Critical Path for Parkinson's: Collaboration to Enable Patient Focused Drug Development and Precision Medicine

Diane Stephenson, PhD, Executive Director, Critical Path Institute

April 27, 2018

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a decade of excellence

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PARKINSON'S CONSORTIUM
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A little about me sets the stage for today…..

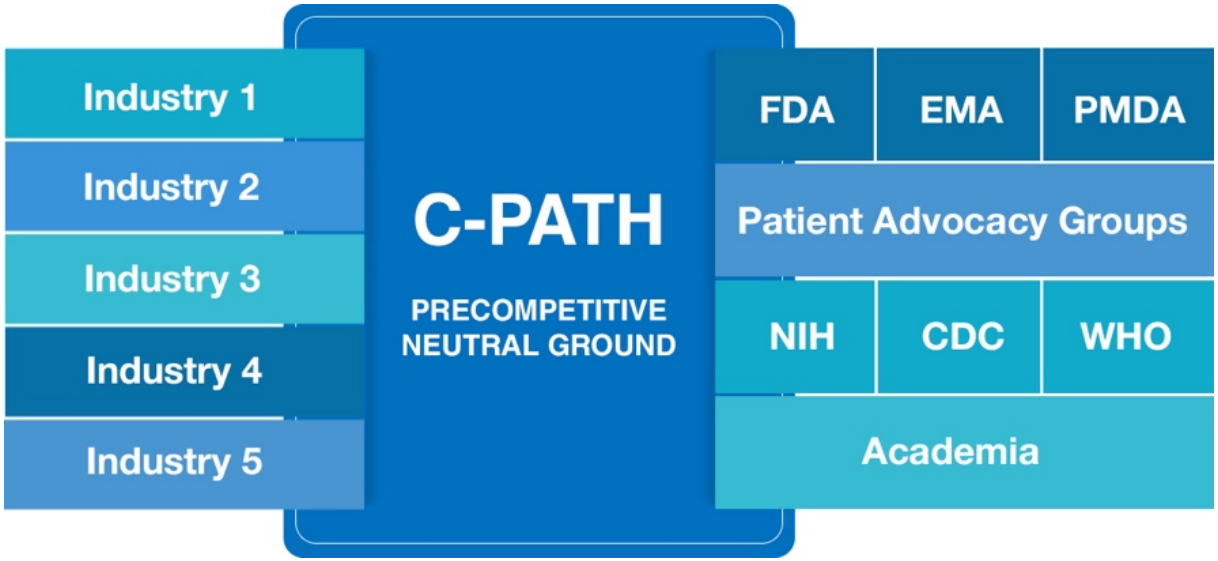
Pharma was taking too long…

Diane, the Executive Director Critical Path for Parkinson's, shares why she left job at the largest pharmaceutical company in the world to create better, faster ways to develop new treatments.

I left my job at the largest pharmaceutical company in the world because I knew that it was taking too long to bring new treatments to people like my brother. I needed to find another way to bring hope to my family. So, I joined the Critical Path Institute, a non-profit organization based in Arizona, which exists to make it faster, cheaper and more efficient to get new therapies to patients.

What is the Critical Path Institute?

A trusted, neutral third party delivering new methods and tools for clinical trials which benefit the whole community.



Critical Path for Parkinson's Consortium –
Accelerating therapies for PD

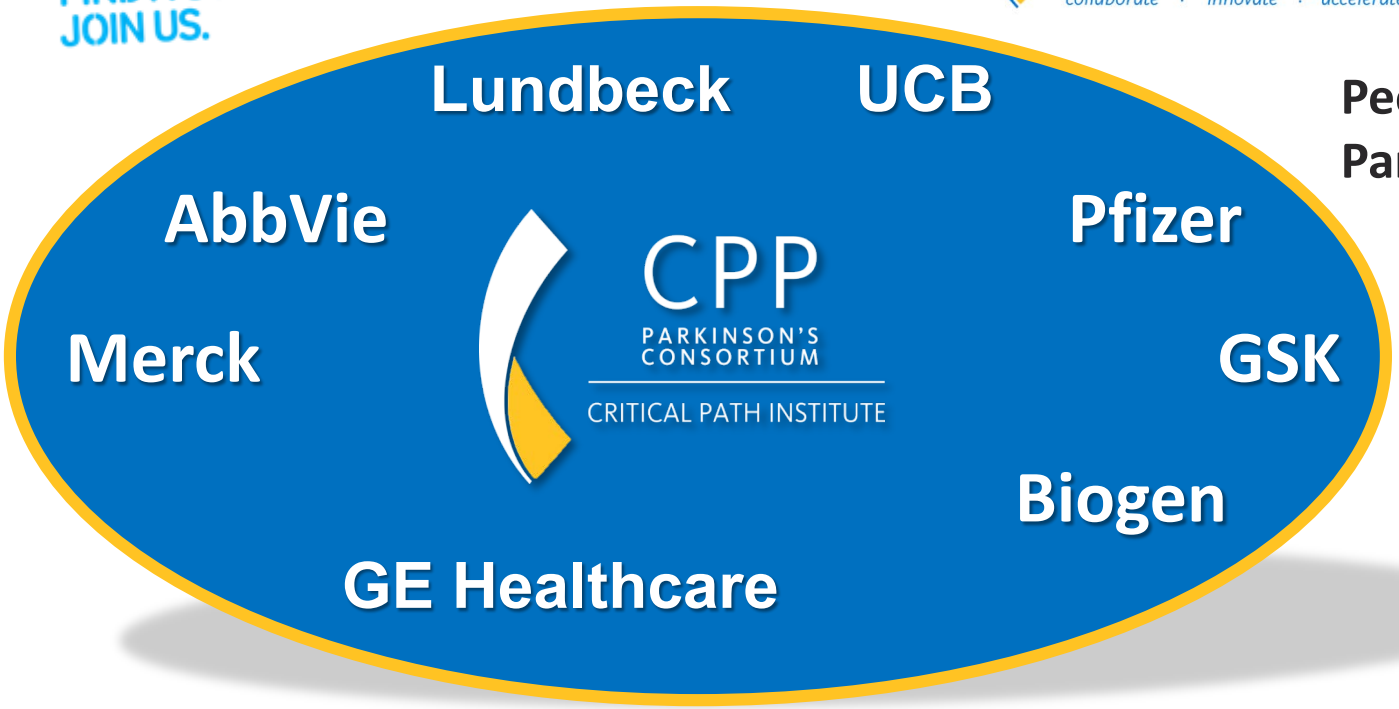
CRITICAL PATH INSTITUTE

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

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

Academic Experts

Individual Advisors



People with Parkinson's

NIH

FDA

Patient-Advocacy Organizations

- Parkinson's Disease Foundation
- Michael J. Fox Foundation
- Davis Phinney Foundation
- The Cure Parkinson's Trust

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

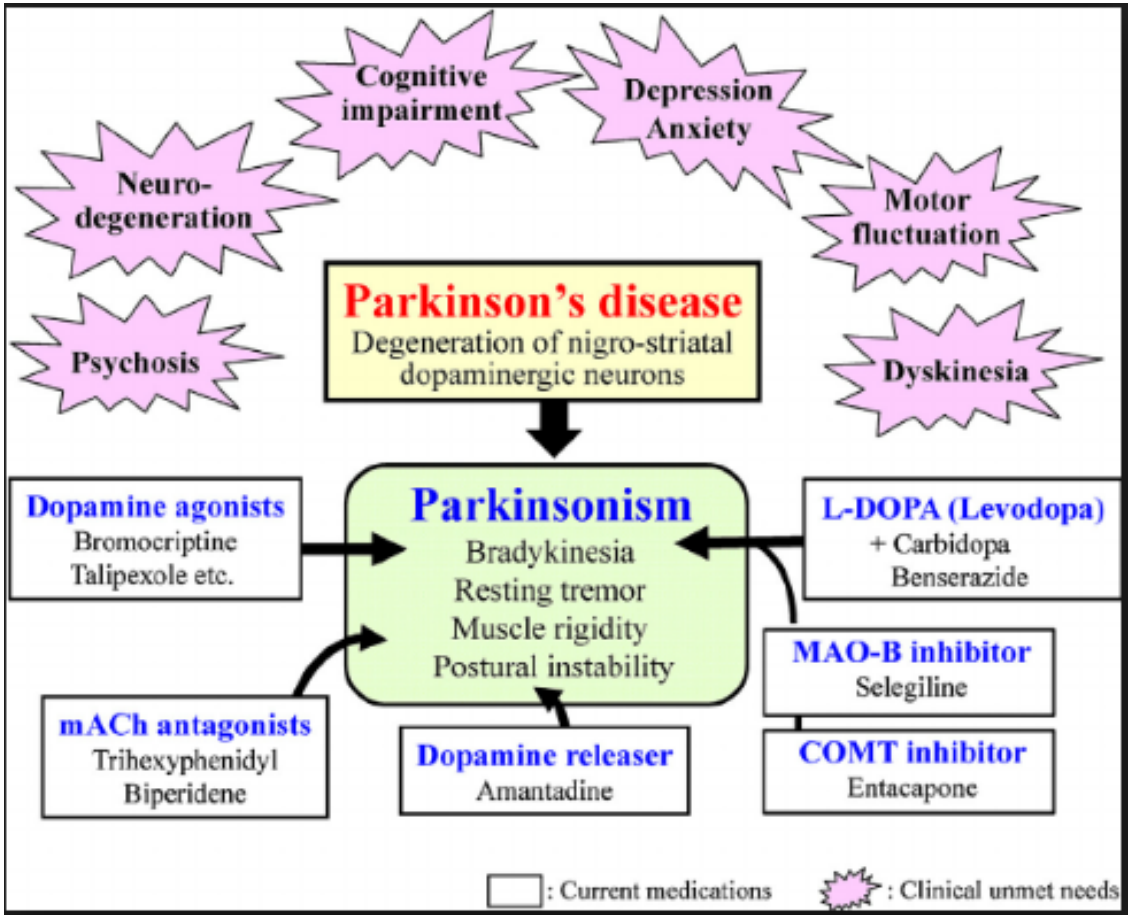
UK Academic Institutions

- University of Oxford
- University of Cambridge
- Newcastle University
- University of Glasgow

‘Pre-competitive’ collaboration

Working together to solve these problems and create tools that will benefit the whole community.

