New Approaches for Future Clinical Trials in 'Neuroprotection' in PD

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University of Rochester School of Medicine

President, Clintrex LLC

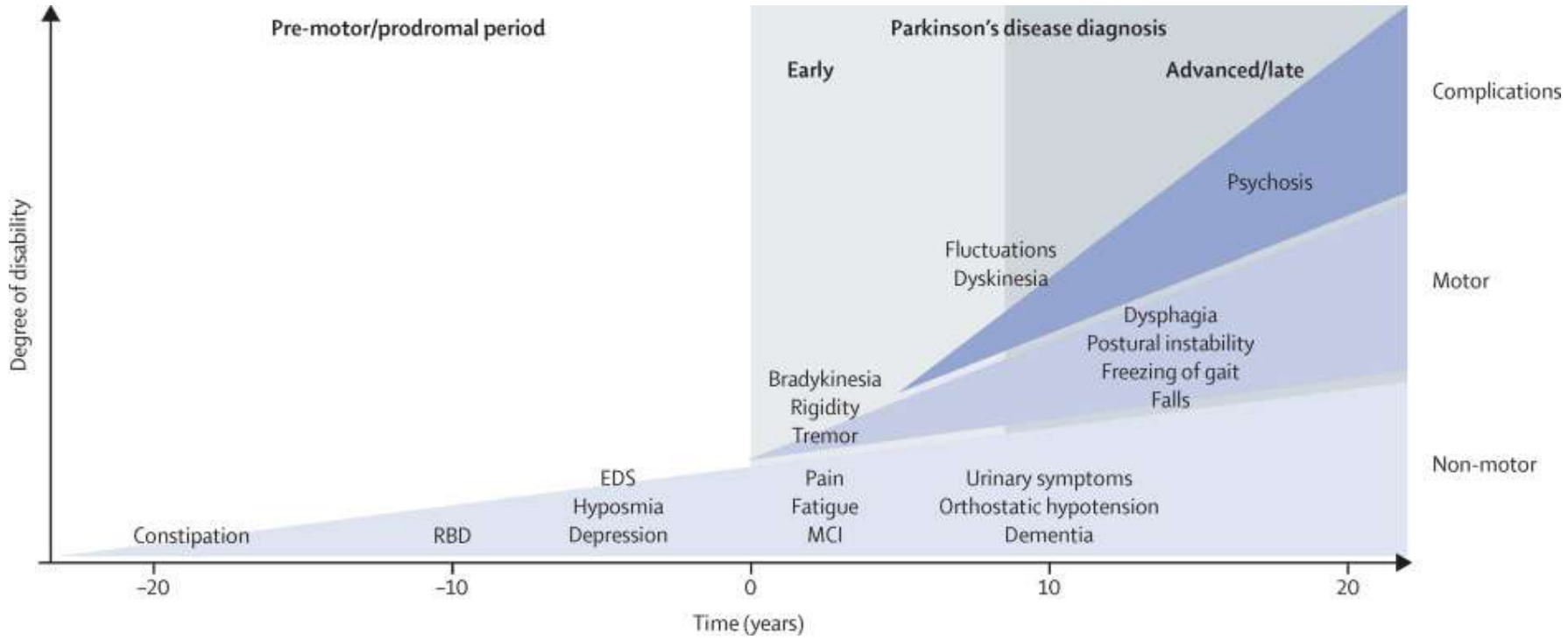
PD Signs and Symptoms

Motor

- Akinesia, rigidity, and tremor at rest- generally 'responsive' to treatment
- Postural stability and gait impairment

Non-Motor

- Autonomic symptoms, cognitive impairment, pain, fatigue, olfactory dysfunction and psychiatric features (depression, hallucination)



Premotor/Prodromal

- Impaired olfaction
- Constipation
- Depression
- Excessive Daytime Sleepiness
- Rapid Eye Movement Sleep Behavior Disorder

Symptomatic

- Emergence and worsening of motor features (initiation of symptomatic treatment)
- Treatment-resistant motor and non-motor features with advancing disease

Parkinson's disease. Lancet 2015

FDA Early AD Guidance (Feb 2018)- Relevant to PD?

