Unmet Needs for Parkinson's Disease Therapeutics

Coalition Against Major Diseases & FDA Workshop
October 20, 2014

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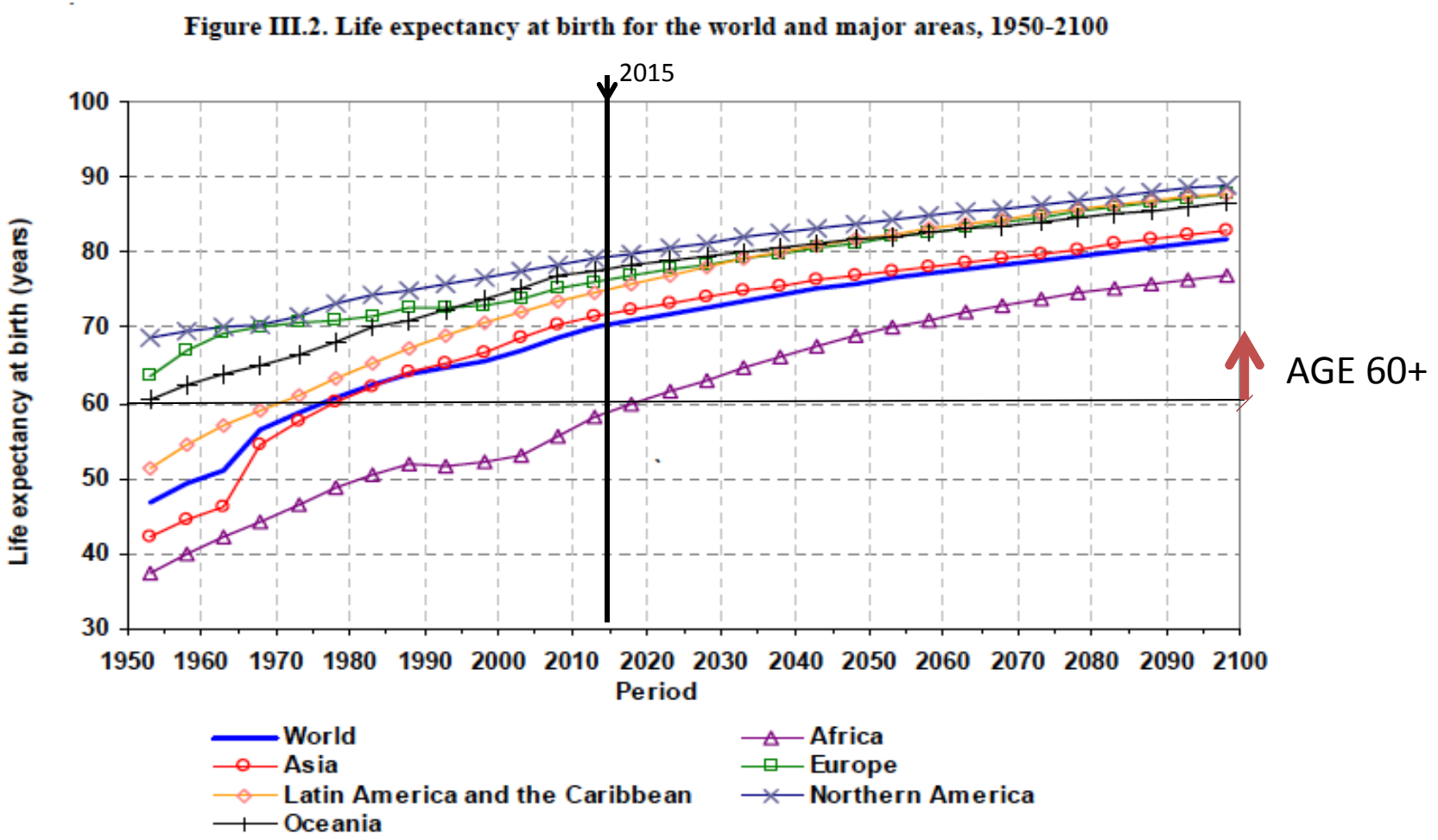
Topics

- **Why Parkinson's Disease therapeutics matters**
- **Therapeutic Gaps**
- **Bridging the Gaps**
  - **New approaches**
  - **Continuing challenges**