New Parkinson's Disease treatments are urgently needed



https://www.researchgate.net/publication/282812862_New_insight_into_the_therapeutic_role_of_the_serotonergic_system_in_Parkinson%27s_disease/figures?lo=1

- There is no cure for Parkinson's disease
- Current medications only help control the symptoms
- None stop the progression of the disease
- In some cases, surgery called Deep Brain Stimulation may help with tremor and rigidity
- Medications have not changed much over the last 25 years
- There is a need for new drug therapies, especially for the non-motor symptoms

Many new promising new therapies are in the pipeline

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VIEWPOINT

New Drugs for Parkinson's Disease: The Regulatory and Clinical Development Pathways in the United States

TABLE 1. Selected promising therapies for PD that are in the pipeline[a]

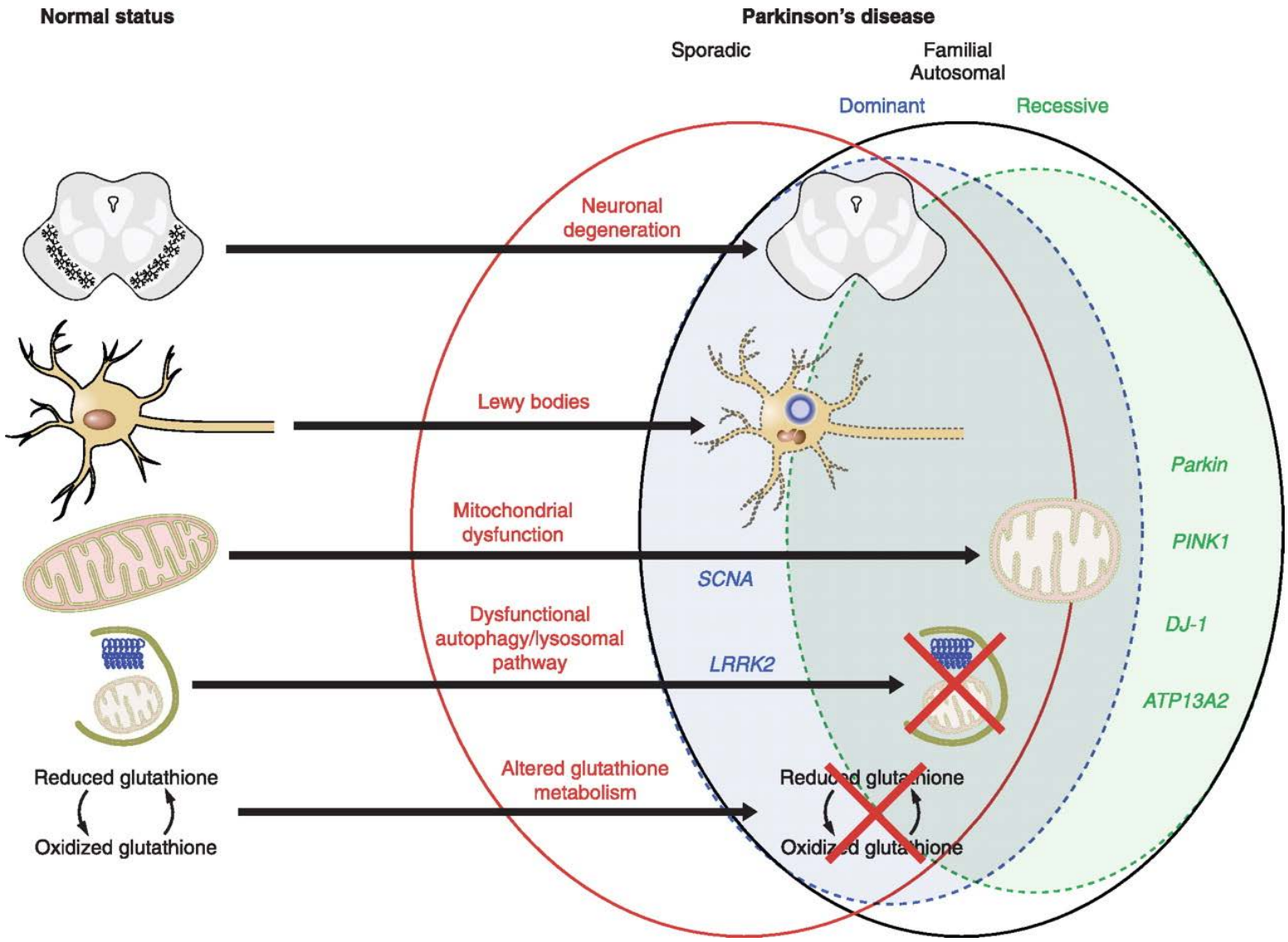
Name	Sponsor	Mechanism/Indication	Stage	Regulatory Comments[b]
Short-term benefits or "Symptomatic"				
Opicapone	Bial	COMT inhibitor	III	Approved in Europe
Istradefylline	Kyowa-Kirin	A2A antagonist	III	Approved in Japan
Tozadenant	Acorda	A2A antagonist	III	505B1 pathway
CVT 301	Acorda	Inhaled L-dopa	III	505B2 pathway
APL130277	Sunovion	Sublingual apomorpine	III	Fast track
Amantadine ER	Adamas	NMDA antagonist for dysk	III	505B2 pathway
P2B001	Pharma2B	Low-dose prami/rasag combo	III	505B2 pathway
ND0612	Neuroderm	SC L-dopa/carbidopa	III	BE/505B2 pathway
Apo Infusion	USWM	Apomorphine infusion	III	505B2 pathway
Accordion pill	Intec	Long-acting L-dopa	III	505B2 pathway
PF-06649751	Pfizer	D1 agonist	IIB	505B1
LU-AE04621	Lundbeck	D1 agonist	IIB	505B1
SER-214	Serina	polymer-linked rotigotine	IIB	BE/505B2 pathway
AAV2-hAADC	Voyager	AAV2-gene delivery of AADC	II	Submitted through CBER
Light therapy	Photopharmics	Altered circadian rhythm	II	Device pathway
Dopafuse	Synagile	Continuous oral L-dopa delivery	II	Drug/device (505B2)
Disease modifying				
Isradipine	NIH	Ca+ + channel blocker	III	505B2
Inosine	NIH	Increase Urate as antioxidant	III	505B2
Nicotine Patch	Fox	Enhance nicotine levels	II	505B2
Affitope	Afferis	ImmunoRx target alpha syn	II	505B1 submitted through CDER
PRX002	Prothena	Monoclonal AB to alpha syn	IIa	505B1 submitted through CDER
BIIB054	Biogen	ImmunoRx target alpha syn	IIa	505B1 submitted through CDER
NPT 200-11	UCB	Antialpha syn aggregate	II	505B1
Nilotinib	Fox	CAbl kinase inhibitor	II	505B2 (approved in leukemia)
GZ/*SAR402671	Genzyme/Sanofie	GBA enhancer	II	505B1
Ambroxol	Weston Found	Enhances GCase activity	II	505B1
Exenatide	Cure PD Trust	Glucagon-like peptide 1	II	505B2
Deferiprone	APO Pharma	Iron chelator	II	505B2

)[1,3*]

"A better appreciation of regulatory pathways and requirements by scientists, clinical Investigators, and the pharamaceutical industry will likely help reduce the Cost and time of Drug Development, and speed the approval process"

