PPMI - A biomarker engine for therapeutic development for PD and related synucleinopathies

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Parkinson's Progression Markers Initiative

Disclosures

Consultant for the Michael J Fox Foundation, Mitro, Roche, Calico, Neuron23, Teva, Biohaven, Novartis, Koneksa, Merck, GEHC, Lilly, Inhibikase, and Prothena. Stock in Mitro, Realm, Biohaven, Inhibikase.

PPMI

Overall Goal:
Identify Biomarkers of NSD/PD progression to accelerate therapeutics to slow disability

- Biomarker signature that predict progression
- Biomarker signature that identify disease subsets

Key PPMI pillars

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

Study Synopsis

CLINIC STUDY POPULATION N=5500

- 1100 PPMI current participants
  - 700 PD
  - 100 HC
  - 300 Prodromal
- 1000 newly enrolled at clinical site
  - 900 PD
  - 100 HC
- 2000 Prodromal PD – Enrolled through staged risk (DAT deficit first) paradigm
- 1000 Prodromal PD – Enrolled through staged risk (asyn SAA positive first) paradigm
- 500 PD Enrolled through staged risk (normosmic, asyn SAA negatve
- Subjects followed for 5 to 13 years

ASSESSMENTS/ CLINICAL DATA COLLECTION

- Motor assessments
- Neuropsychiatric/ Neurobehavioral testing
- Autonomic, olfaction, sleep
- DaTSCAN. MRI – imaging sub-studies
- myPPMI
- PPMI Online
- ST DIRECT
- Digital data
- Online cognitive