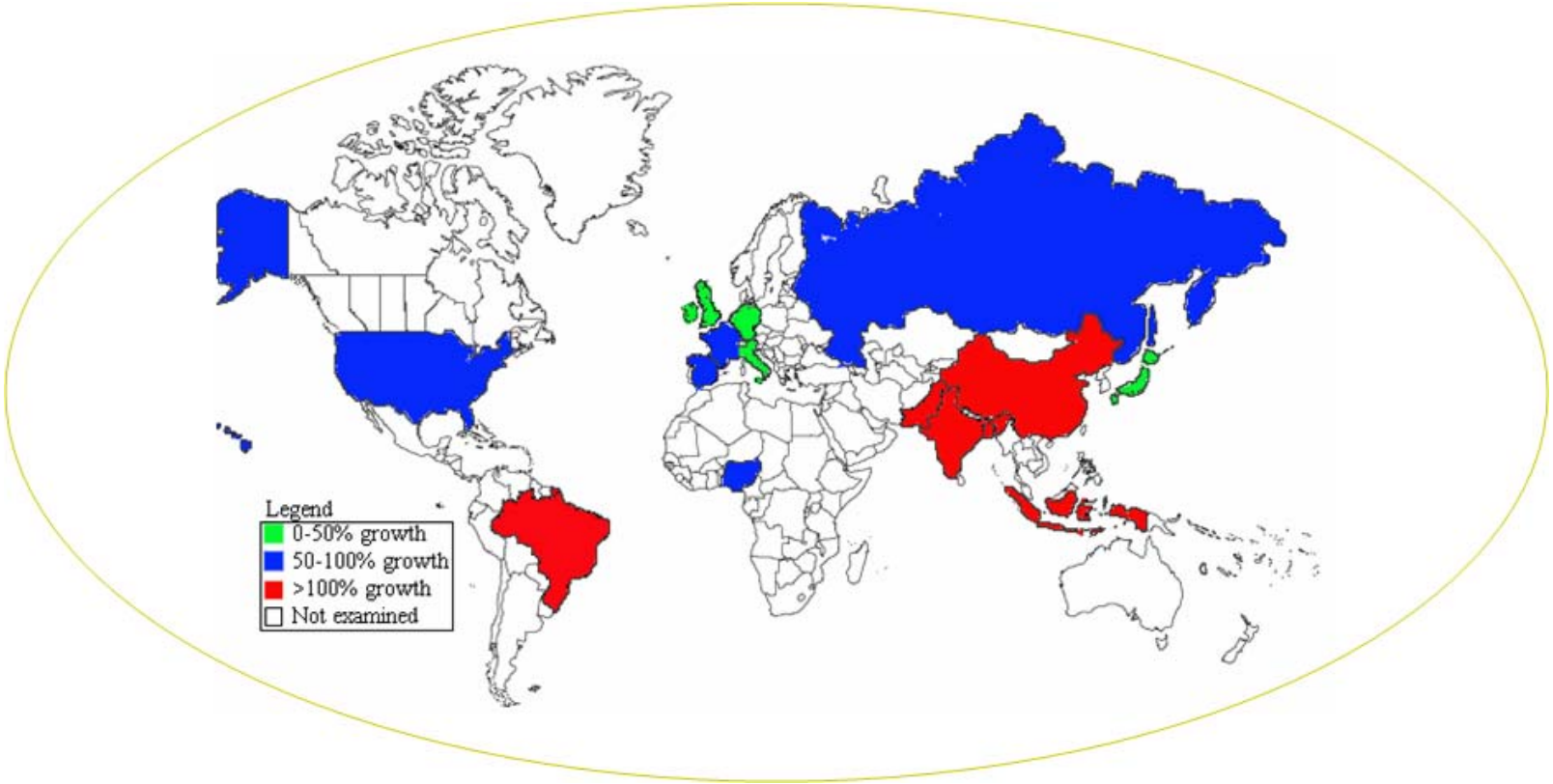
Global Burden of Parkinson's Disease Is Expected to Increase As Life Expectancy Increases World Wide



Source: Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2013). *World Population Prospects: The 2012 Revision*. New York: United Nations.