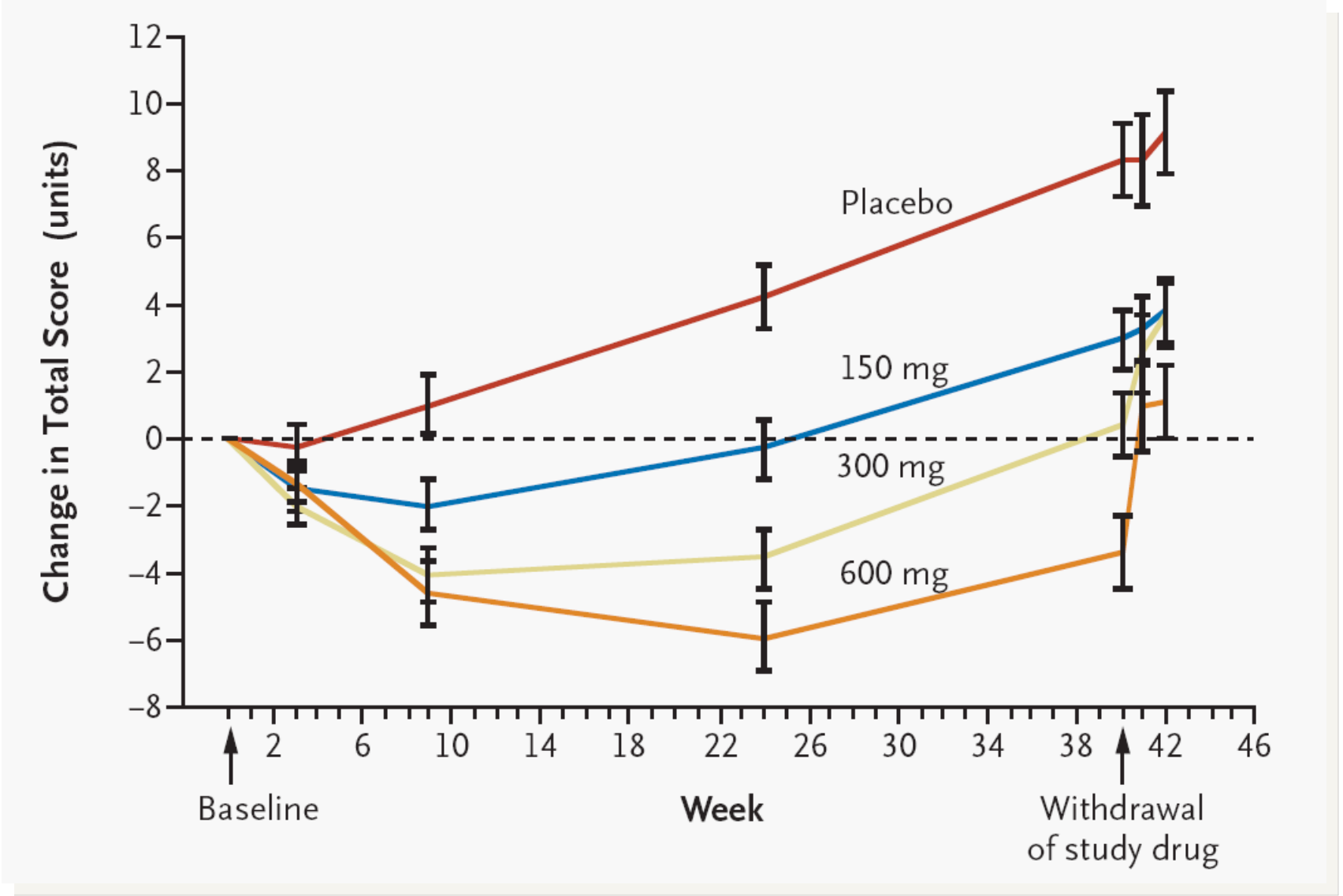
Stage 1: Patients with characteristic pathophysiologic changes of AD but no evidence of clinical impact. These patients are truly asymptomatic with no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures. The characteristic pathophysiologic changes are typically demonstrated by assessment of various biomarker measures.

Stage 2: Patients with characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment. The emergence of subtle functional impairment signals a transition to Stage 3.

Stage 3: Patients with characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment. The functional impairment in this stage is not severe enough to warrant a diagnosis of overt dementia.

Stage 4: Patients with overt dementia. This diagnosis is made as functional impairment worsens from that seen in Stage 3. This stage may be refined into additional categories (e.g., Stages 4, 5, and 6, corresponding with mild, moderate, and severe dementia) but a discussion of these disease stages is not the focus of this guidance.

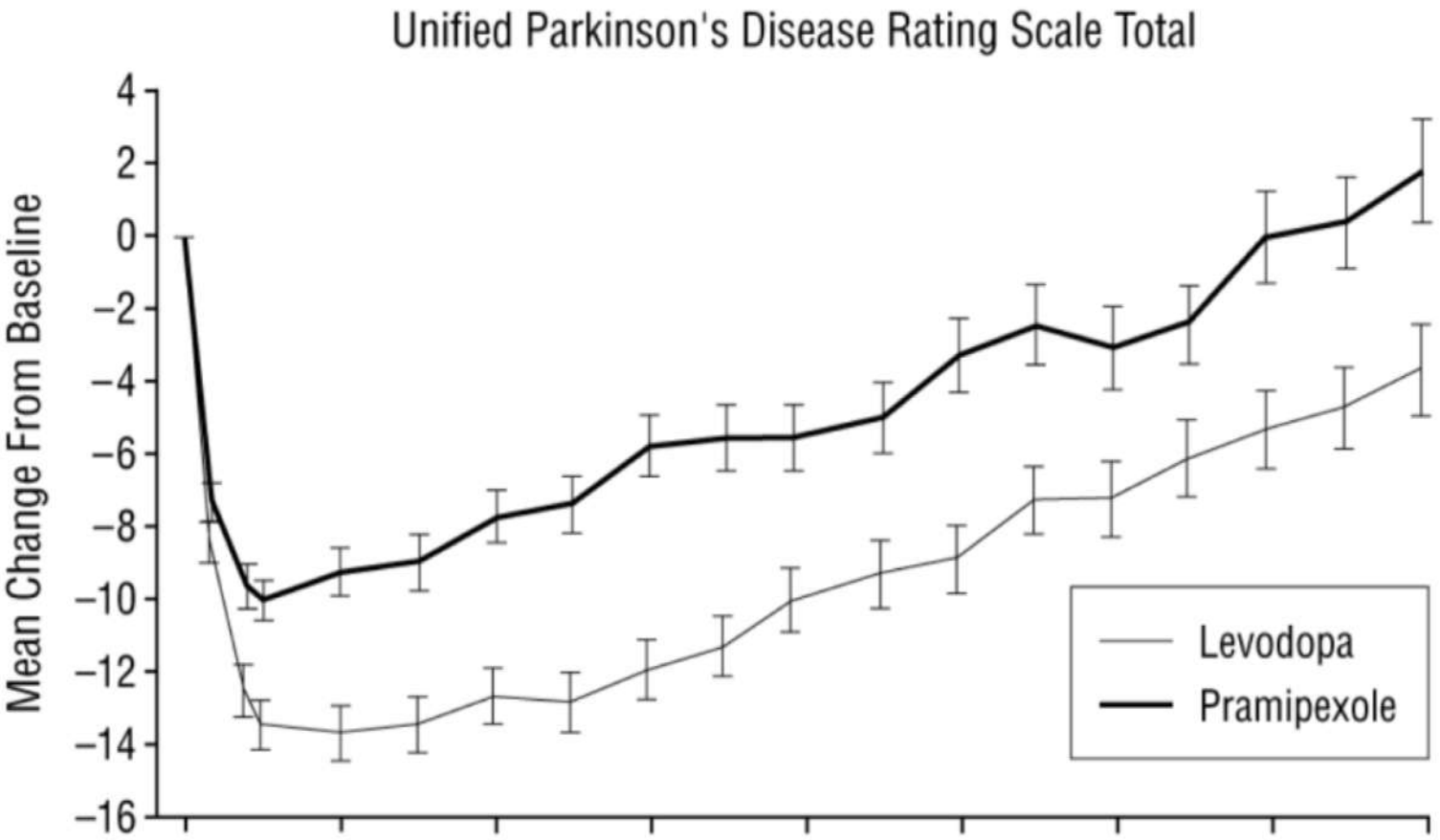
Levodopa and the Progression of Parkinson's Disease



