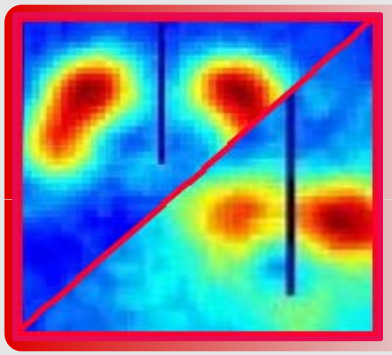

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Early Detection of Parkinson's Disease

will begin shortly…

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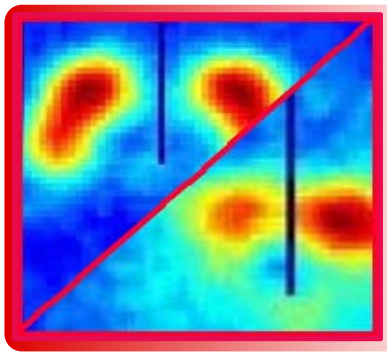

Science Webinar Series

Early Detection of Parkinson's Disease

The Challenges and Potential of New Biomarkers

April 27, 2011

Brought to you by the *Science*/AAAS Business Office

Participating Experts:

Andrew Siderowf, M.D., MSCE
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Philadelphia, PA

Michael G. Schlossmacher, M.D., FRCPC
University of Ottawa
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Norbert Schuff, Ph.D.
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Moderator: Todd Sherer, Ph.D., The Michael J. Fox Foundation\
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In association with:

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Parkinson's disease: overview and current treatments

- Progressive, neurodegenerative disorder marked predominantly by motor symptoms; non-motor symptoms are also present

- Characterized by selective loss of nigrostriatal dopaminergic neurons and presence of alpha-synuclein positive aggregates (Lewy Bodies)

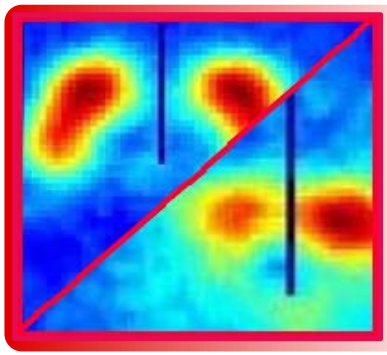
- Current therapies, based on dopamine replacement, treat some motor symptoms, but lose effectiveness over time and are marked by side effects

Biomarkers are critical for developing disease modifying therapies

- Disease modifying therapeutics that target the underlying disease process remain a major unmet need
- Current clinical trial design requires large sample size, long duration
- Trials rely on subjective, clinical outcomes that are influenced by medications
- PD biomarkers would accelerate PD therapeutic development
  - Identify patients at earliest stages of disease
  - Improve patient selection for clinical trials, example DATscan
  - Assess efficacy of new therapies
  - Monitor disease progression

Today's webinar

- Studying individuals at risk for developing PD – Andrew Siderowf
- Overview of promising biological markers of PD – Michael Schlossmacher
- Overview of new neuroimaging methods as PD biomarkers – Norbert Schuff
- Addressing the challenges in developing PD biomarkers – the PPMI study – Ken Marek



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Prevention is the ultimate therapeutic goal in PD

PARS study objectives

- To determine the feasibility of screening for Parkinson's disease using a combination
  - 1st: olfactory testing
  - 2nd: DAT imaging
- To assess clinical and biological features pre-motor PD (defined based on biomarker profile)
- To develop a pre-motor cohort that would be eligible for a preventive interventions