Parkinson's Disease Pathophysiology

--*so many targets for intervention*

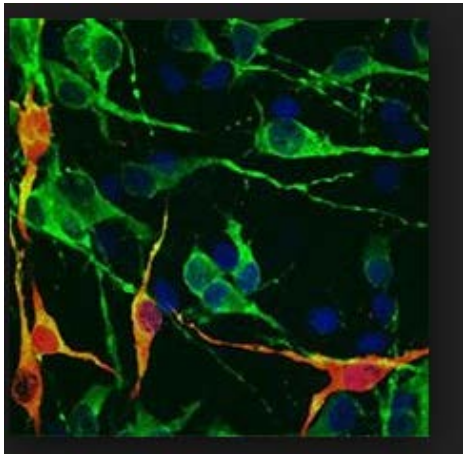


http://physrev.physiology.org/content/91/4/1161

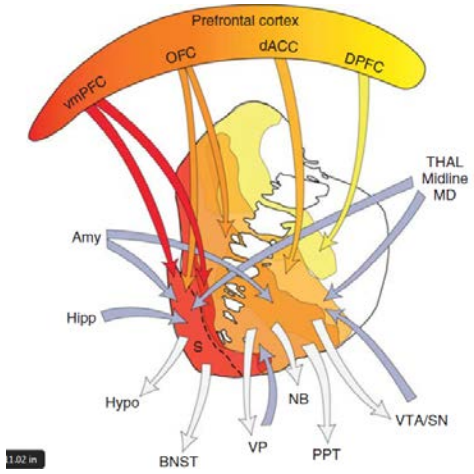
Nonclinical Models for Drug Discovery/Development---

yet none truly represent true Parkinson's disease

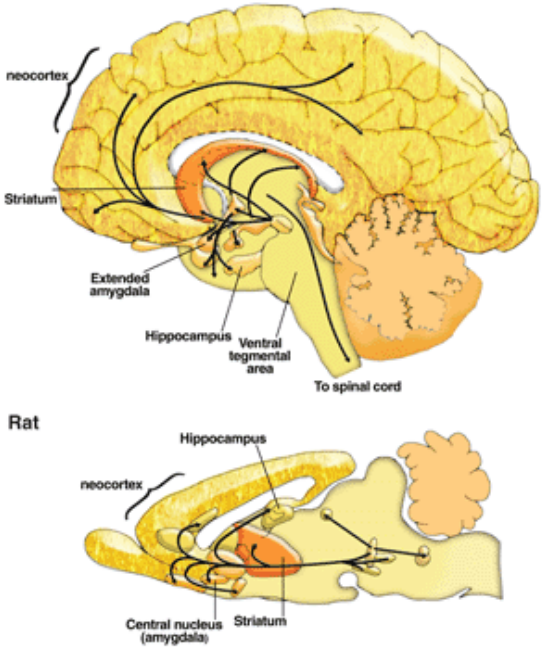
- Cellular Models



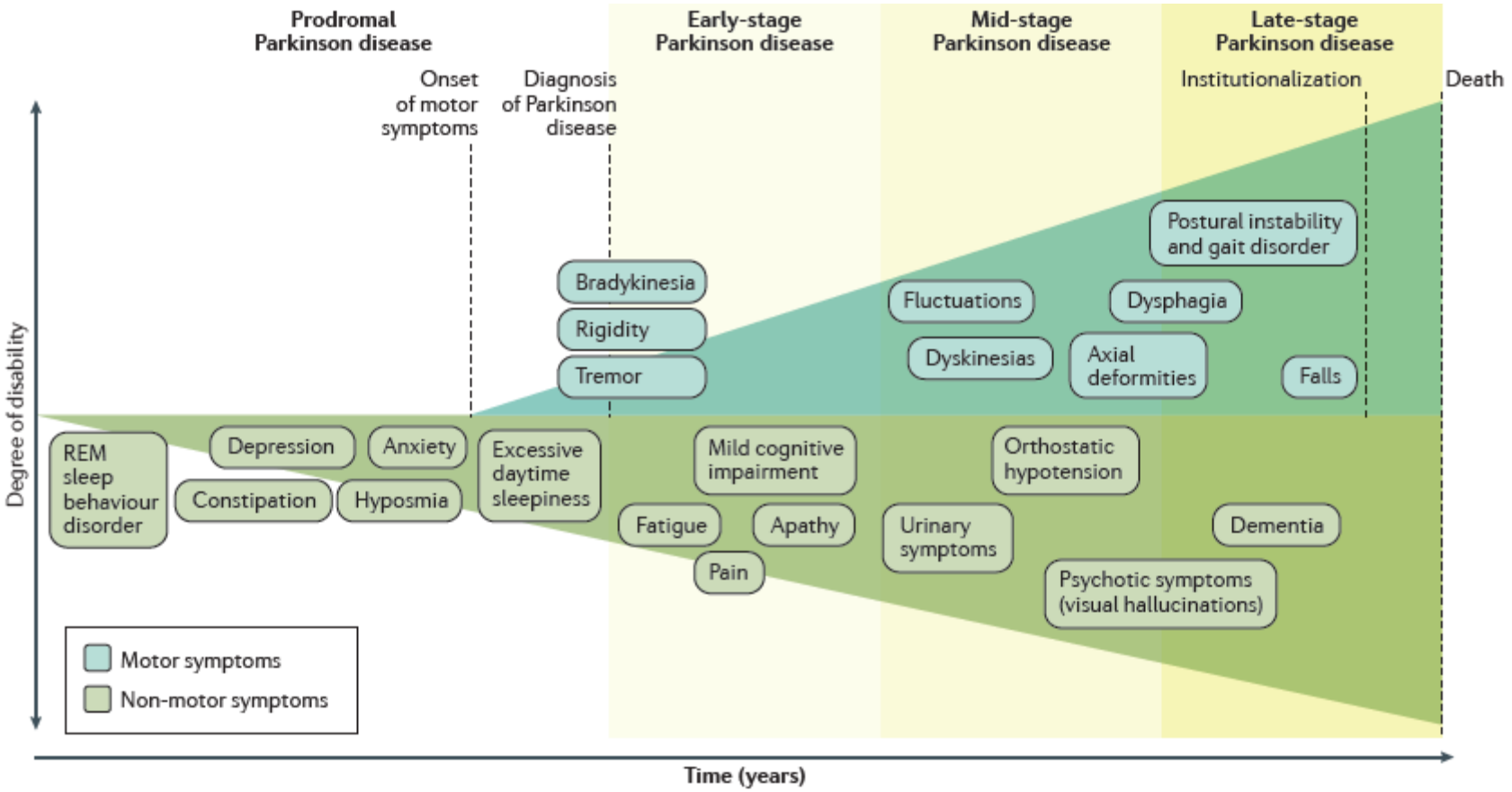
- Primate Models



- Rodent Models



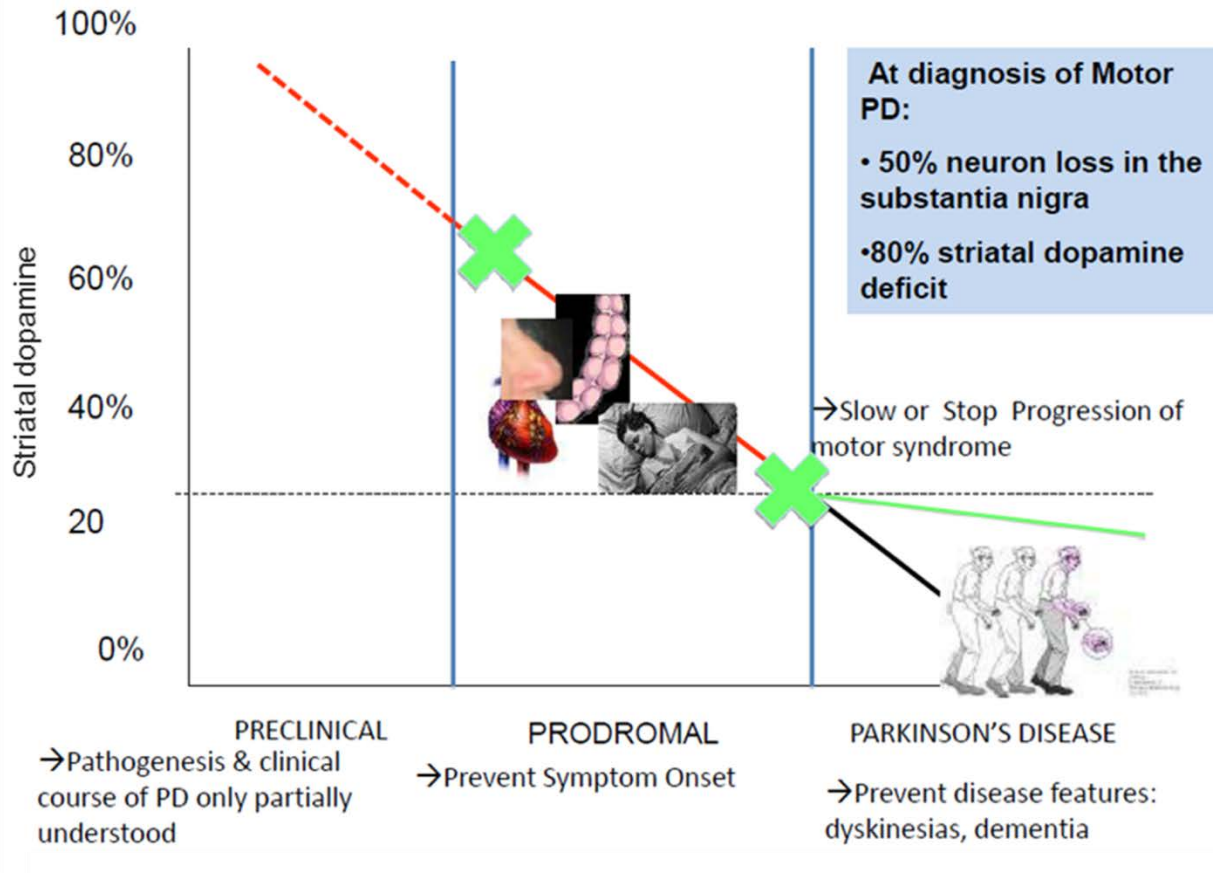
Parkinson's disease symptoms are widespread and disabling