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

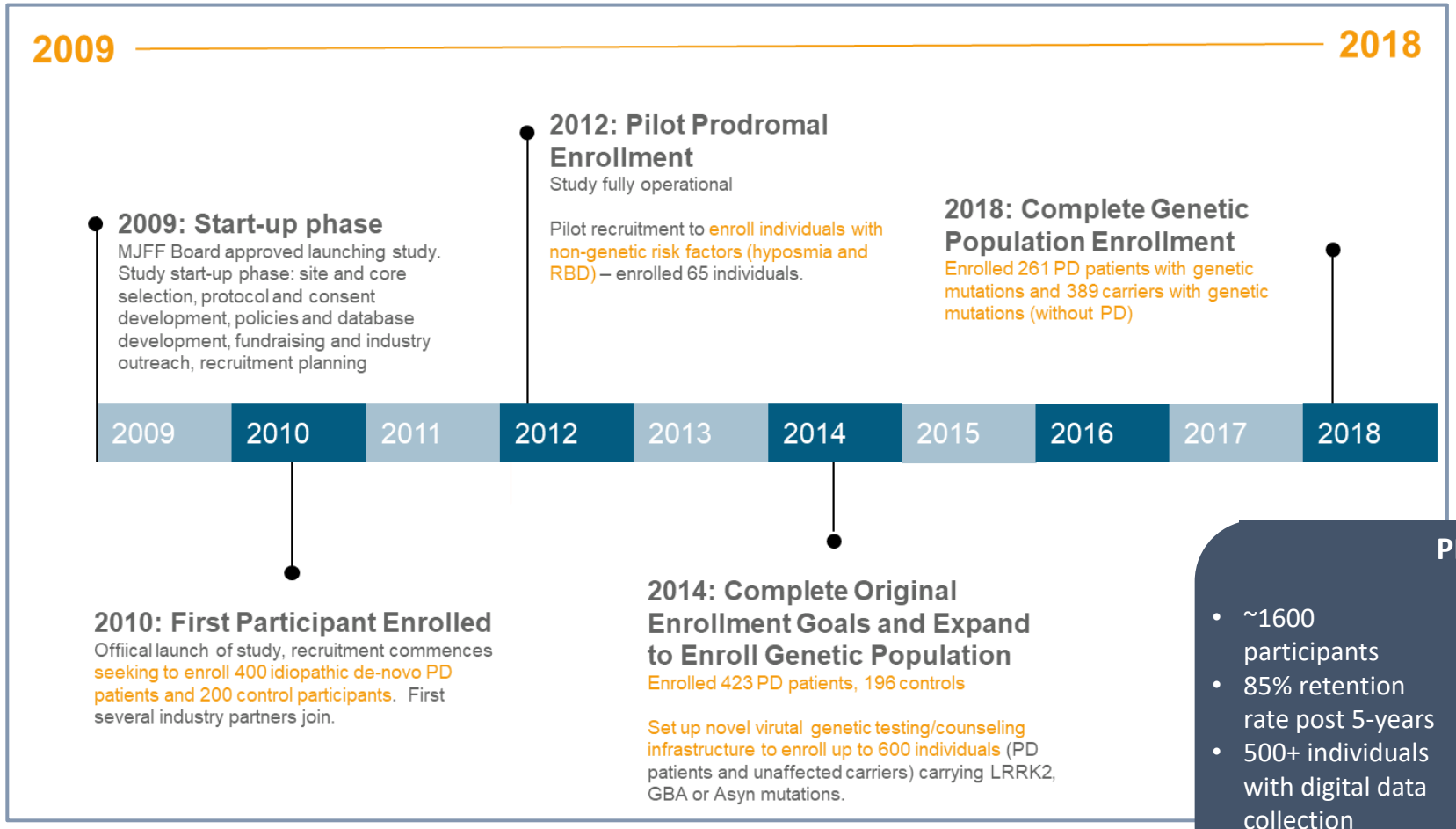
SHARED DATA & BIOSAMPLES

- Open-source data
- > 18.0 M data downloads
- Biosamples availalble; 300+ sample requests via BRC
- Ancillary study opportunity
- Subjects followed for 5 to 18 years

Developing and Maintaining a Comprehensive, Longitudinal, Biomarker Program

- **Public – Private pre-competitive partnership**
- **Commitment to long-term study support**
- **Embracing study evolution and innovation to take advantage of rapidly advancing knowledge and technology**
- **Open access to data as the study is ongoing**
- **Emphasis on collaboration between all study constituencies – academic, industry, foundation, govt, regulators, study participants**

PPMI – A biomarker and study design engine - The first decade



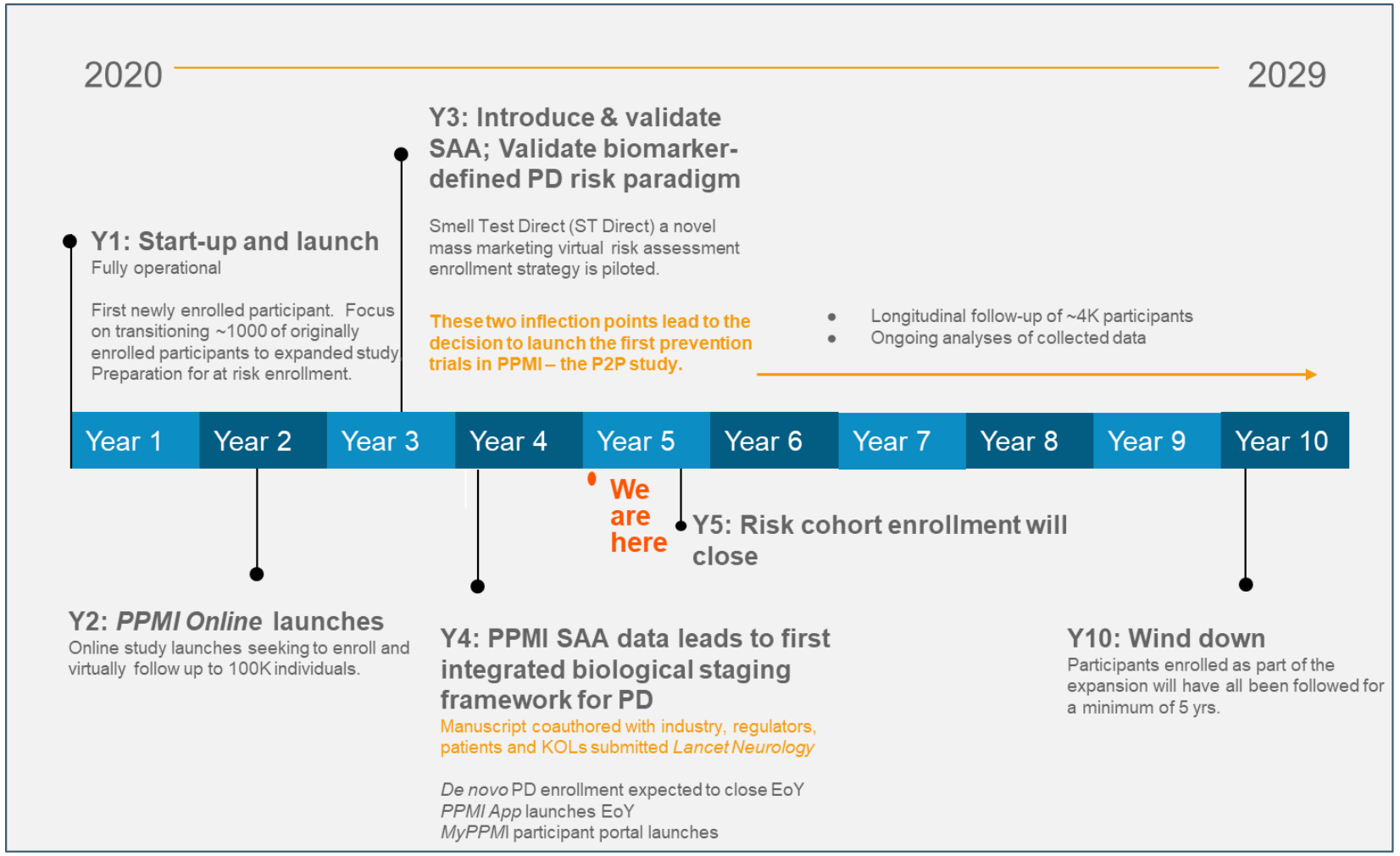
PPMI By The Numbers

- ~1600 participants
- 85% retention rate post 5-years
- 500+ individuals with digital data collection
- 6000+ LPs
- 64K+ biospecimens
- 1M+ genotypes
- 300 publications citing use of PPMI data/ samples
- 5 imaging modalities
- 6K+DaTSCANs
- 18M+ data downloads