Screening for PD requires large numbers of potential subjects

Phase I

Eligible subjects mailed

1. UPSIT
2. Questionnaires
   - BM freq
   - RBD history
   - exposure history
   - motor complaints

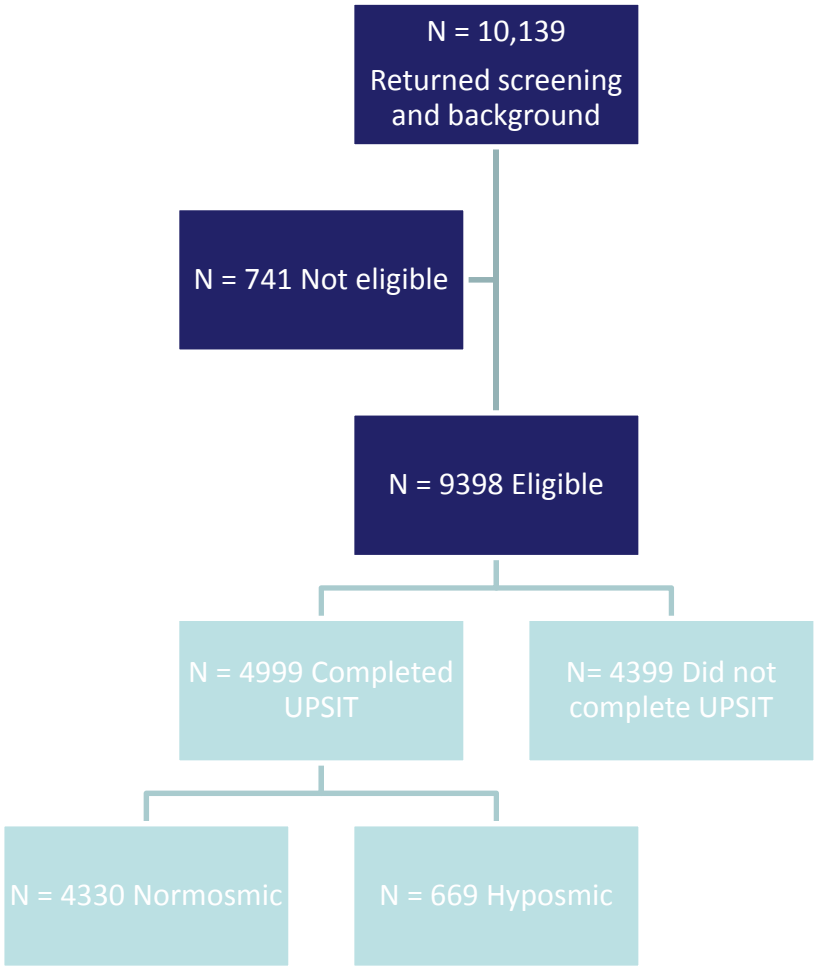
Phase II

Clinic visit

1. UPDRS
2. Diagnostic form
3. SCOPA-aut
4. Non-motor review
5. Neuropsych assess

Imaging Visit

1. DAT Imaging
2. HRV assessment
3. Blood (genetics, RNA profiling, urate, & other "omics")
4. Video UPDRS exam

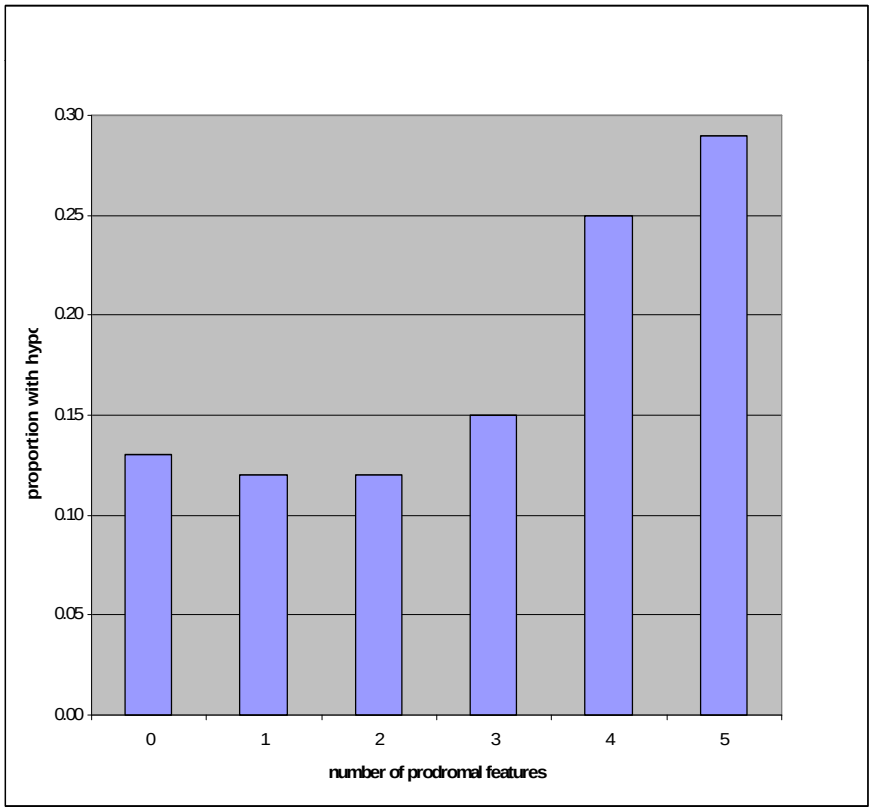


A large number of subjects were initially screened with simple, relatively inexpensive tests

Identifying and targeting highest risk cases improves efficiency

Prodromal PD features cluster in hyposmic individuals, n = 4999

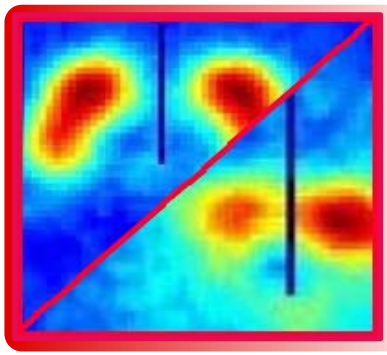
	OR	CI
Constipation	1.37	1.11, 1.68
Depression	1.93	1.55, 2.41
Anxiety	1.38	1.14, 1.67
Motor complaint	1.66	1.36, 2.02
REM sleep behavior	1.62	1.21, 2.15



Two-staged process is reasonably accurate and reduces costs

- Hyposmics have increased risk of abnormal DAT imaging
- Normosmics have very low risk of abnormal DAT imaging
- Two staged process reduces # of imaging studies by 80-90%

	Normosmics	**Hyposmics**	**p-value**
Age expected uptake in lowest putamen	**N = 100**	**N = 203**	
No DAT deficit ≥80%	92 (92%)	146 (72%)	
65 – 80%	7 (7%)	34 (17%)	
<65%	1 (1%)	23 (11%)	<0.0001
<80%	8 (8%)	57 (28%)	<0.0001



