional impairment	S+	D+	Motor and non-motor signs and symptoms defined by a severe degree of functional impairment	Severe: functional impairment severe enough to depend on others for activities of daily living