Parkinson's Progression Markers Initiative

RBD: REM Behavior Disorder; LP: Lumbar Puncture; DaT: Dopamine Transporter Imaging

PPMI – Focus on participants prior to symptoms



PPMI 2020+

Milestones

- 4000 enrolled clinic participants
- 50K+ PPMI Online enrolled participants
- 300K+ participants have gone through ST Direct risk assessment process
- SAA paper published (Siderowf et al., *Lancet Neurology*, 2023)
- NSD-ISS published (Simuni et al., *Lancet Neurology*, 2024
- SAA screening of entire cohort (in process)
- SAA pilots in skin and blood (in process)
- P2P planning for start in 2026

Parkinson's Progression Markers Initiative

P2P: Path to Prevention; SAA: Seeding Amplification Assay; OM: Olfactory Mucosa; PoC: Proof of Concept

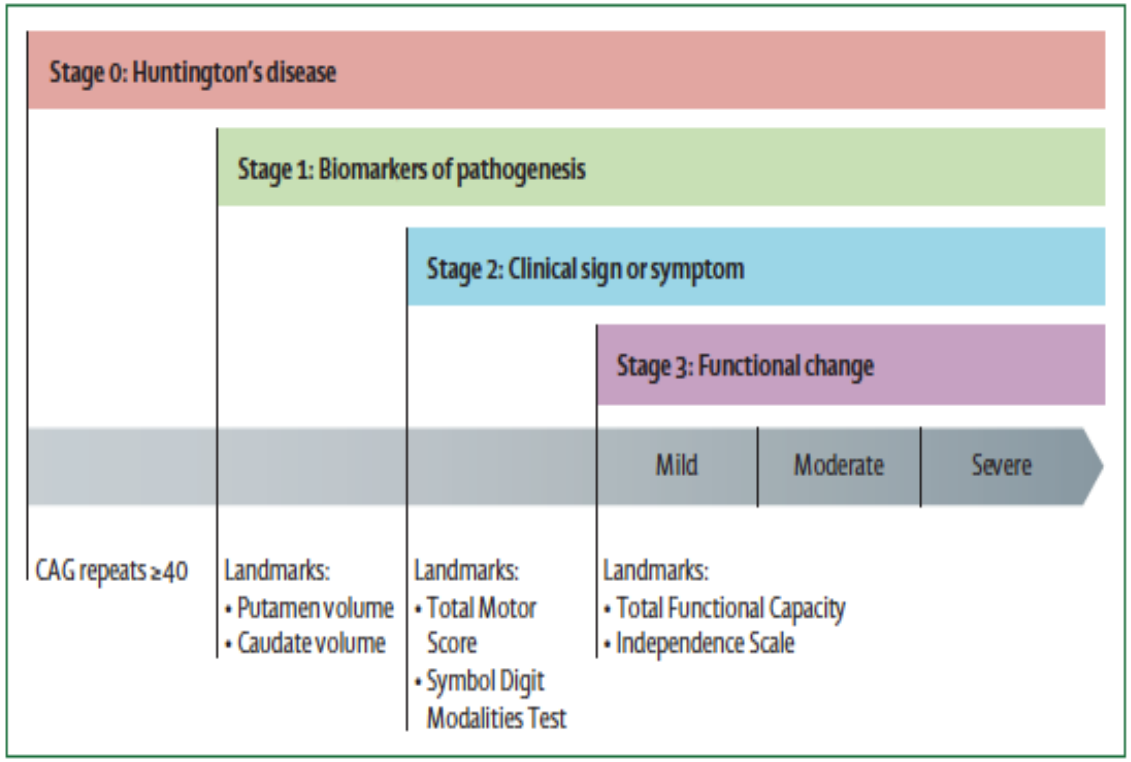
Changing the Paradigm in Parkinson Disease

- **Parkinson Disease Biologic Definition**
- **New terminology - Neuronal Synuclein Disease (NSD) - encompasses all neuronal synucleinopathies including PD and DLB**
- **Integrated Biologic and Clinical Staging for NSD (NSD-ISS)**
- **Planning Path to Prevention - a therapeutic platform study**

- **Rationale**
  - **Enable investigation of the underlying biology of NSD**
  - **Accelerate targeted therapeutics for NSD**

Biologic definition and staging

Huntington's disease



Tabrizi SJ, Schobel S, Gantman EC, et al. A biological classification of Huntington's disease: the Integrated Staging System. *Lancet Neurol* 2022; **21**(7): 632-44.