From: Poewe et al., Nature Revs vol 3, no 17013; 1-21, 2017

Each person with Parkinson's will experience symptoms differently

Parkinson's Disease Drug Development is aiming for disease modification and early intervention



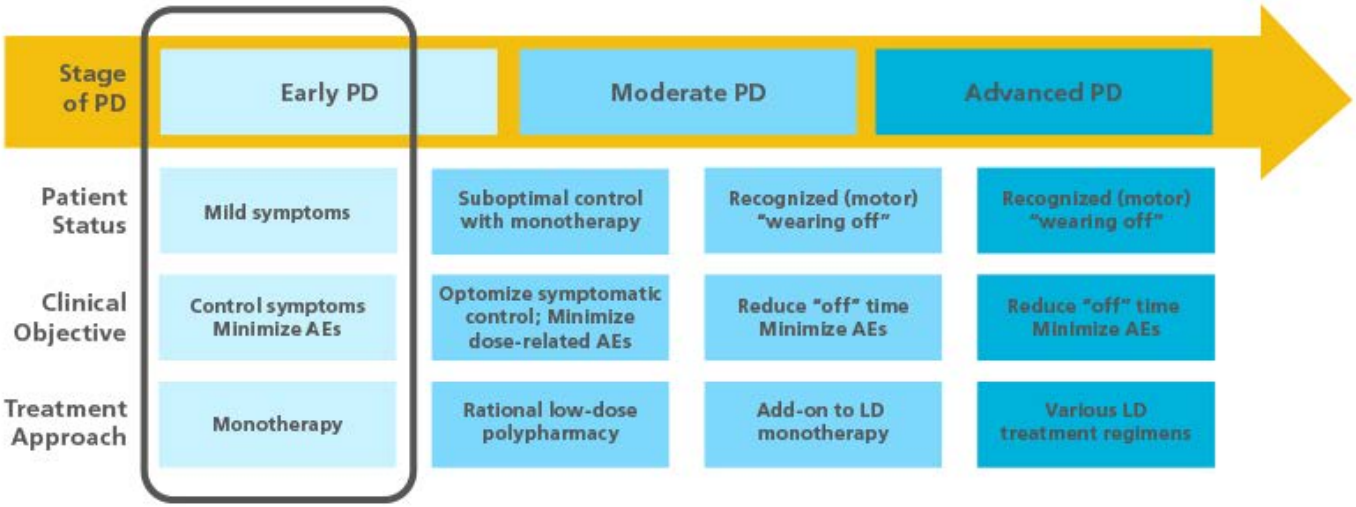
- **Large, global, clinical and observational datasets are available**
- **Increased understanding of disease progression and sub-clinical syndromes**
- **Emerging biomarkers, genes and available technologies and biospecimens**

Patients' Voice on the Need for Early Treatment

- Parkinson's UK 2013-14 survey of patient's needs from research highlighted strong needs for BOTH new symptomatic treatment AND stopping/slowing progression

STOPPING PROGRESSION AT AN EARLY STAGE was the strongest desire of persons with Parkinson's.

This will only be possible through successful trials in early stage patients.



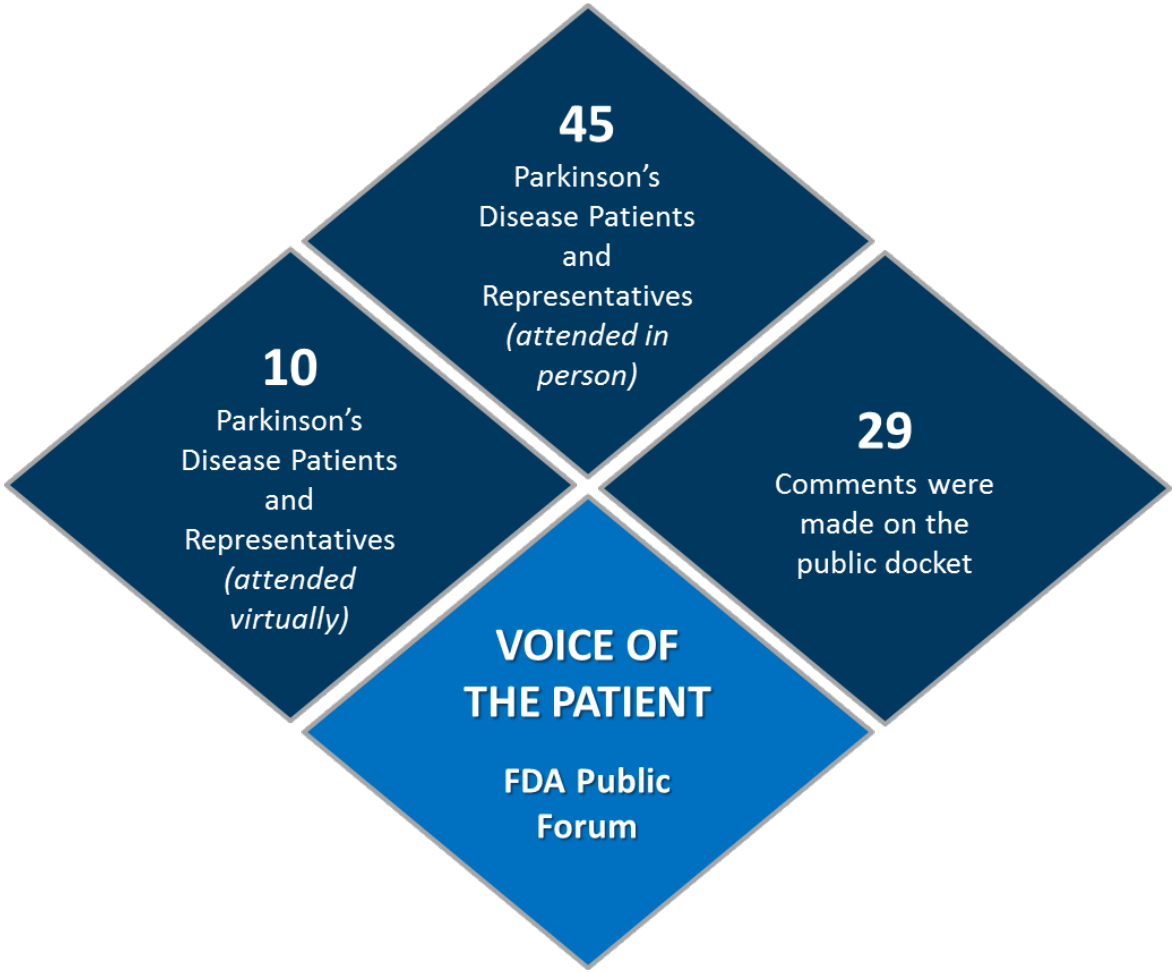
http://parkinsonsed.com/pd-dialogues/early-stage-parkinsons

FDA Listens to the Voice of the Patient

Sept 22, 2015
The FDA held a public meeting on patient focused drug development for Parkinson's and Huntington's diseases

FDA Voice of the Patient

- The 2015 PFDD meeting was their best attended meeting with 45 PD patients attending in person, 10 PD patients attending virtually,
10 FDA regulators were there in person, over 160 people joined by phone to listen to the meeting and 29 comments were made on the public docket following the meeting



September 15, 2015

Comments from FDA Voice of the Patient

TOPIC 1: Disease Symptoms and Daily Impacts that Matter most to patients

- Motor symptoms
  - "I was unable to type or use a computer mouse with my right hand and unable to use my right foot and leg to drive (following diagnosis)"
- Cognitive impairment
  - "I often go from task to task without ever completing anything"
- Sleep disturbances
  - "lack of sleep caused my right arm to tremor all night"
- Other symptoms
  - GI disturbances, orthostatic hypertension, weight loss, restless leg, swallowing difficulties, pain, sweating, speech problems
- Reliance on others
  - **"I fear the people I love most in the world will have to take care of me"**
- Ability to perform at work
- Isolation and impact on relationships

Why do drugs fail to reach people in need?