Consequently, the global burden of Parkinson's disease is expected to increase

Change in number of people with Parkinson's disease in the world's most populous nations from 2005 to 2030*



*Among individuals over 50 in the world's ten most and Western Europe's five most populous nations

Source: Dorsey et al, Neurology 2007;68:384-6

Consequences for Society

Costs:

- **Direct costs of health care**
- **Indirect costs:**
  - **Loss of years worked, lost societal contributions**
  - **Mental & physical costs**
  - **Affects person with PD & family members, colleagues, friends**

The Current and Projected Economic Burden of Parkinson's Disease in the United States

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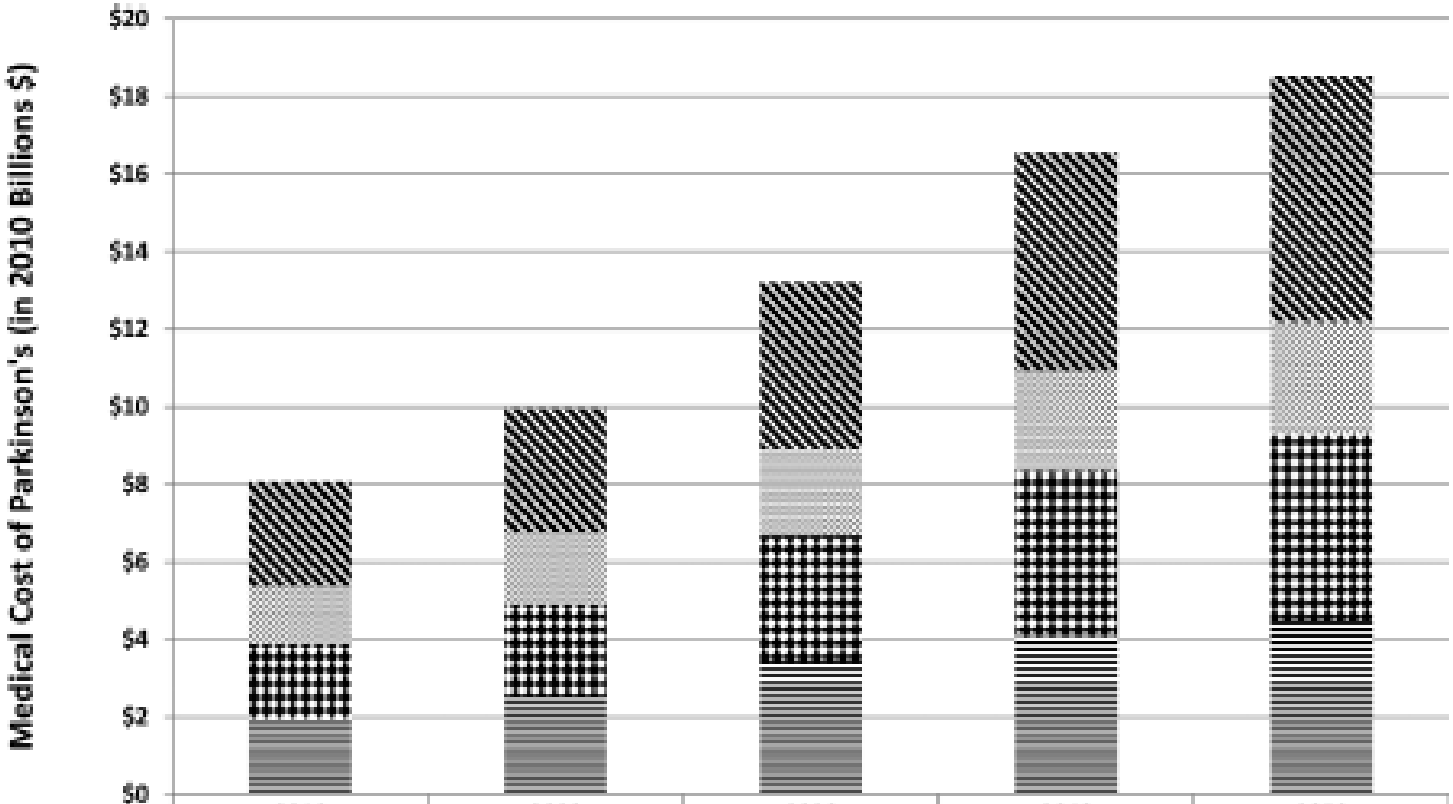


	2010	2020	2030	2040	2050
Self/Family	$2.7	$3.2	$4.3	$5.6	$6.3
Commercial	$1.5	$1.9	$2.2	$2.6	$2.9
Medicaid/Public	$1.9	$2.3	$3.2	$4.3	$4.8
Medicare	$1.9	$2.6	$3.5	$4.1	$4.5

= Medicare + Medicaid/Public ⁜ Commercial ⁂ Self/Family

FIG. 2. Medical costs of PD over time.