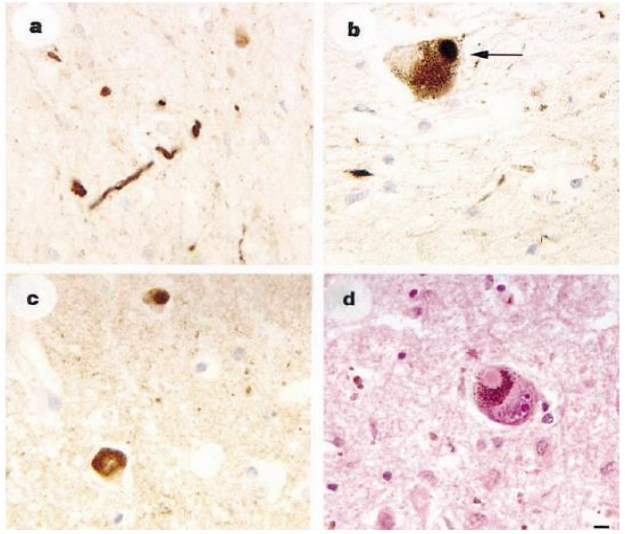
Alzheimer disease (2024)

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau 217, p-tau 181, p-tau 231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau 205, non-phosphorylated mid-region tau fragments*)	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA*	

Jack CR, Jr., Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup, Alzheimer's Dement. 2024;20:5143–5169

Synuclein Pathology → Synuclein seed amplification assay (asyn SAA)

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



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

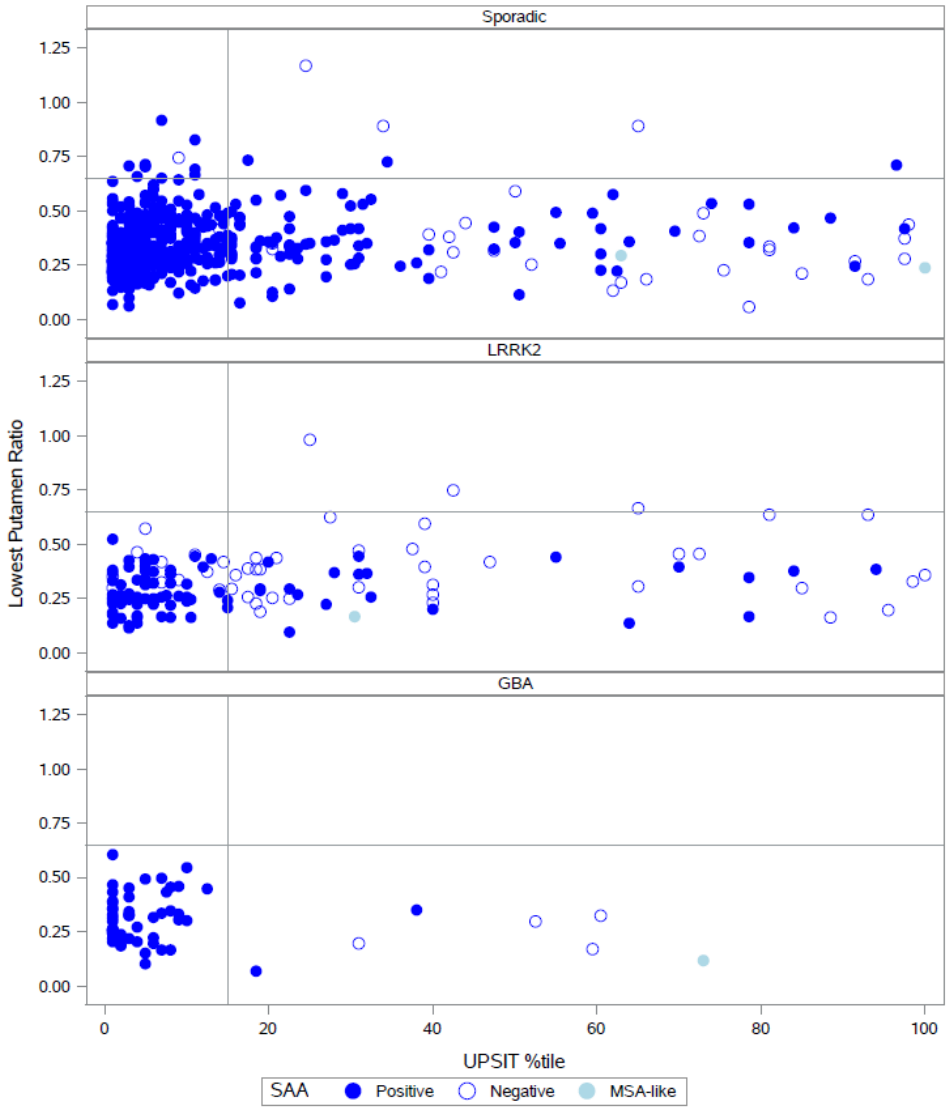
- **Asyn SAA Round Robin show agreement between different assays (Russo et al Neuropathologica 2021)**
- **Asyn SAA reflects disease pathology (Rossi et al. Acta Neuropathologica 2020)**