Wrong target

Inadequate efficacy

Poor drug candidate

Wrong patient population

Toxicity in Select patients

Wrong Dose

Inadequate efficacy

New approaches are needed to tackling drug development challenges

Traditional Drug Development Approach

Reliance on limited information and experience based on:

- A small set of KOLs
- Small, possibly outdated, datasets
- Last paper bias

Data and Quantitative Model Based Drug Development Approach

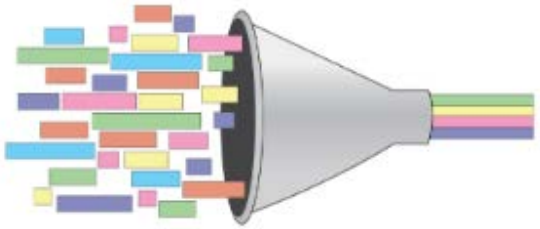
A modern approach based on:

- Integrated global datasets including relevant populations and endpoints
- Quantitative models of disease progression, patient population and endpoint behavior

What could we do if we had all the data from Parkinson's studies in one place?

Data from clinical trials and cohorts

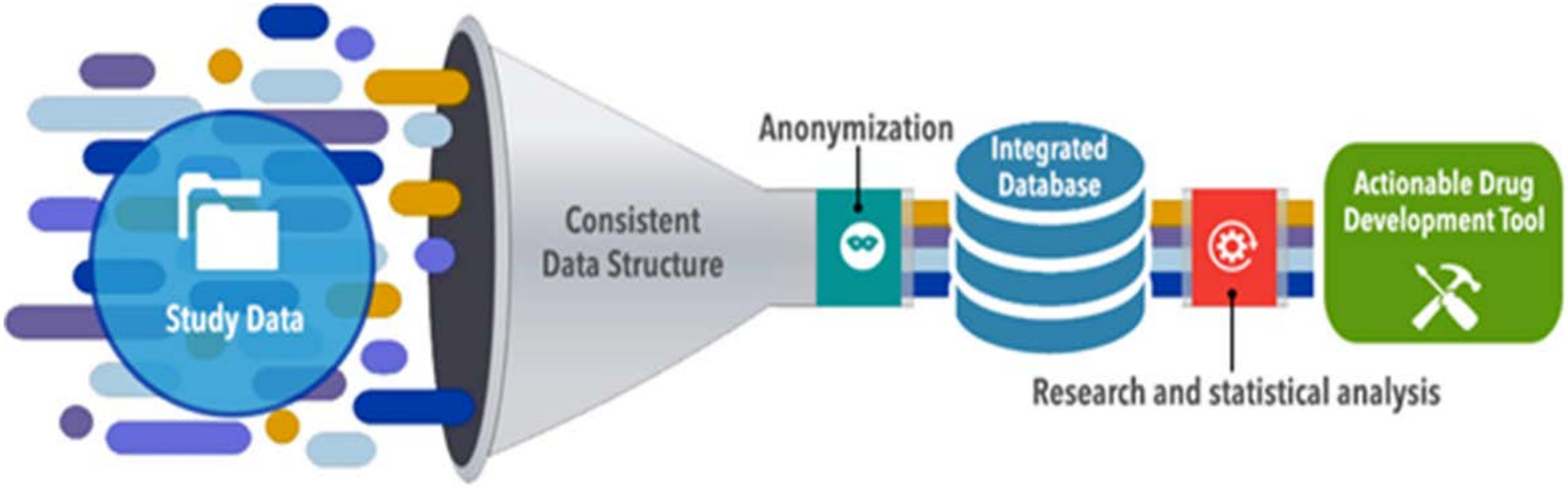
Standardization and integration



CDISC Data Standards

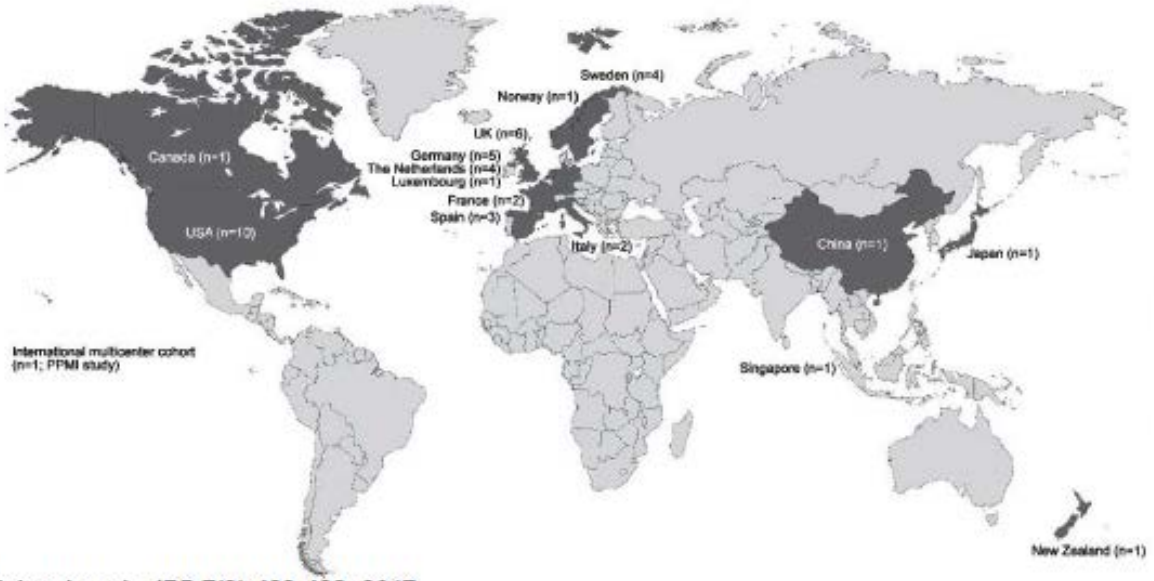
Researchers
Regulators
Industry

C-Path Data Mapping and Integration Process



Critical Path for Parkinson's Worldwide Database

CPP v3.0 Integrated Parkinson's Database Available to Members



Heinzel et al., JPD 7(3):423-432. 2017

PPMI (n=1223)

CamPaIGN (n=142)

OPDC Discovery Cohort (n=877)

ICICLE (n=314)

Tracking Parkinson's (n=1998)

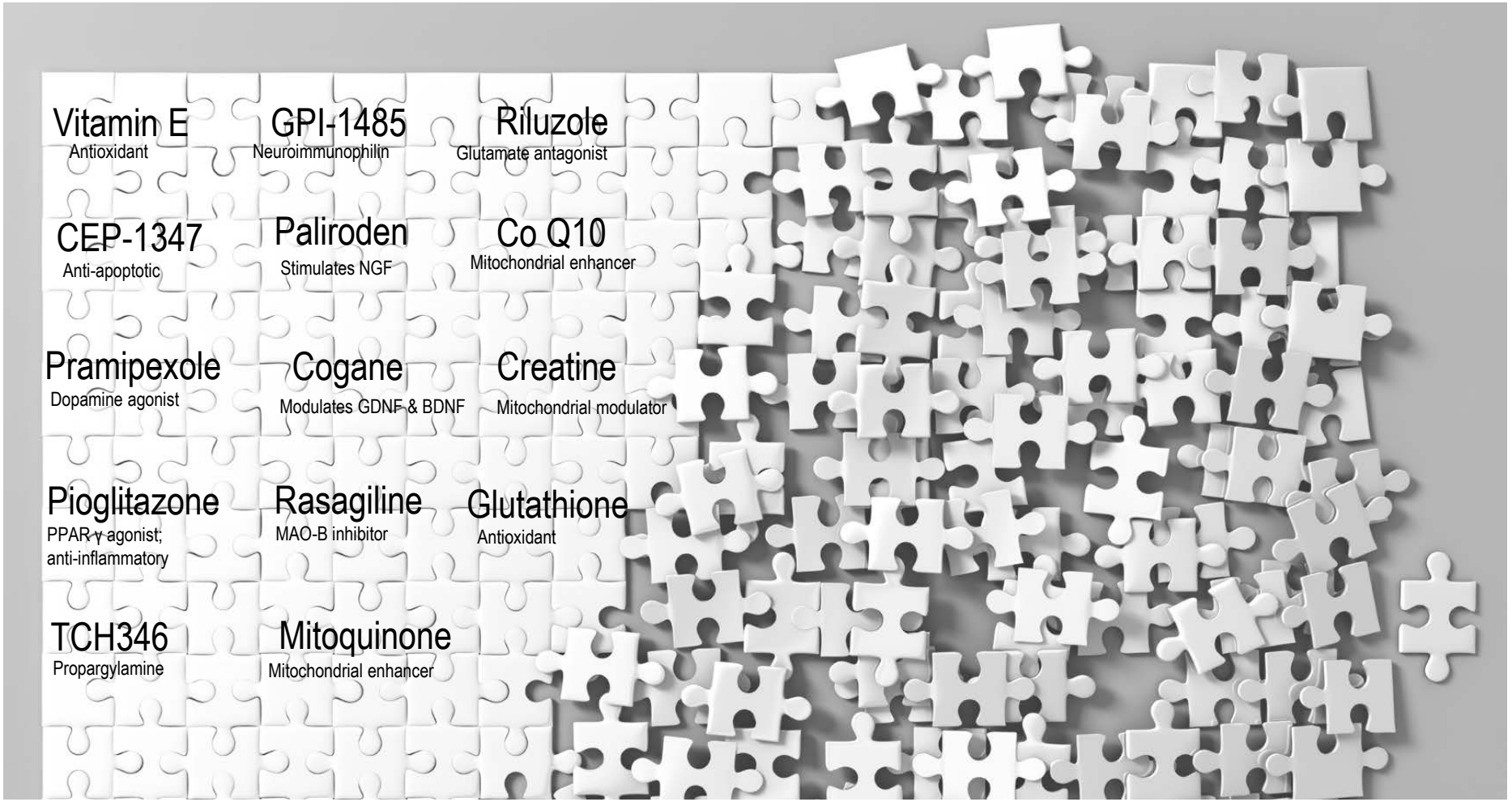
PRECEPT (n=806)