Mov Disord 2013

Can We Reduce the Burden?

Education

Research

Advocacy

Health Services

Better Treatment

History of PD Therapy in the US

1817: Parkinson described Paralysis agitans
Late 1800's: Belladonna alkaloids as Rx
1950's: Synthetic anticholinergics as RX
Late 1960's: L-dopa
1970's:
- L-dopa + decarboxylase inhibitor (dci)
- Amantadine
- Bromocriptine as adjunct to l-dopa

1980's:
- ~~Pergolide as adjunct to l-dopa~~ *Withdrawn 2007*
- Sustained release l-dopa/dci
- Selegiline as adjunct to l-dopa

1990's:
- **1997** Pramixpexole (mono, adjunct)
- **1997** Ropinirole (mono, adjunct)
- **1998** Tolcapone (with l-dopa/dci) ***Black box hepatic failure***
- **1999** Entacapone (with l-dopa/dci)

2000's:
- **2004** Apomorphine s.c. (Intermittent hypomobility)
- **2006** Rasagaline (mono, adjunct)
- **2007** Rotigotine patch ***Recall 2008***
- **2006/7** Rivastigmine oral & patch Dementia

2010- …:
- **2012** Rotigotine patch ***Reintroduced***
- **?**

→ ALL BUT 1 DRUG: SYMPTOMATIC TREATMENT FOR MOTOR SYNDROME

Clinical Knowledge Gaps in Parkinson's Disease

CLINICAL COURSE:

- No diagnostic test
- No predictor of risk (for most)
- No reliable marker of progression
- No reliable predictor of prognosis

TREATMENT:

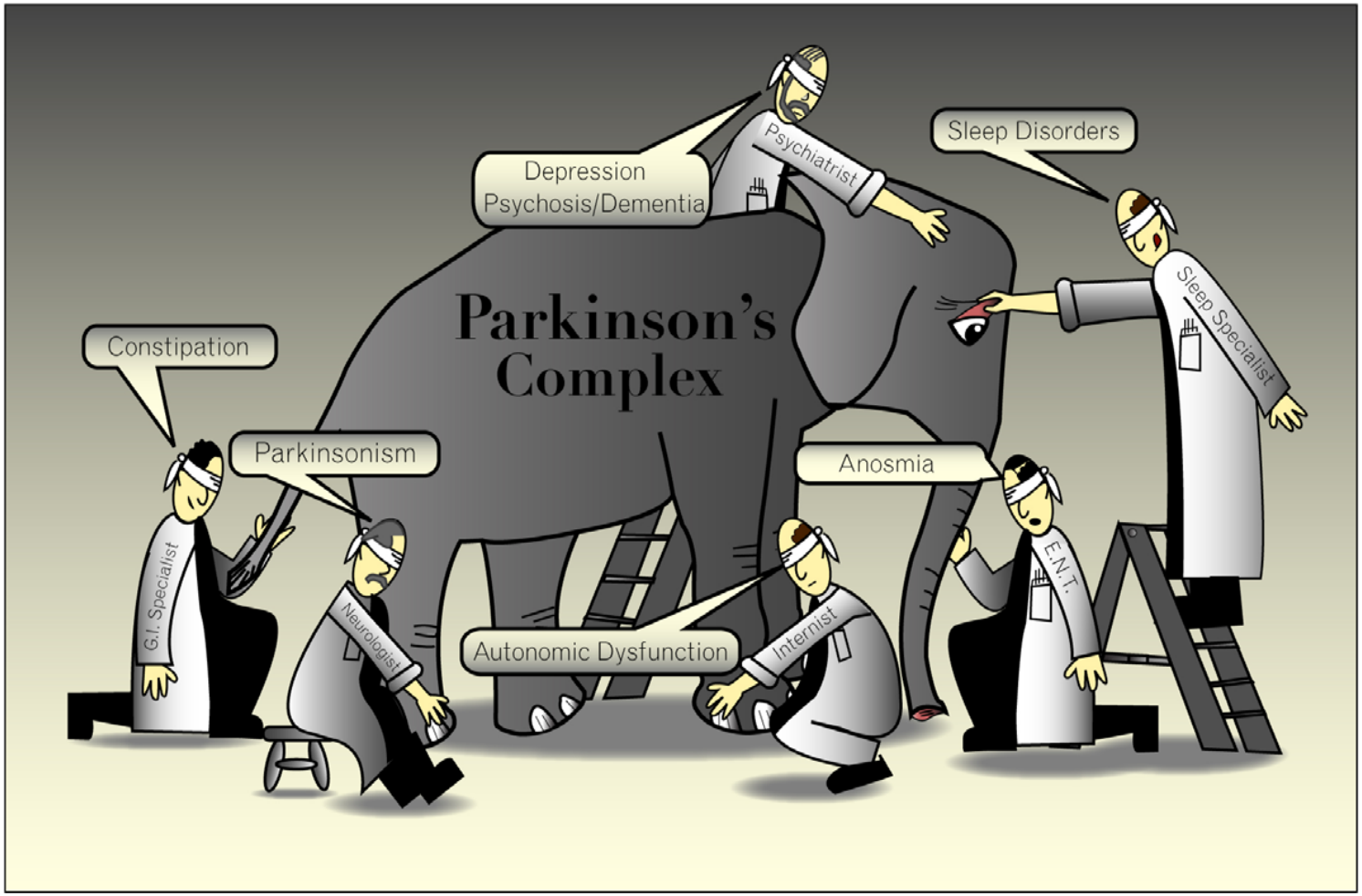
- No way to prevent disease
- No cure
- No way to slow disease progression
- Inadequate Symptomatic Treatment:
  - Motor – imperfect control of symptoms , and with side effects
  - Nonmotor – many and diverse problems, few treatments