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Example of patient enrollment in past PD trials without biomarkers

>1,600 patients screened with subjective rating scales

Selected phenotype: 'Typical PD' patients with AOO >50 yrs. Enrollment number for treatment arm of study, n = 800

Subjects without evidence of dopaminergic degeneration: 10 % (n = 80)

+

Multiple system atrophy (type *P*) and other atypical cases of parkinsonism: 5 % (n = 40)

+

Inclusion-positive and synuclein-associated typical PD patients: >75 % (n = 600)

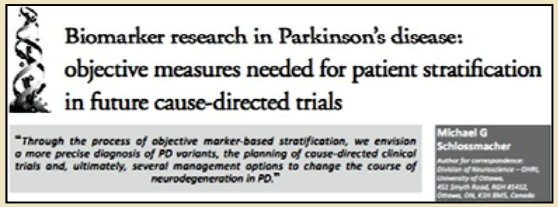
+

Inclusion-negative and NON-synuclein-associated cases of PD: <10 % (n = 80)

No stratification. 800 pts in treatment arm. If the drug targets synuclein metabolism: no monitoring of target engagement in vivo

At a response rate of 20 % in synuclein-related PD cases (n=120 / 600)

P value not significant between the two groups: only 15% (120 / 800) of patients show response **= TRIAL FAILURE**



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Marker candidates awaiting validation and / or definition: genetically linked proteins in biological fluids, e.g., α-synuclein (total, oligomeric, modified variants); DJ-1; sequence variants, e.g., *GBA1*, *SNCA, LRRK2*; urate in CSF and plasma (? progression); metabolome markers in plasma; transcriptome changes in blood cells (e.g., *ST13* mRNA levels); and exploration of dementia-associated tau and amyloid β protein species as markers of cognitive changes in PD subjects.

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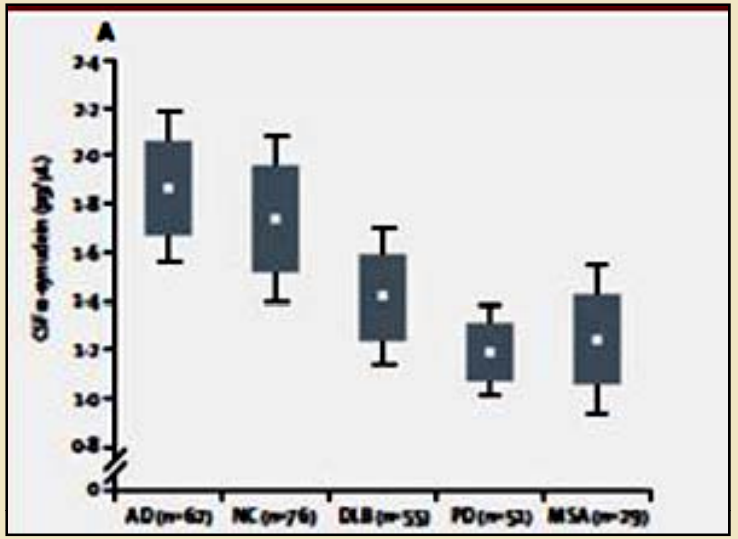
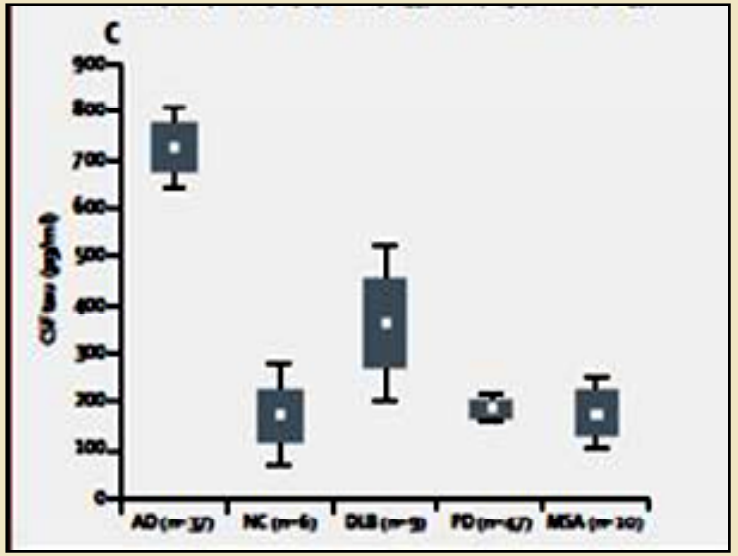
Total alpha-synuclein levels in CSF