Accuracy of Asyn SAA for PD vs HC

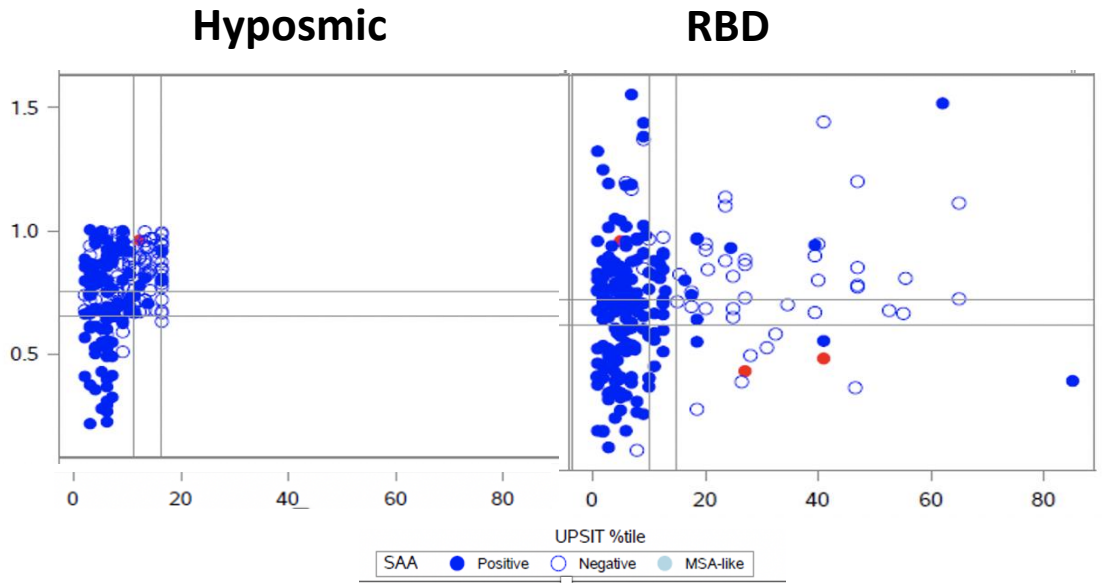
Patients (#)	CTRL (#)	Max Sens	Max Spec	Reference
PD (20)	HC (20)	95%	100%	Fairfoul et al. (2016)
PD (12)	HC (28)	92%	100%	Groveman et al. (2018)
PD (105)	HC (79)	96%	90%	Kang et al. (2019)
PD (15)	HC (11)	100%	100%	Manne et al. (2019)
PD (108)	HC (85)	97%	87%	Orru` et al. (2020)
PD (88)	HC (56)	94%	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)

Majority of people with currently defined PD or at risk for PD are asyn SAA+/DATdef/hyposmic



- Sporadic PD - Sensitivity 93%, Specificity 94%
- Sporadic, GBS, SNCA PD are >90% asyn SAA pos; LRRK2 PD has 65% asyn SAA pos/ 35% asyn SAA neg
- Prodromal with RBD are about 80% asyn SAA pos and Hyposmia are about 50% asyn SAA pos