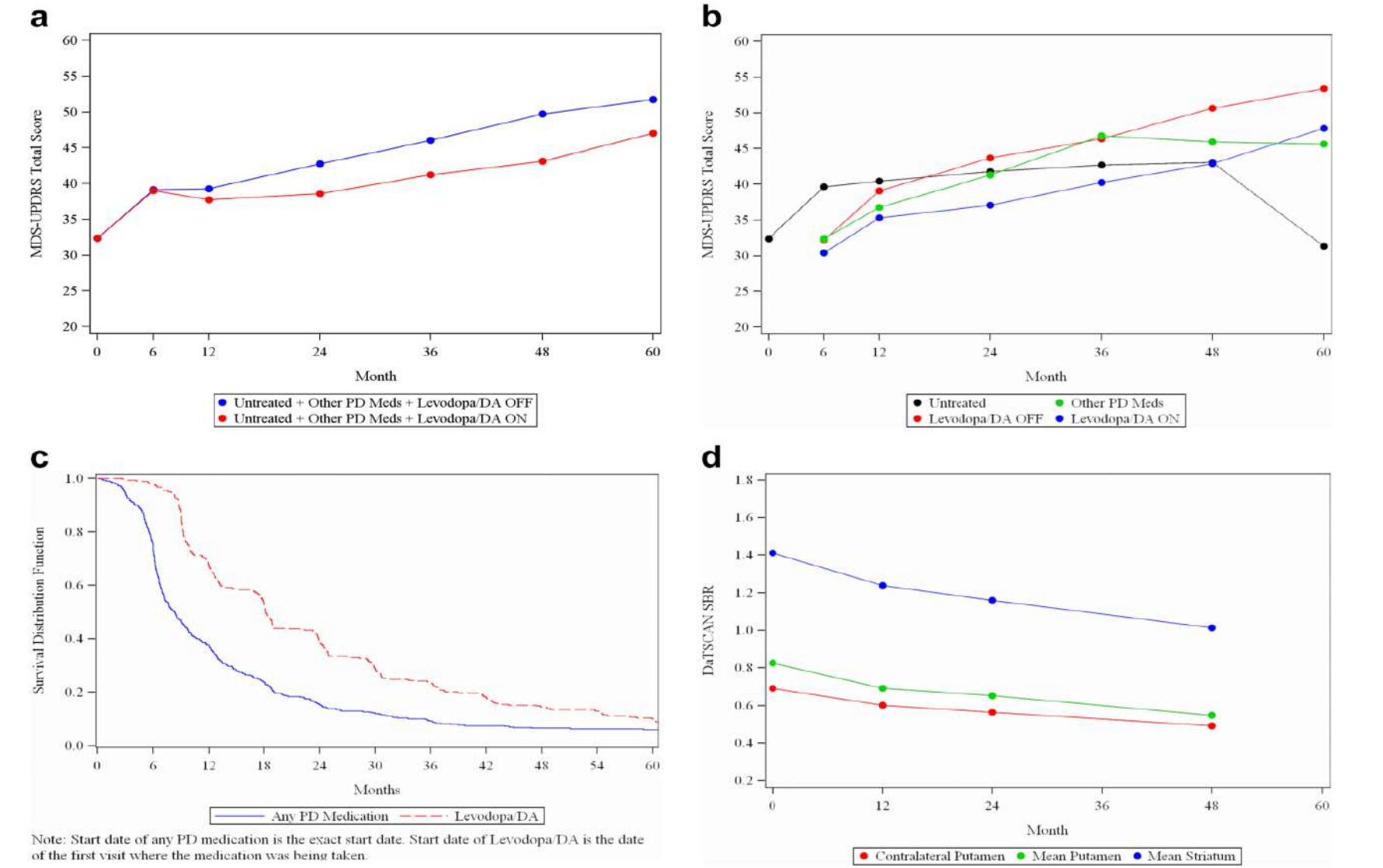
Parkinson Study Group N Engl J Med 2004;351(24):2498-508

From: **Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease: A 4-Year Randomized Controlled Trial**