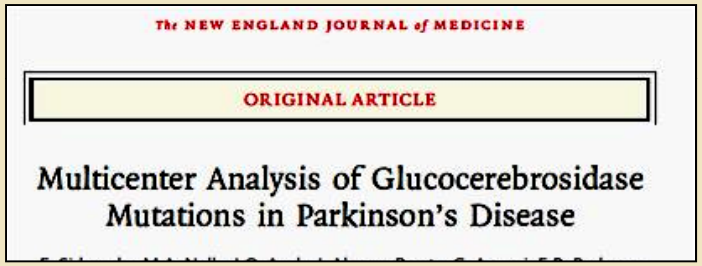
Total tau concentration in CSF



e.g., Hong et al., 2010; Tokuda et al., 2010; Mollenhauer et al.,2011

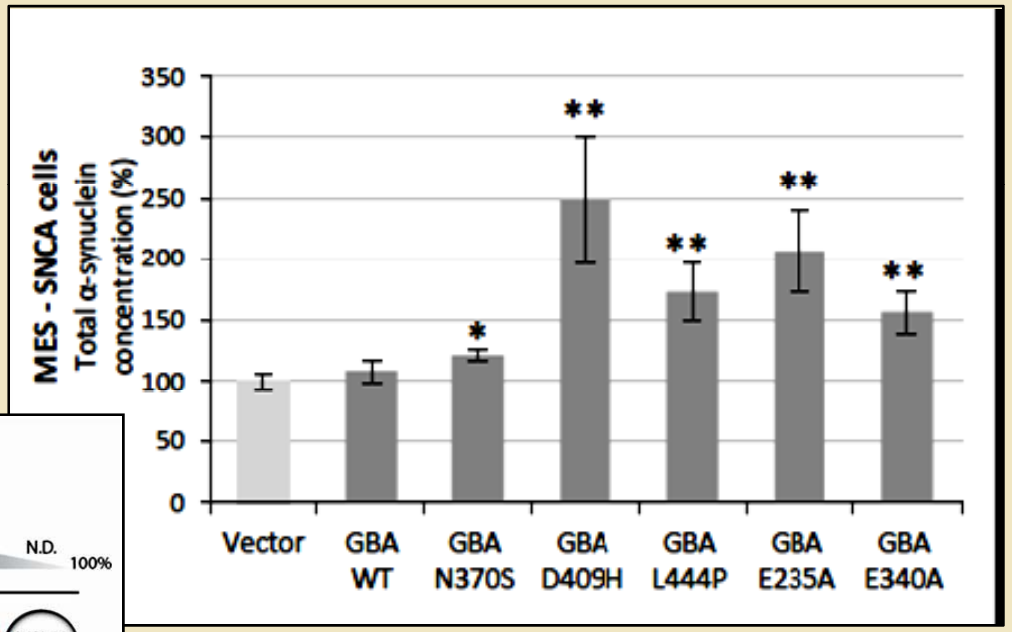
8-20% of typical PD patients carry a mutation in one ***GBA1*** allele; all these subjects feature α-synuclein-positive Lewy body pathology at autopsy. Mutant GBA proteins appear to elevate neural α-synuclein. Thus, *GBA1* carrier status in PD (and DLB) can be considered a reliable surrogate for the process of synucleinopathy in the brain.

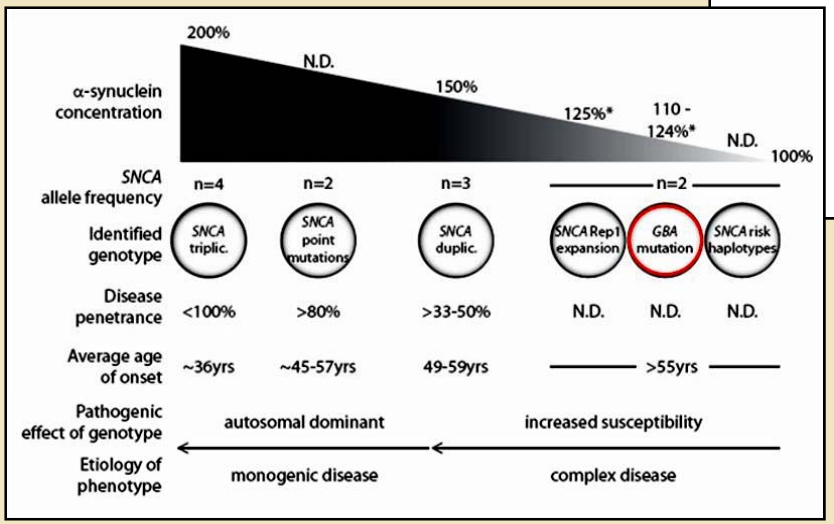
Eblan N et al., NEJM 2005
Goker-Alpan O et al., Neurology 2006
Neumann J et al., Brain 2009