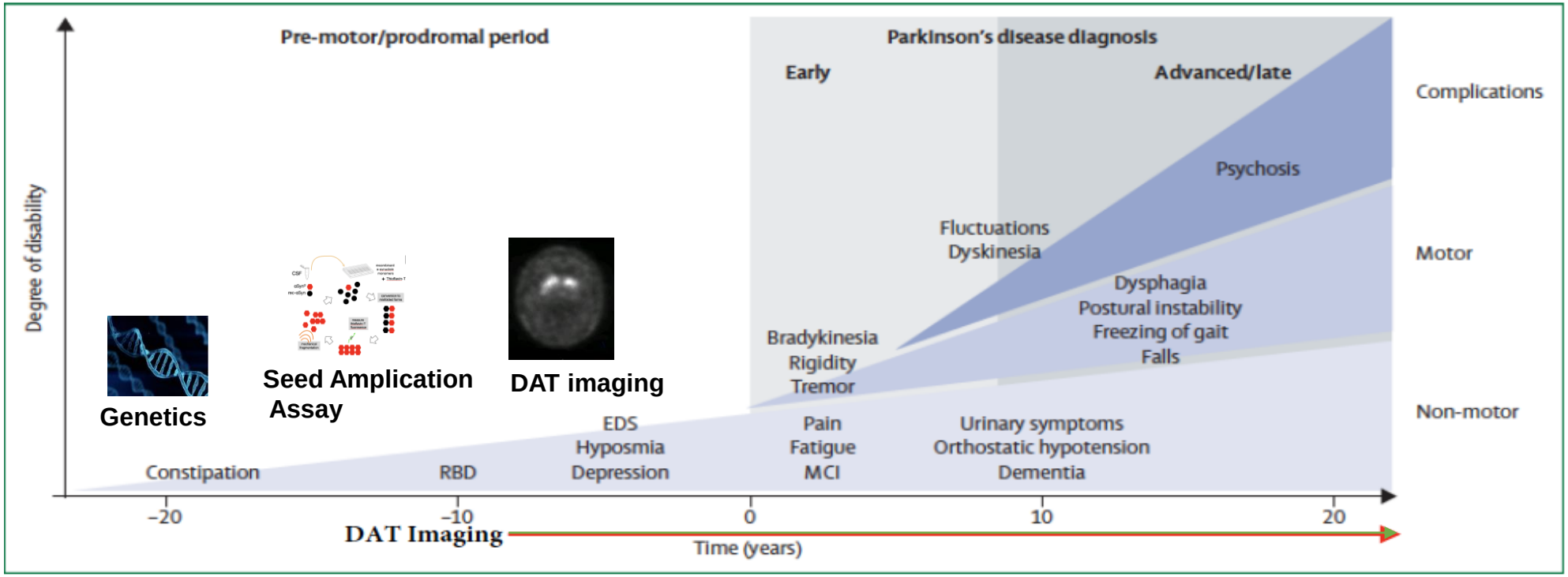


Siderowf A, Concha-Marambio L, Lafontant D-E, et al. Assessment of heterogeneity and disease onset in the Parkinson's Progression Markers Initiative (PPMI) cohort using the α-synuclein seed amplification assay: a cross-sectional study. *Lancet Neurol* 2023; **22**(5): 407-17.

A paradigm shift - Biologic definition for PD

Clinical Outcomes

Biologic Outcomes



- **Synuclein pathology - SAA**
- **DA Dysfunction - DAT imaging**

2023 PD Staging Roundtable

Aligning on an integrated biological and clinical staging system to advance therapeutic development for Parkinson's

CPP PARKINSON'S CONSORTIUM

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Parkinson Canada

PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

LBDA LEWY BODY DEMENTIA ASSOCIATION

SHAKE IT UP AUSTRALIA FOUNDATION

CURE PARKINSON'S

NSD-ISS (Simplified)

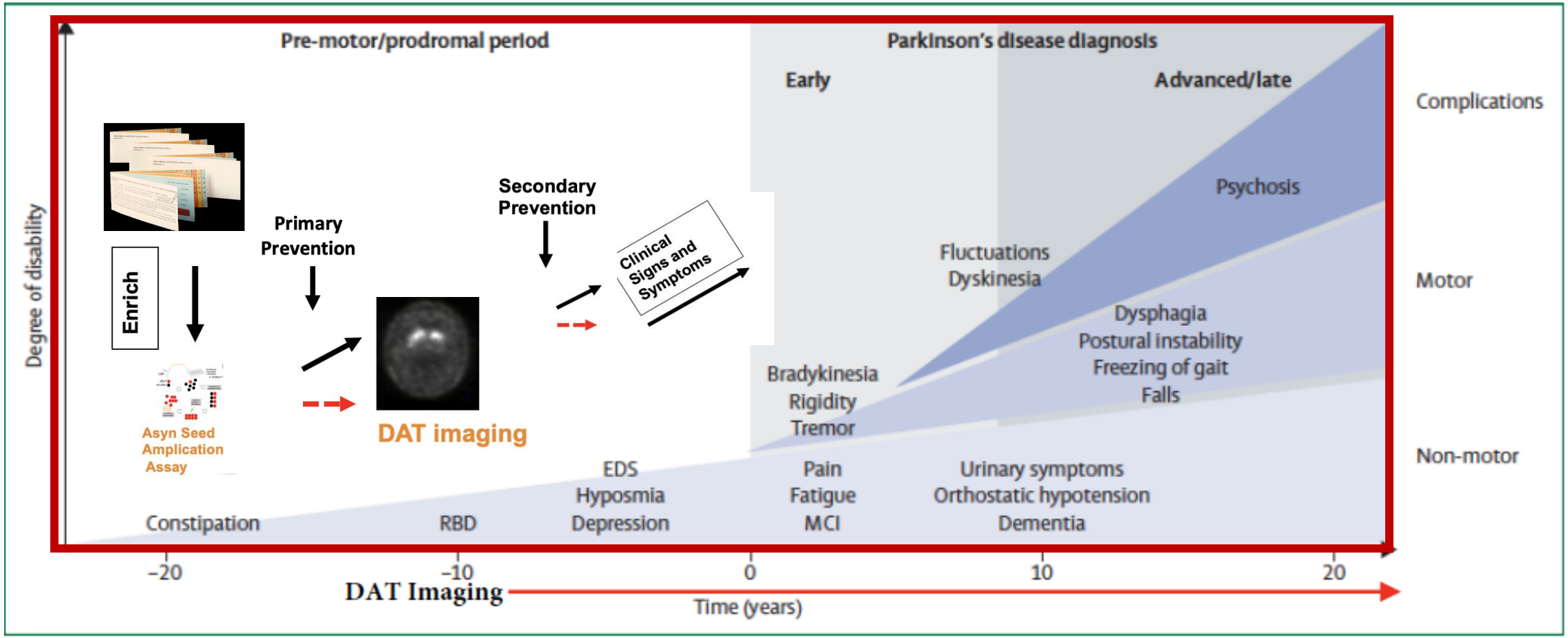
		A-Syn (S)	DA Dysfunction (D)	Clinical Signs, Symptoms, Functional Impairment	
				Clinical Signs and Symptoms	Functional Impairment
	Genetic risk (L vs H)				
R^L	G+ low risk	-	-	-	-
R^H	G + high risk	-	-	-	-
NSD stage	NSD				
0	G+ (SNCA)	-	-	-	-
1A/B		+	-/+	-	-
2A/B		+	-/+	+	-
3		+	+	+	SLIGHT
4		+	+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