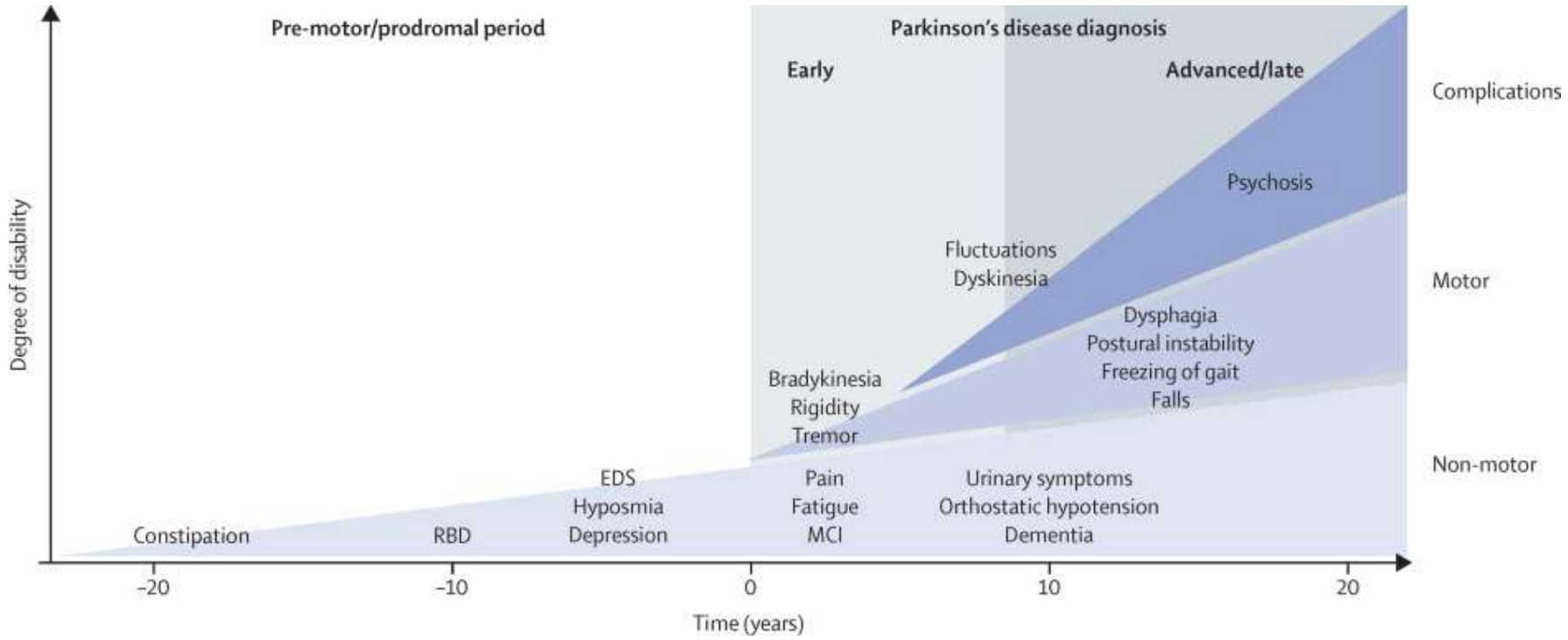
Arch Neurol. 2004;61(7):1044-1053. doi:10.1001/archneur.61.7.1044



Longitudinal Change of Clinical and Biological Measures in Early Parkinson's Disease: Parkinson's Progression Markers Initiative Cohort



Longitudinal Change of Clinical and Biological Measures in Early Parkinson's Disease: Parkinson's Progression Markers Initiative Cohort, Volume: 33, Issue: 5, Pages: 771-782, First published: 23 March 2018, DOI: (10.1002/mds.27361)



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Parkinson's disease. Lancet 2015

From: **Effect of Creatine Monohydrate on Clinical Progression in Patients With Parkinson DiseaseA Randomized Clinical Trial**

JAMA. 2015;313(6):584-593. doi:10.1001/jama.2015.120

Table 2. Components of the Global Statistical Test by Treatment Group for LS-1 Cohort 1; Change From Baseline to Year 5[a]

Components Included in the Computation of Global Outcome	Treatment Group, Mean (SD)		Difference, Mean (95% CI)[b]
	Placebo (n = 478)	Creatine (n = 477)	
Ambulatory capacity score	2.8 (5.0)	3.1 (5.5)	−0.3 (−1.0 to 0.4)
Modified Rankin[c]	2.1 (1.5)	2.2 (1.6)	−0.1 (−0.3 to 0.1)
PDQ-39 Summary Index	13 (23.2)	14.2 (23.5)	−1.2 (−4.2 to 1.7)
Schwab and England ADL[d]	14.8 (26.0)	16.8 (28.3)	−2.0 (−5.5 to 1.5)
Symbol Digit Modalities[d]	4.5 (16.8)	4.9 (17.7)	−0.4 (−2.7 to 1.8)

Abbreviations: ADL, activities of daily living; LS-1, Long-term Study 1; PDQ-39, 39-Item Parkinson's Disease Questionnaire.

[a] Cohort 1 includes those participants (n = 955) eligible for a 5-year follow-up visit at the time ofinterim analysis (July 17, 2013). Missing values are imputed.

[b] Placebo-treatment as reference group.

[c] Modified Rankin is the actual score at 5 years. All others outcomes are change from baseline to 5 years.

[d] Reverse coded such that higher scores indicate worse outcomes. Higher raw values are worse for all outcomes.

Comp

From: **Effect of Creatine Monohydrate on Clinical Progression in Patients With Parkinson Disease A Randomized Clinical Trial**

Table 3. Secondary Outcome Measures for Cohort 1[a]

Outcomes	Placebo		Creatine		Difference, Mean (95% CI)
	No.	Mean (SD)	No.	Mean (SD)	
Total LEDD, (mean at year 5), mg[b]	365	782 (408)	366	738 (401)	45 (−14 to 103)
UPDRS (mean change)[c]					
Total	336	10.4 (13.8)	330	11.3 (15.3)	−0.9 (−3.1 to 1.3)
Mental	339	1.1 (1.8)	333	1.2 (1.9)	−0.1 (−0.4 to 0.1)
ADL	339	4.0 (5.1)	333	4.5 (5.7)	−0.5 (−1.3 to 0.3)
Motor	336	5.3 (9.8)	330	5.6 (10.2)	−0.2 (−1.8 to 1.3)
Total functional capacity (mean change)[c]	343	−1.7 (2.4)	334	−1.9 (2.7)	0.2 (−0.2 to 0.6)
Scales for Outcomes in Parkinson disease-Cognition (mean change)[c]	315	−2.0 (4.9)	309	−1.9 (5.4)	−0.1 (−0.9 to 0.7)
EQ-5D (mean change)[c]	342	−0.1 (0.2)	334	−0.1 (0.2)	0.005 (−0.03 to 0.04)
BDI score (mean at year 5)[c]	335	8.5 (6.7)	329	8.6 (6.3)	−0.1 (−1.1 to 0.9)
BDI score >17 (at year 5), No. (%)[b]	335	29 (8.7%)	329	29 (8.8%)	0.002 (−0.04 to 0.04)
BMI, mean change[c,d]	341	−0.4 (3.3)	338	−0.1 (2.9)	−0.3 (−0.8 to 0.2)