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease

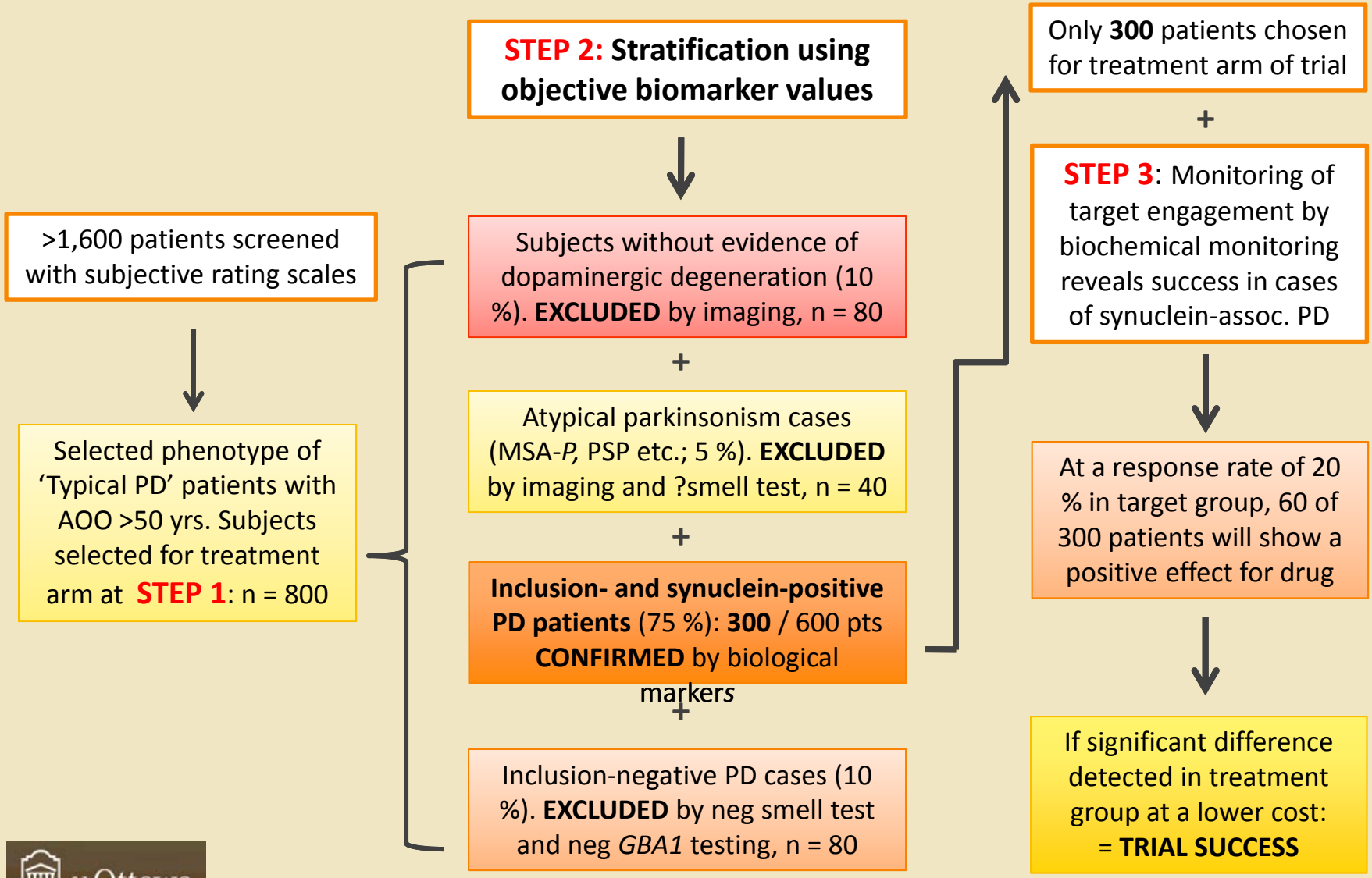




ANNALS of Neurology
THE OFFICIAL JOURNAL OF THE AMERICAN NEUROLOGICAL ASSOCIATION AND THE CHILD NEUROLOGY SOCIETY

Cullen V et al., Ann Neurol 2011

Scenario for a biomarker-supported clinical trial of PD in the future



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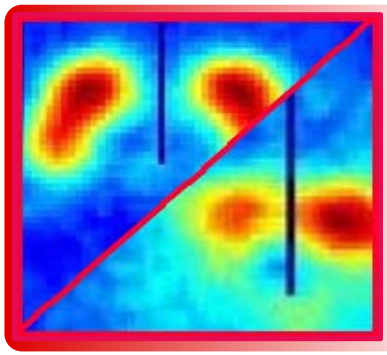
Klein C et al., Arch Neurol 2011



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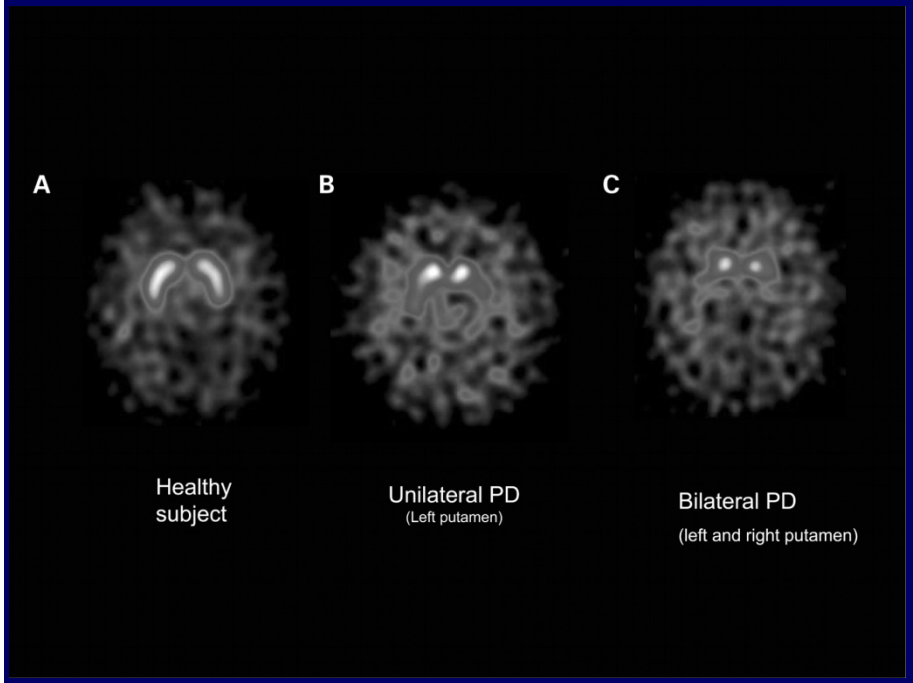
Approaches In Neuroimaging