TOTAL NUMBER OF SUBJECTS: 5360

DATATOP and ADAGIO will be integrated next

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

We can learn from past clinical trials



Future model of Parkinson's therapies

Parkinson's -
Not all one flavor

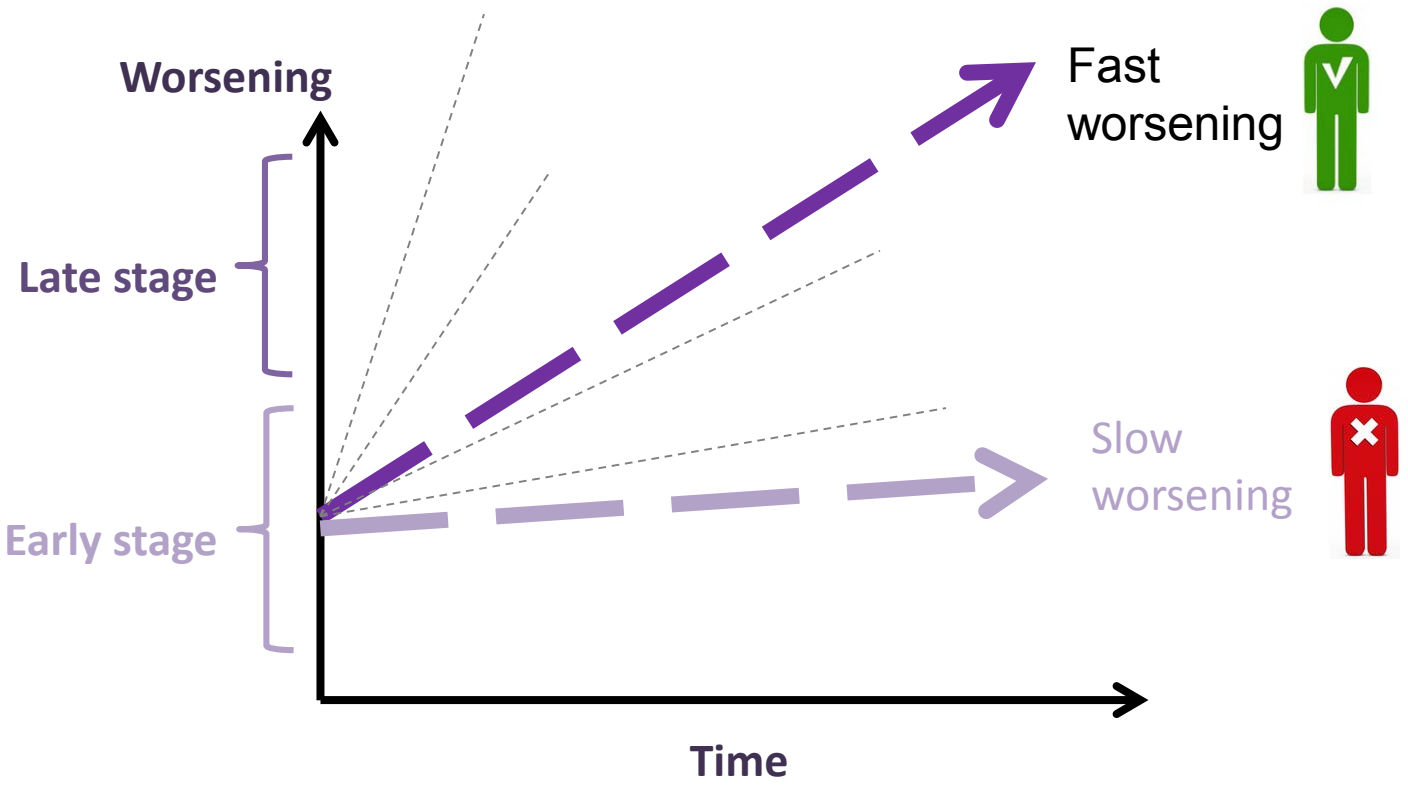
Personalized Medicine
targeted treatments

As modified from Alberto Espay

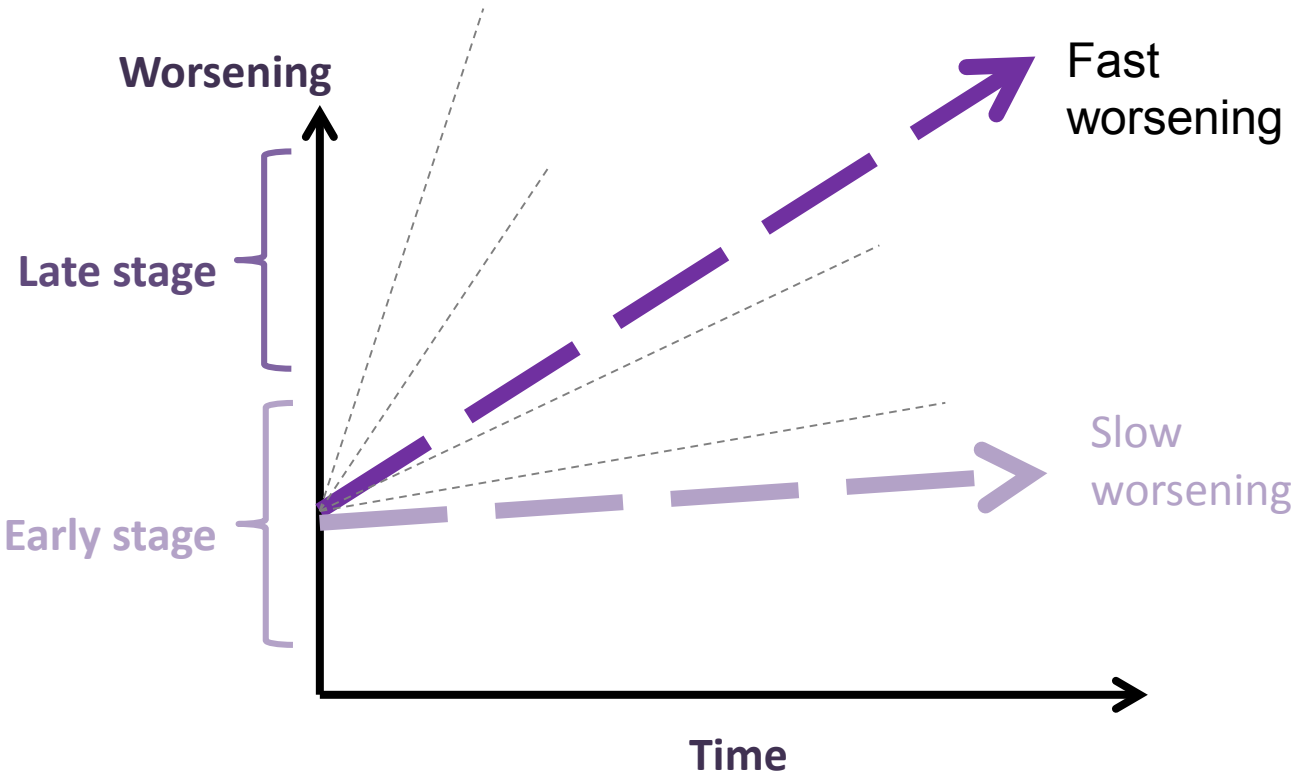
Up to 15% of people with early Parkinson's who take part in trials may not have the condition at all

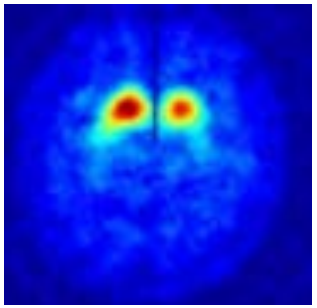
Beth Vernaleo, Parkinson's Disease Foundation