Abbreviations: ADL, activities of daily living; BDI, Beck Depression Inventory; BMI, body mass index; EQ-5D, EuroQOL instrument; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson Disease Rating scale.

[a] Data reported from final interim analysis (July 17, 2013) with the exception of BMI and total LEDD, which are reported from the final locked database (May 5, 2014).

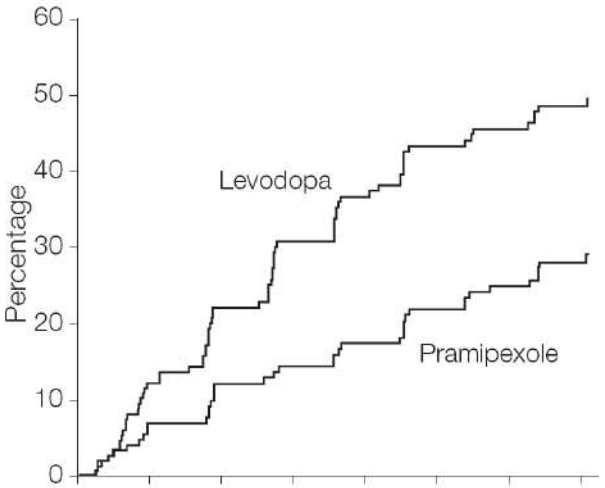
[b] Values are means at year 5; BDI score greater than 17 is the difference in proportions at year 5.

[c] Values are mean change from baseline to year 5.

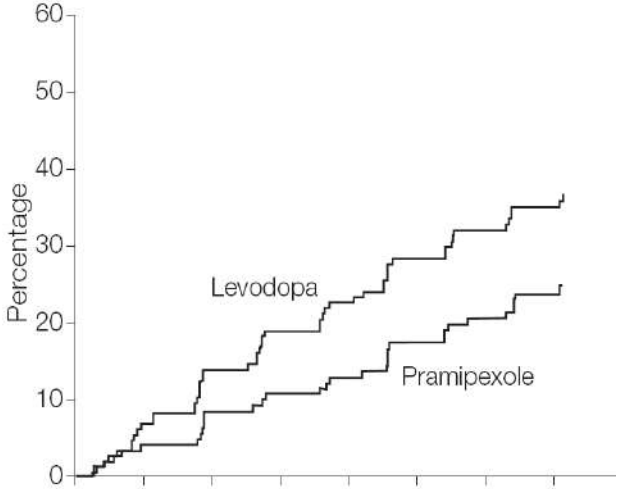
[d] Calculated as weight in kilograms divided by height in meters squared.

Pramipexole vs. Levodopa as Initial Treatment for Parkinson Disease. A randomized Controlled Trial