- Functional Changes
  - Receptor availability for neurotransmitters (SPECT, PET)
  - Cerebral metabolism and blood flow (PET, SPECT, MRI)
  - Brain networks (functional MRI)
- Morphological Changes
  - Regional brain volumes (MRI)
  - Brain iron content (MRI, Transcranial sonography)
  - Tissue microstructure (DTI)
  - Brain connectivity (DTI-tractography)
  - β-amyloid deposition (PET)

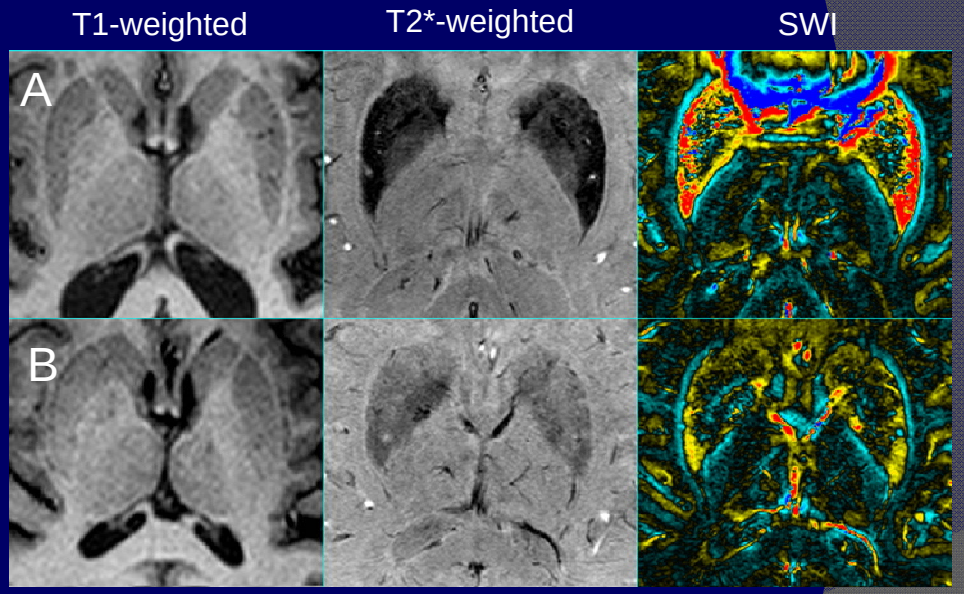
Some Existing Imaging Methods

Dopamine Transporter SPECT



With permission: BMJ Publishing Group Ltd
Kägi G et al. J Neurol Neurosurg Psychiatry 2010;81:5-12