Bridging the Gap

Table 1. Highest Priority Recommendations in Each Research Topic Area

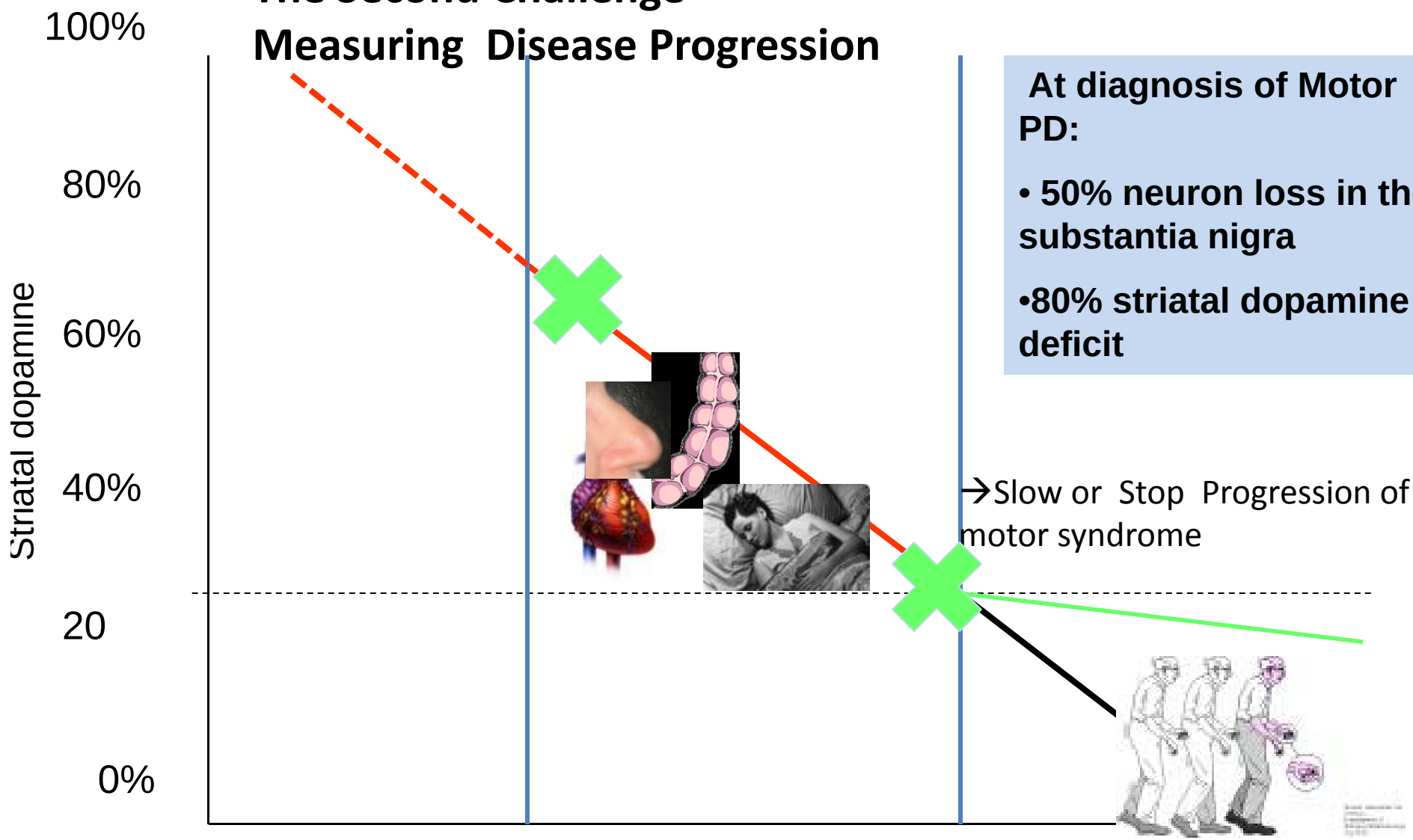
Topic Area	Recommendation	
Clinical Research	1	Define the features and natural history of prodromal PD including progression, events that underlie phenoconversion to clinically manifest PD, and biomarkers or other determinants of prodromal subtypes with the goal of providing sufficient rationale to initiate proof-of-concept prevention trials that initially target high-risk populations.
	2	Develop effective treatments and companion biomarkers for dopa-resistant features of PD. These features include both motor symptoms, particularly gait and balance problems, such as freezing of gait, and non-motor symptoms, especially cognitive impairment, psychosis, and dysautonomia.
	3	Characterize the long-term progression of PD and understand the mechanisms that underlie the heterogeneity in clinical presentation and rates of progression. Factors related to disease heterogeneity may include clusters of clinical features as well as biological factors such as genotype and biomarkers.