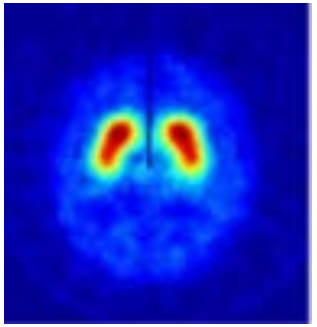
Some people worsen fast, others slowly…



Using imaging to predict the future

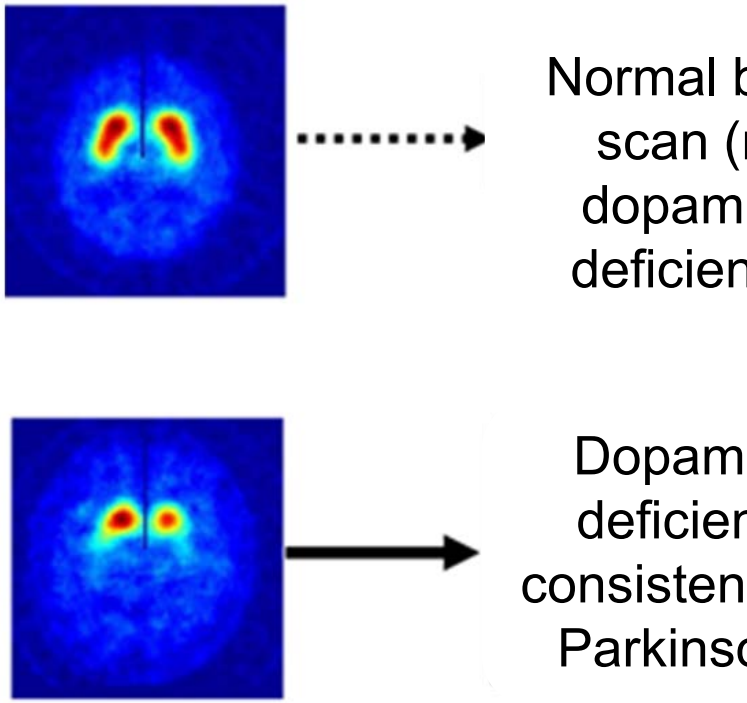






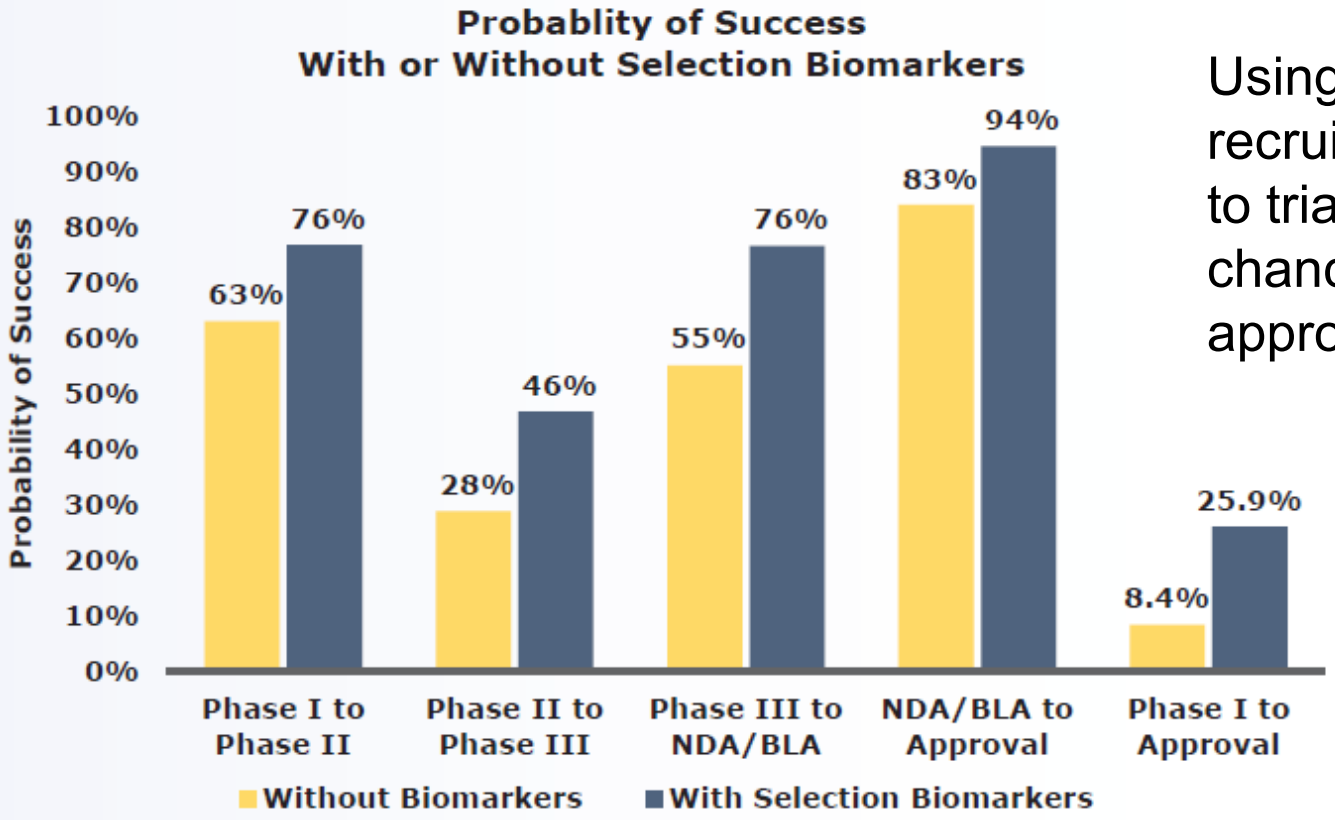
Using imaging as a biomarker in trials endorsed by EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



The Parkinson's disease imaging biomarker is the first biomarker to be qualified By Regulatory Authorities

What impact could this make?

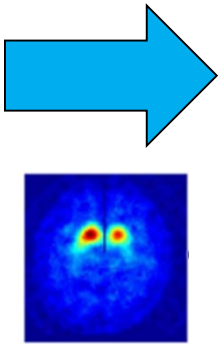


Using biomarkers to recruit the right people to trials increases chances of drug approvals.

Amplion/BIO report, 2016

Critical Path for Parkinson's is already changing the landscape

Before

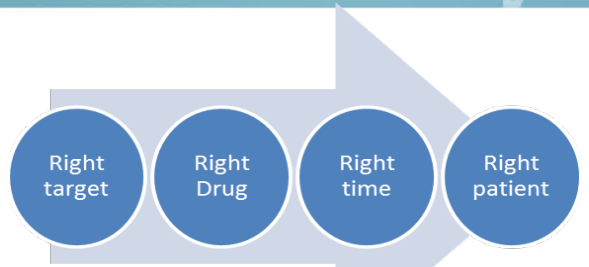


Now

Selecting more appropriate subjects for clinical trials will reduce the numbers needed and make trials more efficient.

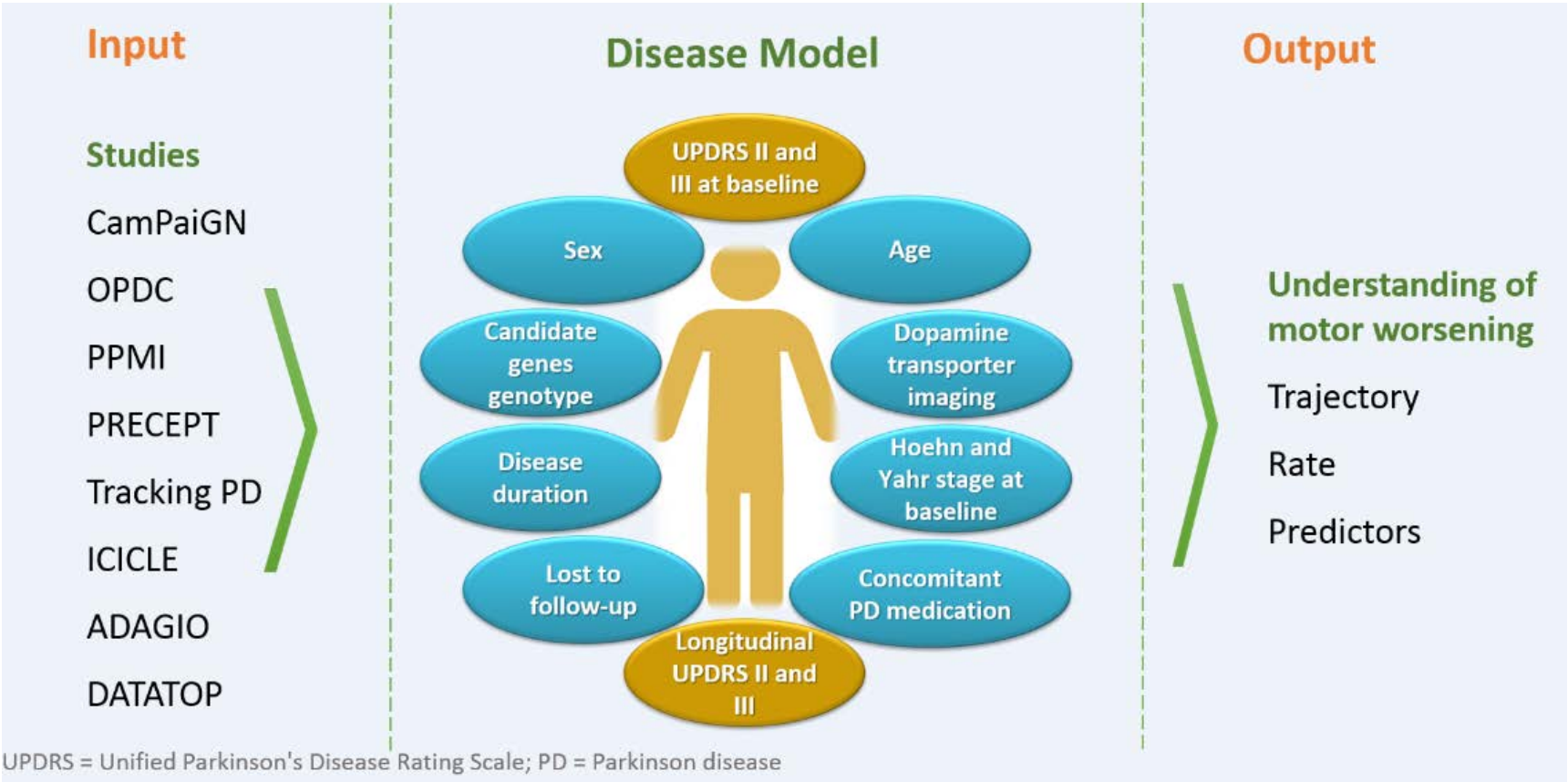
What's next for Critical Path for Parkinson's?