MRI

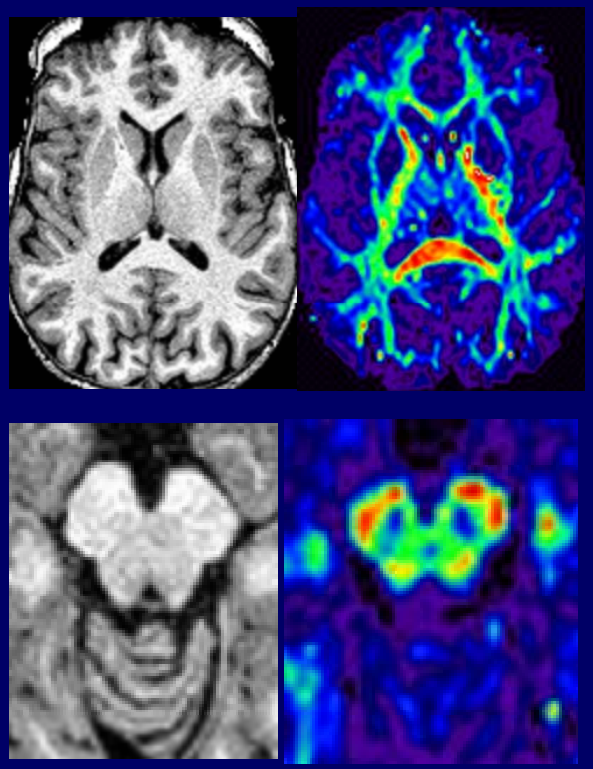


A: Patient with multiple system atrophy
B: Patient with Parkinson's disease

SWI = susceptibility weighted imaging ; sensitive to brain iron content

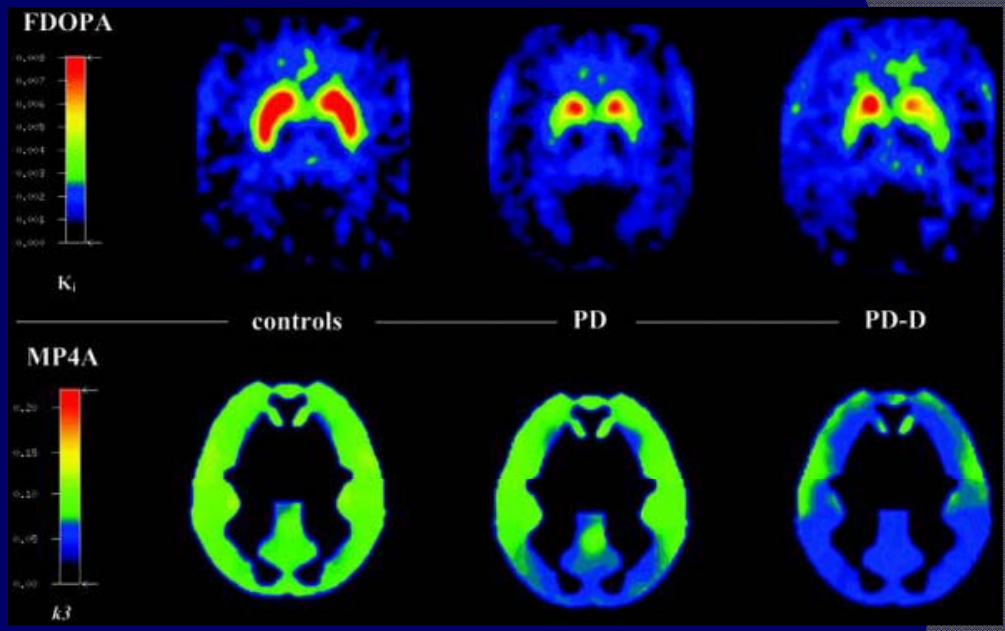
Some Emerging Imaging Methods

MRI DTI*



*maps of fractional anisotropy (FA), an index of microstructural integrity. Smaller FA of the substantia nigra completely separated PD patients from controls (Vaillancourt et al. Neurology, 2009, 21;72(16):1378-84

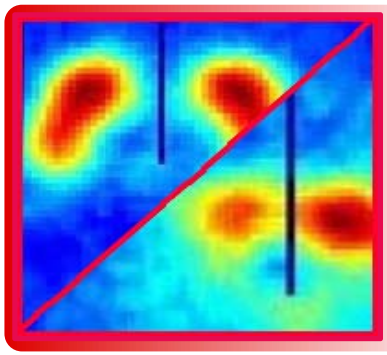
PET: Dopaminergic and glutaminergic pathways



Averaged FDOPA (first row) and MP4A k3 images (second row) of the study subgroups. Note the severe global k3 reduction in Parkinson disease dementia, whereas only a slight parieto-occipital k3 decrease is obvious in Parkinson disease. Hilker, R; et al, Neurology. 65(11):1716-1722, December 13, 2005.

Key Points: Neuroimaging Markers For PD

- Existing methods
  - DAT SPECT and PET are reasonably effective in identifying dopamine deficits but not reliable for a differentiation of idiopathic PD from atypical PD.
  - MRI mapping of structural changes in PD are valuable but a large overlap with normal values remains
- Emerging methods
  - New PET ligands will be useful to study the effect of PD on other neurotransmitters
  - β-amyloid PET will be useful to study the role of amyloid in PD
  - DTI has potential as an early marker for PD and to study the impact of PD on white matter
  - Resting state functional MRI will be useful to study the consequences of dopamine depletion on brain functional connectivity