THE FIRST CHALLENGE:
Defining Parkinson's Disease



Langston, 2008

The Second Challenge
Measuring Disease Progression



At diagnosis of Motor PD:

- **50% neuron loss in the substantia nigra**
- **80% striatal dopamine deficit**

→Slow or Stop Progression of motor syndrome

PRECLINICAL

→Pathogenesis & clinical course of PD only partially understood

PRODROMAL

→Prevent Symptom Onset

PARKINSON'S DISEASE

→Prevent disease features: dyskinesias, dementia

The 3rd Challenge: Define Measures of Risk, Onset & Progression in Parkinson's Disease

HEALTH	DISEASE		DISEASE OUTCOMES
Markers of risk	Prodromal	Diagnosis	Progression
Genes • Exposure group?	•Hyposmia •ANS •RBD • Tissue*? • Imaging	• Clinical • Post-mortem • Imaging (adjunct) •Tissue*?	• Clinical exam • Tissue*? • Imaging?

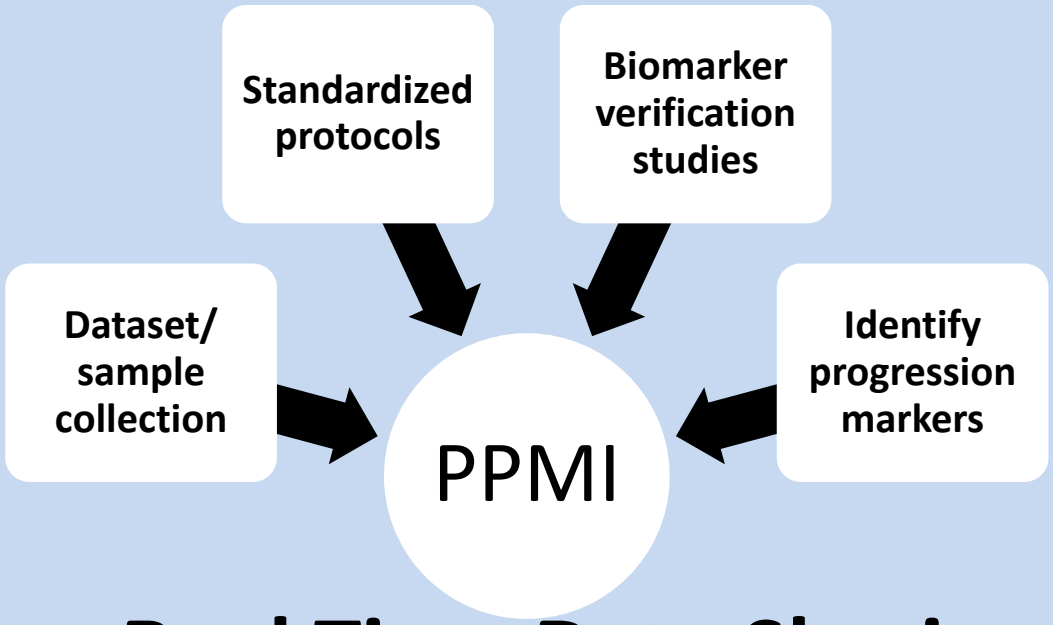
RELIABLE BIOMARKERS NEEDED!