NSD definition and NSD-ISS – Current Goals

- Accelerating Therapeutics -
  - Create a standard lexicon for study design
  - Reducing heterogeneity in the study sample
  - Enable Treatment prior to Symptoms

- Creating a framework for investigating the biology and for biomarker definition throughout disease course

Investigating the start of neurodegeneration: a paradigm shift to NSD (Parkinson, Dementia with LEWY Bodies)



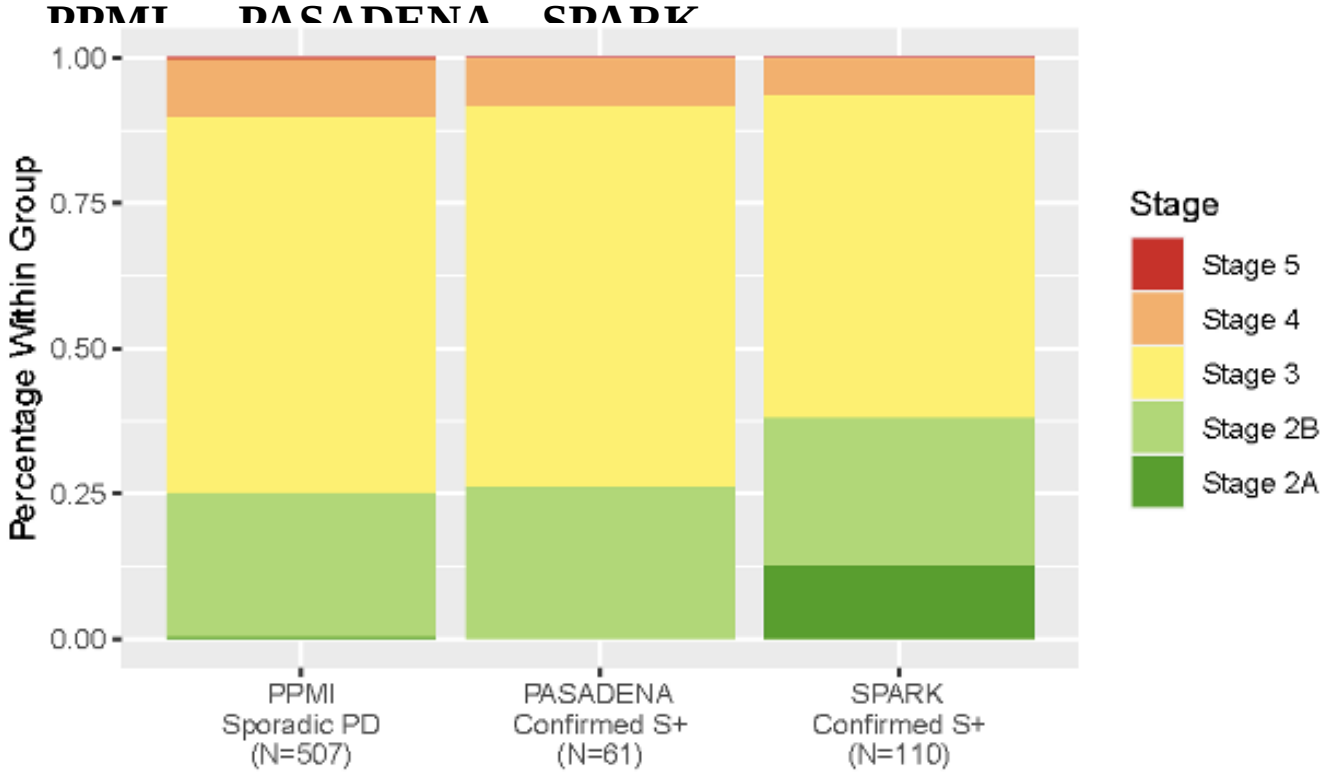
3-5yr	Immune Function	Mitochondrial Function	Lysosomal Markers	Synaptic Density Markers	Protein Aggregation Markers