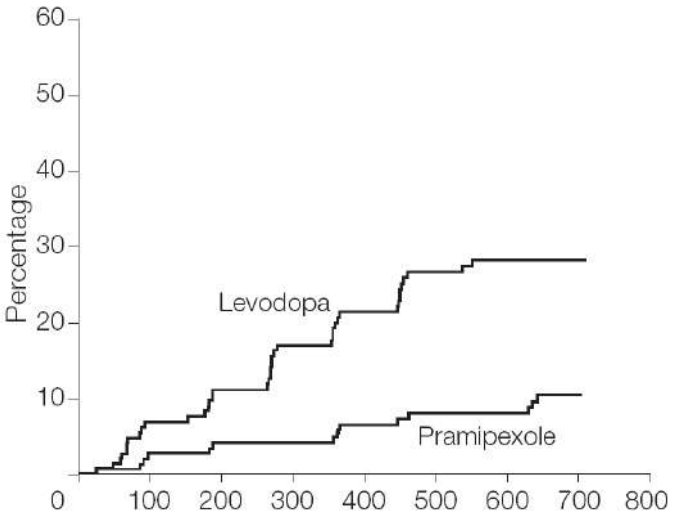
first dopaminergic complication



wearing-off

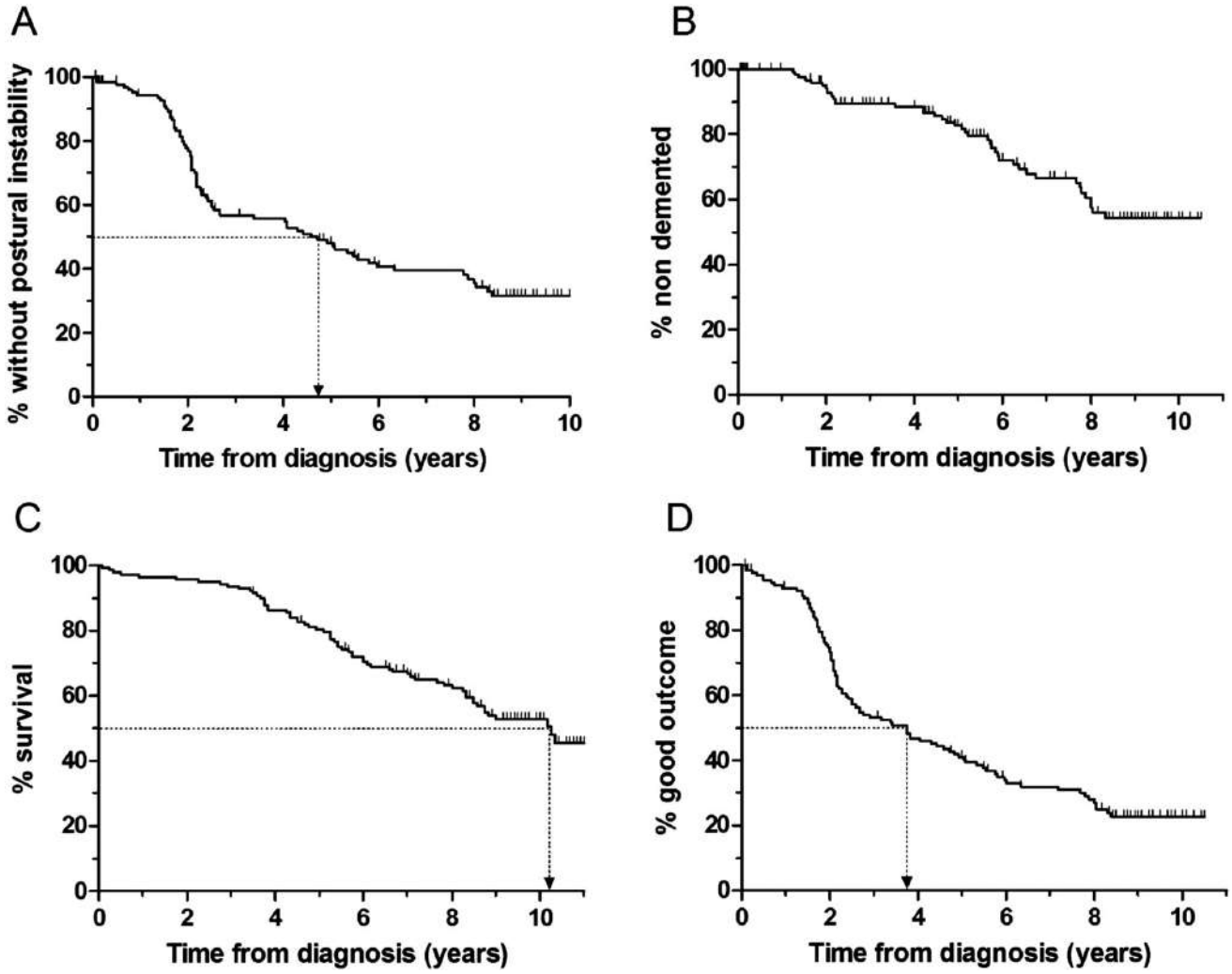


dykinesias



PSG JAMA 2000; 284:1931-1938

Kaplan–Meier survival curves illustrating the cumulative probability of (A) remaining free of postural instability, (B) remaining free of dementia, (C) survival, (D) maintaining a good outcome (surviving without postural instability or dementia).



Caroline H Williams-Gray et al. J Neurol Neurosurg Psychiatry 2013;84:1258-1264

JNNP

Despite our Knowledge Base, Traditional Clinical Trials have Failed What new methods may help?

Complex Innovative Trial Designs may allow more response to emerging data in trial execution (Adaptive Designs)

The FDA has made multiple efforts to advance this effort: public meetings, guidance, pilot programs, and publications

Emerging clinical and biological data may help us identify meaningful subsets (eg genetic subgroups) to target with specific therapies

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research (CDER)/Center for Biologic Evaluation and Research (CBER)

Public Meeting on Promoting the Use of Complex Innovative Designs in Clinical Trials
FDA Great Room, Building 31, Room 1503
10903 New Hampshire Avenue, Silver Spring, MD 20993-0002

March 20, 2018

AGENDA

Meeting Website: https://www.fda.gov/Drugs/NewsEvents/ucm587344.htm
Docket No. FDA-2018-N-0049

Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018
Clinical/Medical

Complex Innovative Designs

Why the need to innovate?

- Small populations: leverage other data sources to provide additional power
- Improve decision-making when reliable prior information is available
- Optimize product development with coordinated trial structures

→Ensure the trial will be able to answer the relevant questions and provide regulators with information needed for decisions

Innovative Design Possibilities

- Adaptive randomization and/or adaptive enrichment
- Use of external or historical control data
  - In conjunction with concurrent controls (with 2:1 or higher randomization ratios); potential adaptation to ratio based on similarity between two sources of controls
- Sharing of control groups across protocols – *within a specific pathway or marker subgroup*
- Model-based analysis methods (e.g., hierarchical Bayes) for pooled analysis of multiple disease or tumor types, markers, body sites, etc.

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

N Engl J Med
Volume 377(1):62-70
July 6, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Types of Master Protocols.