* Blood, CSF, skin, GI (ENS), salivary gland, other?

PPMI

The Parkinson's Progression Markers Initiative: A Prospective Biomarkers Study

OBJECTIVES



POPULATIONS

- Early Untreated PD
- Matched Controls
- RBD
- Hyposmics
- LRRK2, SNCA PD & Families

Real Time Data Sharing

Imaging & Biologic markers may increase efficiency of clinical trials

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Frasier et al, 2010; Marek et al 2011

Overcoming Barriers to Success in Studies of Parkinson's Disease

Slow enrollment is a major cause of delay and expense

Only about 10% of persons eligible to participate in studies enroll

Can changes in outcomes & study conduct speed things up?

Improve Outcome Measures

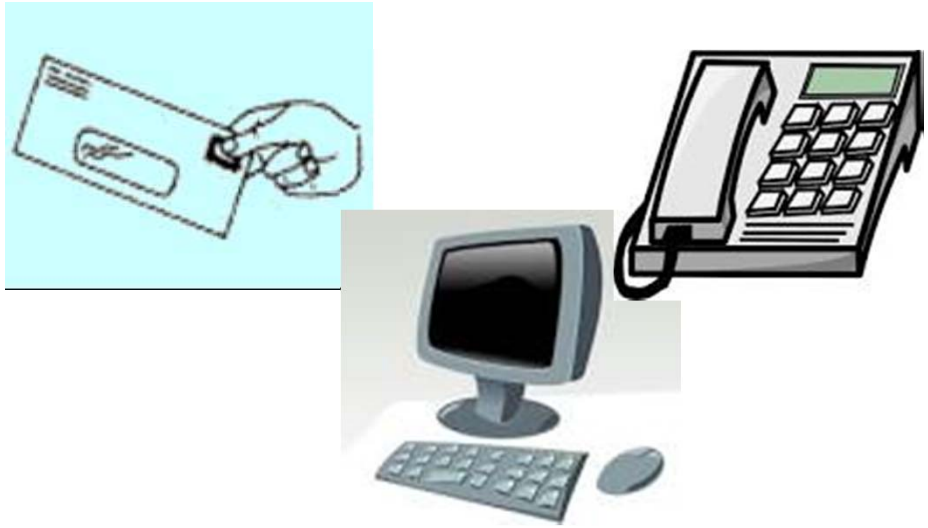
Develop Measures Not Dependent on Motor Disease:

- Imaging: brain (DaTScan), other organs
- Physiological measures: Tremor recording, tapping time, EEG spectral analysis
- Global clinical measures: self-reported or examination & interview-based (UPDRS, QOL)
- Other biomarkers: laboratory measurements of body tissues (blood, urine, CSF, saliva,biopsied tissue)

→FUTURE: Combinations of measures

Increase Enrollment & Retention In Clinical Trials

Remote Assessment



Telemedicine

Randomized Controlled Clinical Trial of "Virtual House Calls" for Parkinson Disease

E. Ray Dorsey, MD, MBA; Vinayak Venkataraman, BS; Matthew J. Grana, BA; Michael T. Bull, BS; Benjamin P. George, MPH; Cynthia M. Boyd, MD, MPH; Christopher A. Beck, PhD; Balaraman Rajan, MBA, MS; Abraham Seidmann, PhD; Kevin M. Biglan, MD, MPH