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

RBD: REM-sleep Behavior Disorder; EDS: Excessive Daytime Sleepiness; MCI: Mild Cognitive Impairment

Baseline NSD-ISS Stage in PPMI, Pasadena, and Spark

(based on S+/D+/Functional motor, cognitive, non-motor)



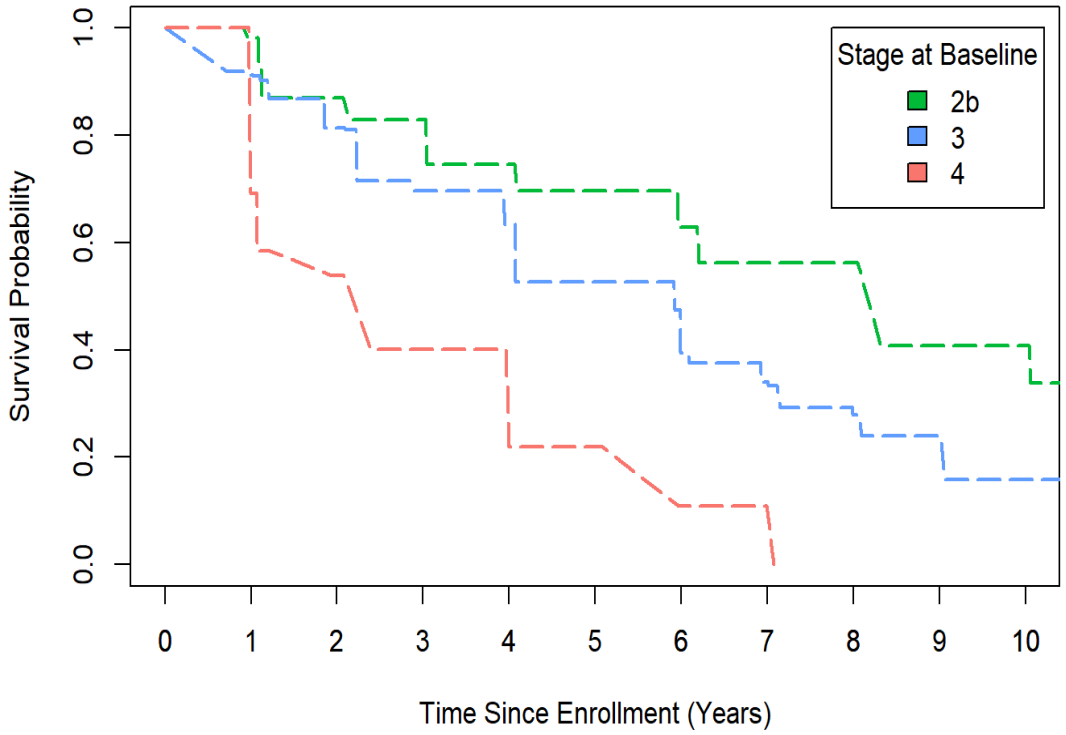
Similar distribution - approx 65% stage 3, 25% Stage 2, 10 % stage 4

Demonstrate - Face validity

Heterogeneity of early PD

Time to Severe Progression Milestone Depends on NSD Stage

PPMI sporadic PD cohort



Stage	N	Median survival time (95% CI)
2B	123	8.5 (7.0, 9.3)
3	323	5.6 (4.8, 6.1)
4	48	2.4 (1.1, 3.7)

Median time to developing a new milestone ranged from 2.4 vs 8.3 years.

Brumm, Siderowf, Simuni et al, Parkinson's Progression Markers Initiative:
A Milestone-Based Strategy to MonitorParkinson's Disease Progression, JPD, 2023

What's next Quantitative Biomarkers

- Synuclein – asyn SAA, IHC, Is this the year of Syn imaging?
  - Asyn SAA screening using CSF and Skin
- Co-pathology – pTau, Amyloid, possible NFL, GFAP
- Imaging – Synuclein, Dopamine tracers, Inflammation,
- Digital – Gait +
- Omics - Multiplex strategy to identify other biologic targets
- Genetics – Whole genome Sequencing, RNA fragments

myPPMI - PPMI Participant Portal

What is myPPMI

An online platform available widely to enable participants to both provide research data and receive research and educational information

Online consenting is managed within myPPMI

Opportunities to request and/or provide specific data can be personalized based on the data already received

PPMI participant and participants from other research project can join and maintain data independently

Opportunities in myPPMI – current and in development

<u>PPMI assessments</u>
Cognitive testing

Roche Digital

PPMI Online

Targeted enrollment - DEI

Biomarker acquisition

<u>Info to Participants</u>
Return of research results

Study outcomes

Educational information

Parkinson's Progression Markers Initiative

WHAT'S NEXT – DATA

- Biology is an anchor
- Focus on both clinical and remote data acquisition
- Understand the disease – Target biologically defined disease subsets
- Treatment with rational therapy – Prior to symptom onset