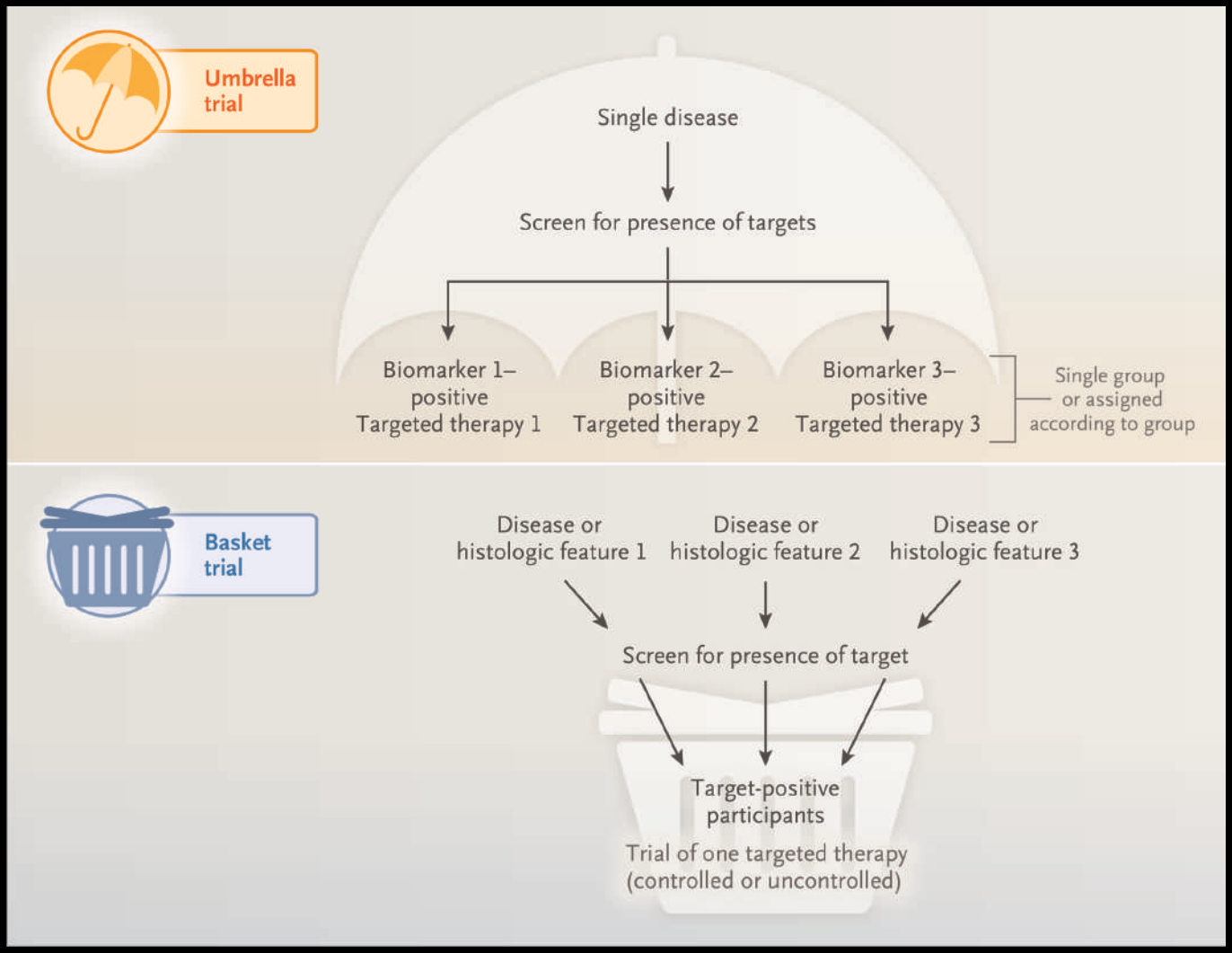
Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock J, LaVange LM. N Engl J Med ;377:62-70

The NEW ENGLAND JOURNAL of MEDICINE

Umbrella Trial and Basket Trial.



Woodcock J, LaVange LM. N Engl J Med ;377:62-70

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Master Protocols

- Multiple diseases, multiple patient subgroups (biomarker-defined), and/or multiple therapies studied under one, over-arching protocol*
  - I-SPY 2, Lung-MAP, DIAN-TU, ADAPT
- Areas of innovation:
  - Establish a trial network with infrastructure in place to streamline trial logistics, improve data quality, and facilitate data sharing and new data collection
  - Develop a common protocol for the network that incorporates innovative statistical approaches to study design and data analysis

- **Segmentation**
- Adaptation
- Simulation and Disease modeling
- Remote Sensing and Automation

Segmentation-
Are there relevant populations?

Genetic forms or modifiers of the disease

Clinical subsets based on phenotype

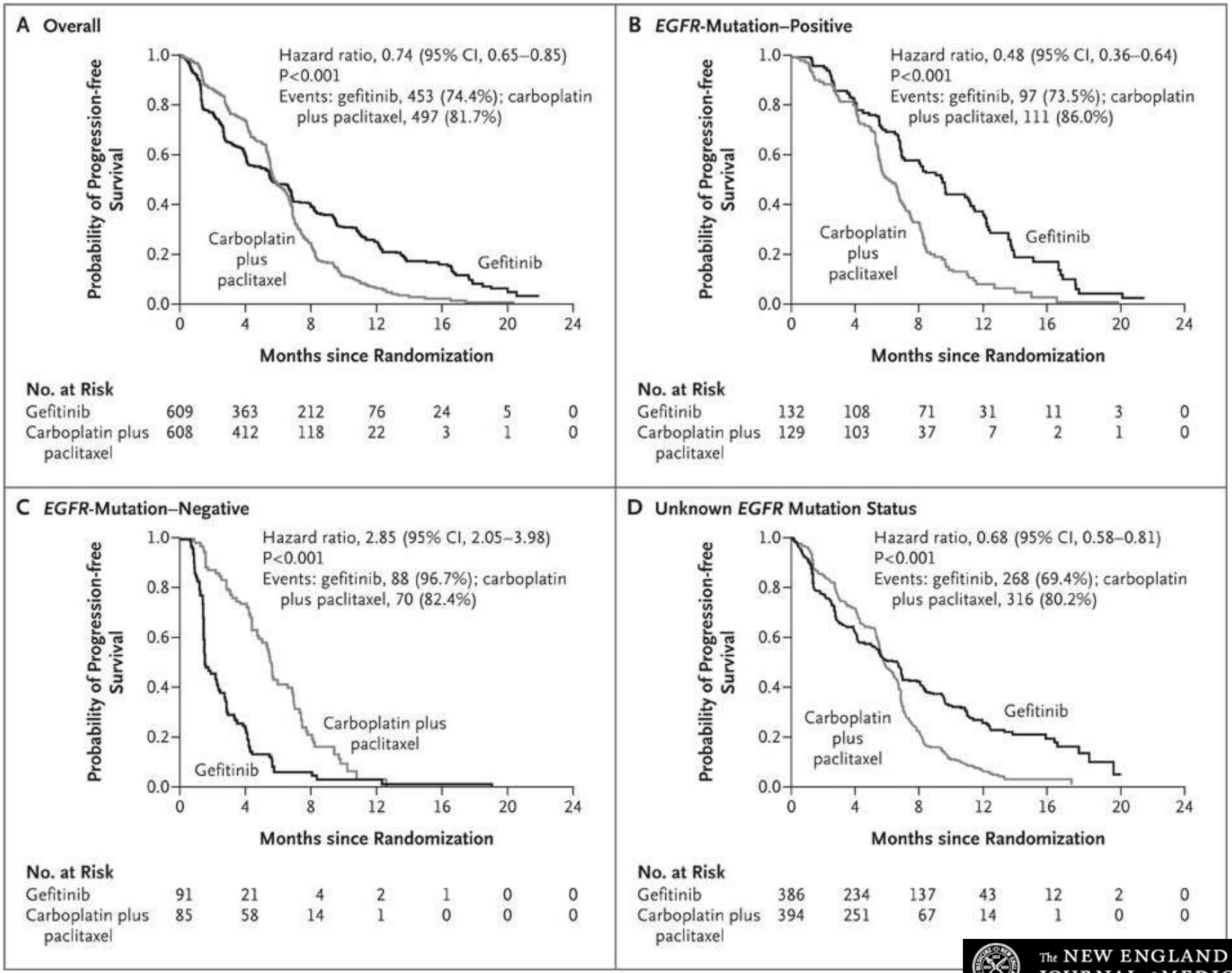
Will subsets (mechanistic or phenotype) have different treatment responses?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.