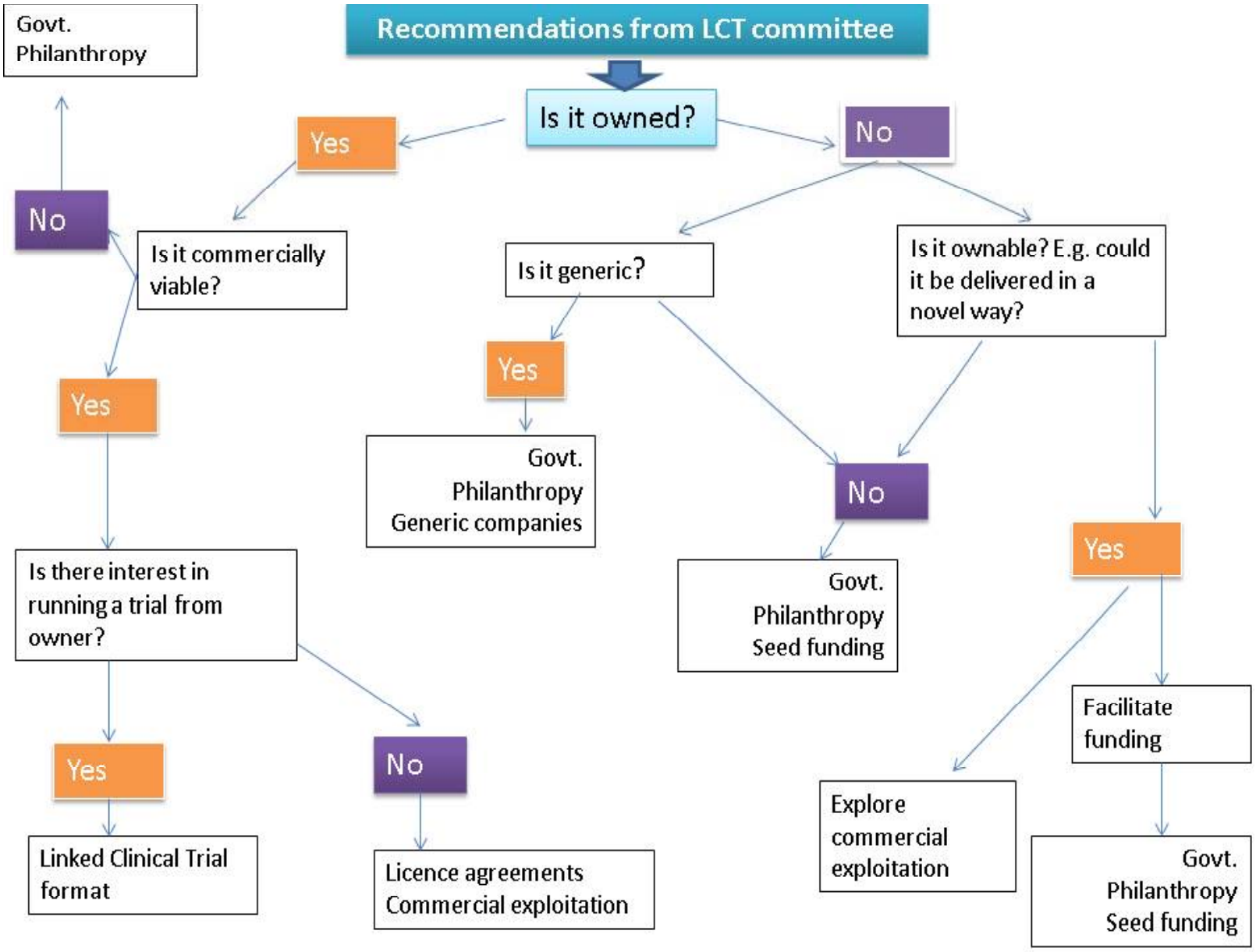
BIG DATA

- Information from continuous monitoring
- Large numbers of people
- Universal platform
- Can combine w/ other info (imaging, genes)

Potential Benefits:

- Identify patterns of disease progression
- Reduce the burden of clinical trial participation
- Identify subgroups more likely to benefit from certain interventions
- Provide new outcome measures?

Linked Clinical Trials: Repurposing



Brundin et al, J PD 2014


THANK YOU!