Integrate even more data from around the world to help create tools that bring:



Can Computerized Modeling Help ?
Model Informed Drug Development

- Using computerized models to simulate different 'what if' scenarios aimed at identifying the ***right drug, right patient at the right time***



UPDRS = Unified Parkinson's Disease Rating Scale; PD = Parkinson disease

The future: a trial ‘flight simulator’?

This has been achieved for Alzheimer's disease: *other diseases are waiting*

THE WALL STREET JOURNAL.

JOURNAL REPORTS: HEALTH CARE

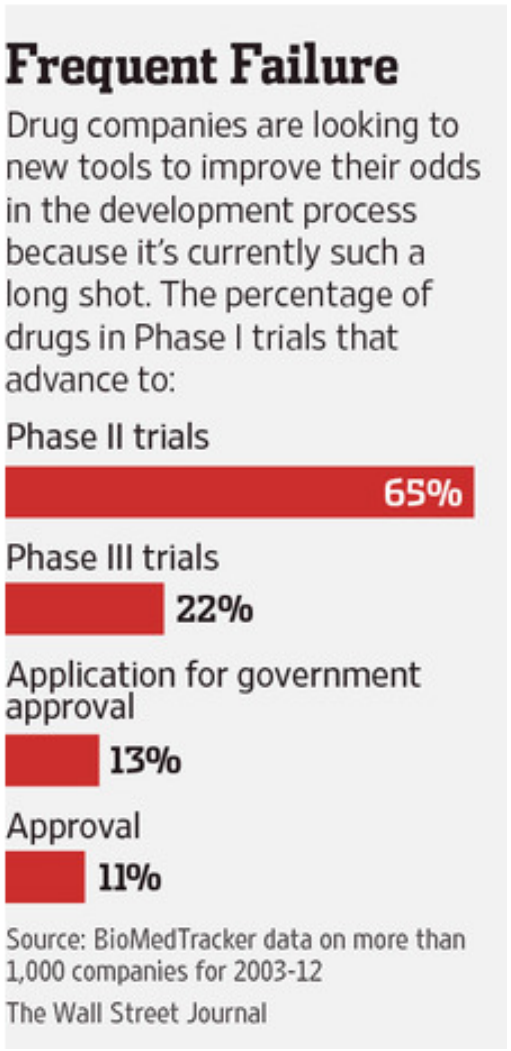
Simulators Help Build a Better Drug Trial

Pharmaceutical firms start to use powerful computer programs to improve human testing

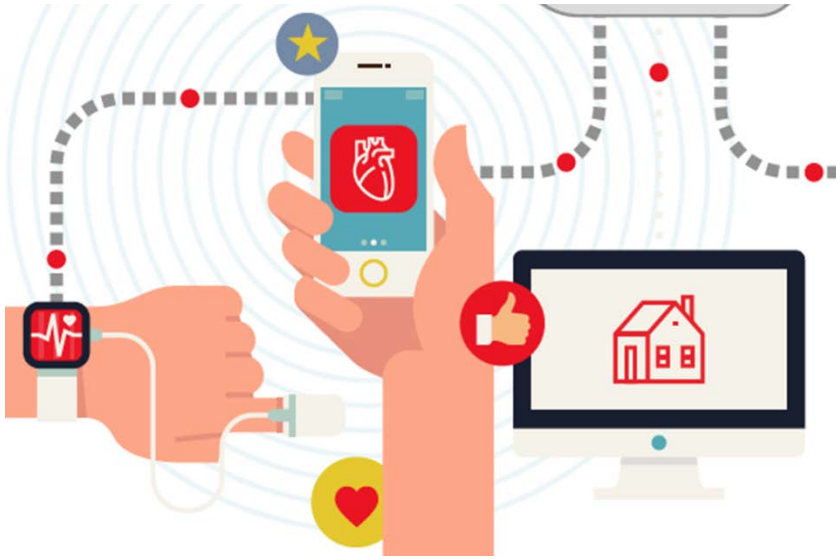
By JONATHAN D. ROCKOFF

Nov. 17, 2013 4:07 p.m. ET

"Model-based drug development was one of the goals defined in FDA's 2004 Critical Path Initiative report, and this new tool sets the stage for applying new technologies to accelerating medical product development,"
Janet Woodcock, FDA



The landscape of digital health promises transformation



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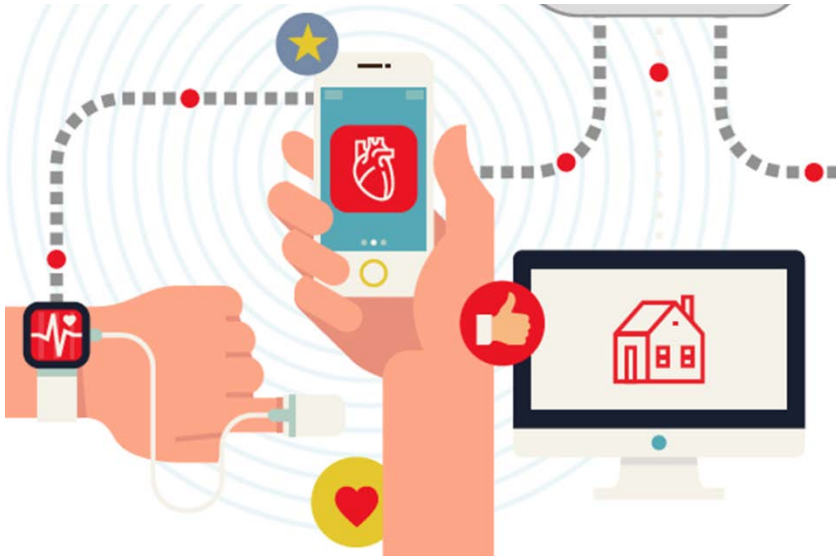
The landscape of digital health promises transformation



Summary

- Parkinson's disease therapies are challenging to develop. Critical Path for Parkinson's is a multinational collaboration set in place to tackle the challenges together
- CPP has created the largest fully curated integrated database for Parkinson's (currently includes data from >5000 patients)
- EMA is poised to qualify the first ever imaging biomarker for Parkinson's. This is being widely used to select the right participants for clinical trial programs currently starting in US and Europe including UK.
- Regulators are incentivized to listen to the voice of the patient to bring meaningful safe and effective therapies to those living with Parkinson's
- Modeling tools are being developed to simulate clinical trials and increase the chances of success of future drug development programs
- Collaboration around the world is urgently needed to speed the path to effective treatments

Remember:
Non pharmaceutical interventions are important

REVIEW

The Best Medicine? The Influence of Physical Activity and Inactivity on Parkinson's Disease

Sara C. LaHue MD,[1] Cynthia L. Comella MD,[2] and Caroline M. Tanner MD, PhD[3]*

[1]*Kaiser Permanente San Francisco Medical Center, San Francisco, California, USA*
[2]*Rush Medical Center, Neurological Sciences, Chicago, Illinois, USA*
[3]*San Francisco Veterans Affairs Medical Center and Department of Neurology, University of California, San Francisco, California, USA*

There is a lot of exciting new evidence that indicates that physical exercise is beneficial for PD patients to keep them mobile and can even relieve some of their symptoms. Whether it's bicycling, yoga, tai chi, swimming or boxing, keeping active is shown to delay and even improve some symptoms

Mov. Disord. 2016 doi:10.10002/mds.26728

Acknowledgements

Thanks to the Food and Drug Administration and Science Foundation Arizona for their
significant funding of Critical Path Institute.