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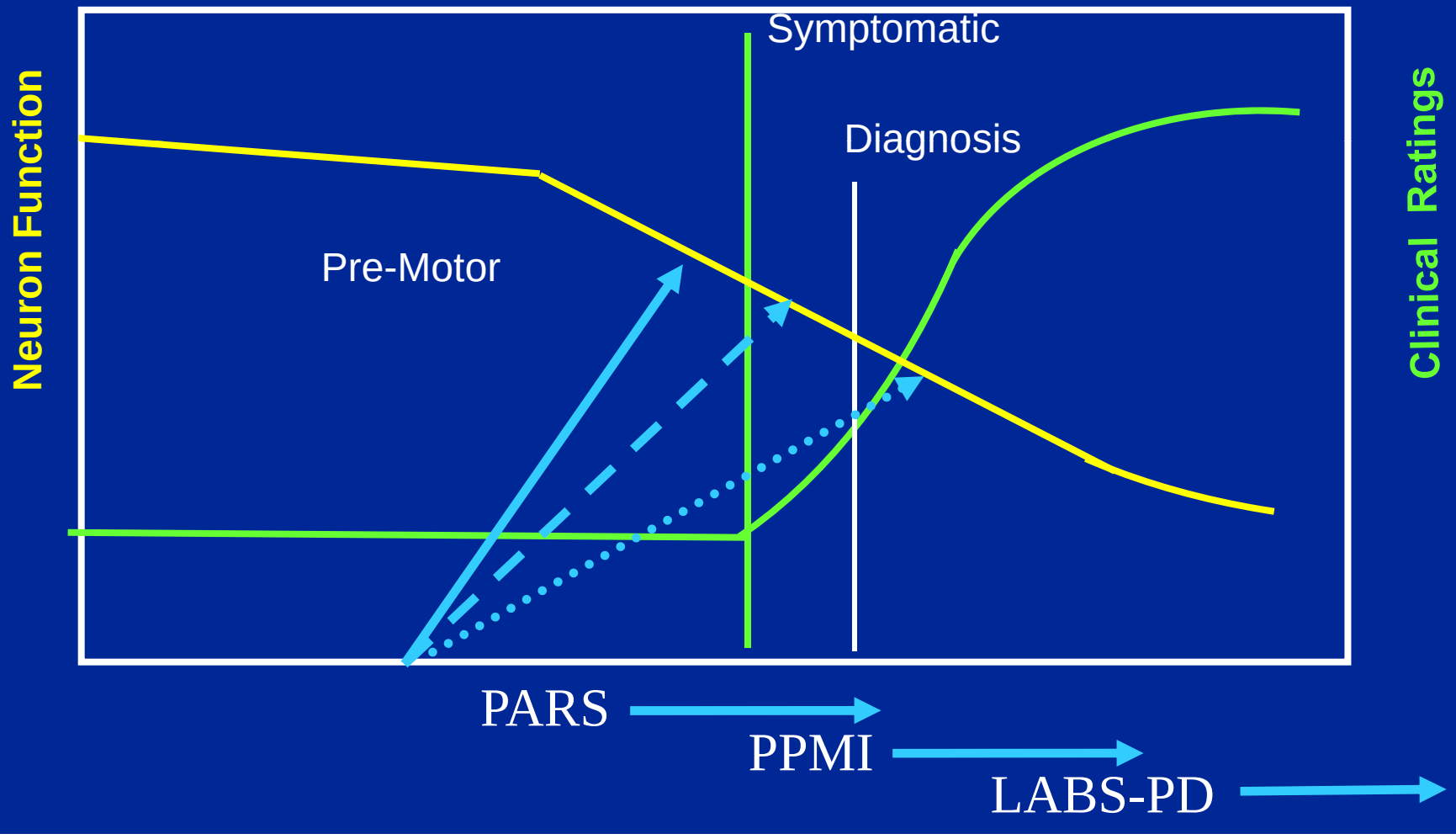
Utility of biomarkers in clinical trials

- Disease mechanism
- Drug mechanism
- Dosage determination
- Study eligibility-early/accurate diagnosis
- Pre-motor diagnosis
- Monitoring disease progression
- Stratification into PD sub-types
- Correlation with clinical signals

- Disease modifying PD therapeutics remain a major unmet need
- Biomarkers will potentially shorten study duration, reduce study sample size, limit study costs.

Biomarkers likely have a temporal pattern
Biomarkers can be used to define and inform at different disease stages



Developing the Parkinson's Progression Markers Initiative

PPMI- A biomarker focused Parkinson disease progression study – comprehensive, longitudinal, cooperative – Public private partnership - MJ Fox, Industry, Government, Academic, Patients and Families

Requirements for Biomarker Infrastructure

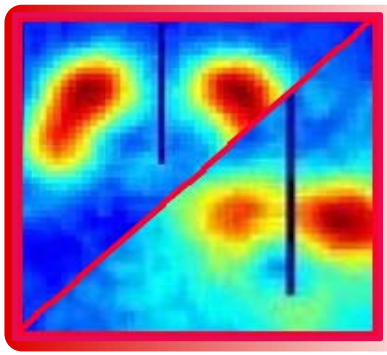
Specific Data Set	• 400 early stage PD and 200 controls • Clinical (motor/non-motor) and imaging data • Corresponding biologic samples (DNA, blood, CSF)
Standardization	• Uniform acquisition of data and samples • Uniform storage of data and samples • Strict quality control/quality assurance
Access/Sharing www.ppmi-info.org	• Data available to research community → data mining, hypothesis generation & testing • Samples available for studies

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

PPMI Study Details: Synopsis

Study population	▪ 400 *de novo* PD subjects (newly diagnosed and unmedicated) ▪ 200 age- and gender-matched healthy controls ▪ Subjects will be followed for a minimum of 3 years and a maximum of 5 years
Assessments/ Clinical data collection	▪ Motor assessments ▪ Neuropsychiatric/cognitive testing ▪ Olfaction ▪ DaTSCAN imaging, MRI
Biologic collection/	▪ DNA collected at screening ▪ Serum and plasma collected at each visit; urine collected annually ▪ CSF collected at baseline, 6mo 12 mo and then annually ▪ Samples aliquotted and stored in central biorepository
Initial Verification studies	▪ Lead biologic candidates to be tested: • Alpha-synuclein (CSF) • DJ-1 (CSF and blood) • Urate (blood) • Abeta 1-42 (CSF) • Total tau, Phospho-tau (p-181) (CSF)
PD treatment	▪ *De novo* for ~6 months ▪ Can participate in other clinical trials (including interventional trials) after 12 months



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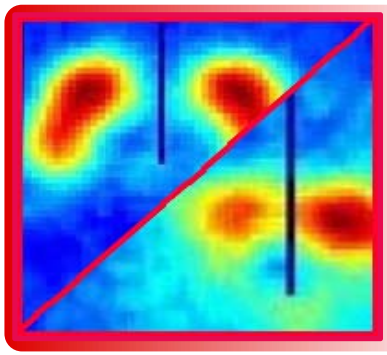

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