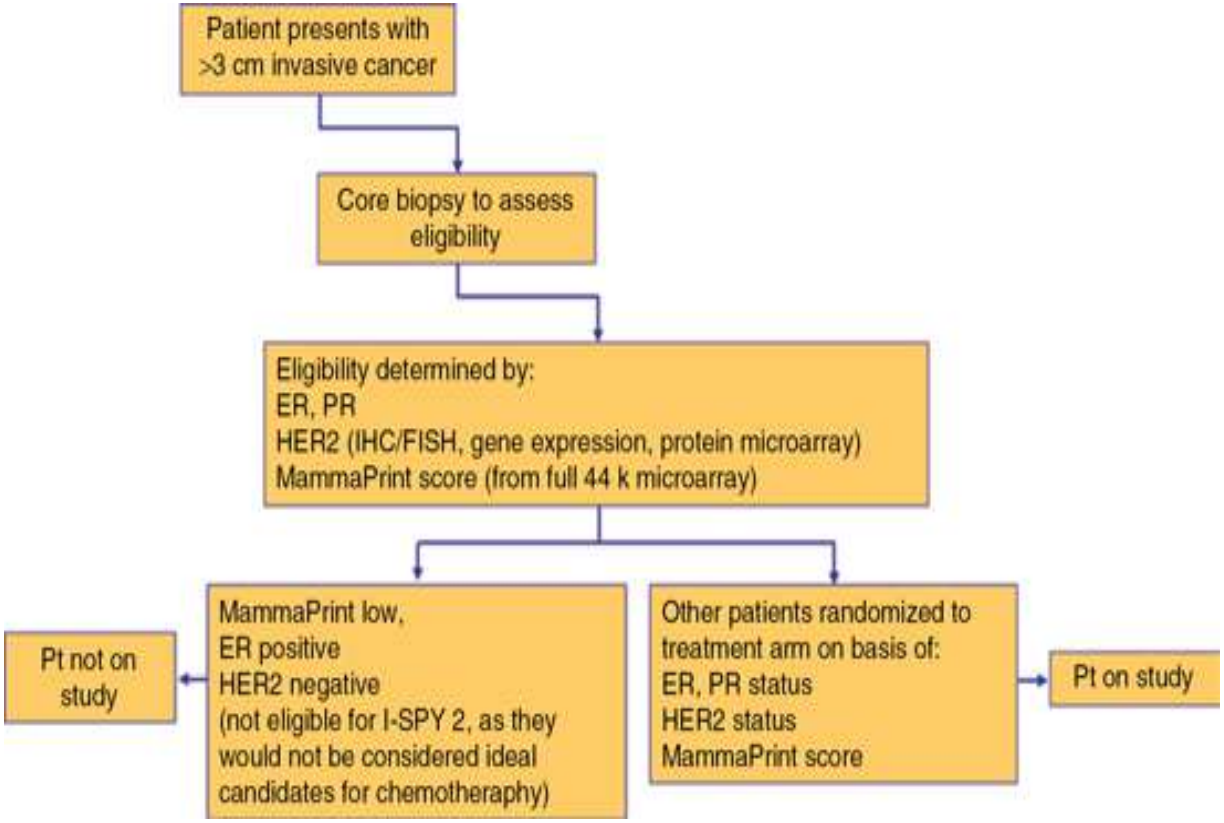
Considerations for Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease

Robert N. Schuck[1], Janet Woodcock[2], Issam Zineh[1], Peter Stein[3], Jonathan Jarow[2], Robert Temple[2], Thomas Permutt[4], Lisa LaVange[4], Julia A. Beaver[3], Rosane Charlab[1], Gideon M. Blumenthal[3], Sarah E. Dorff[1], Christopher Leptak[3], Steven Lemery[3], Hobart Rogers[1], Badrul Chowdhury[3], E. David Litwack[5] and Michael Pacanowski[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 104 NUMBER 2 | AUGUST 2018

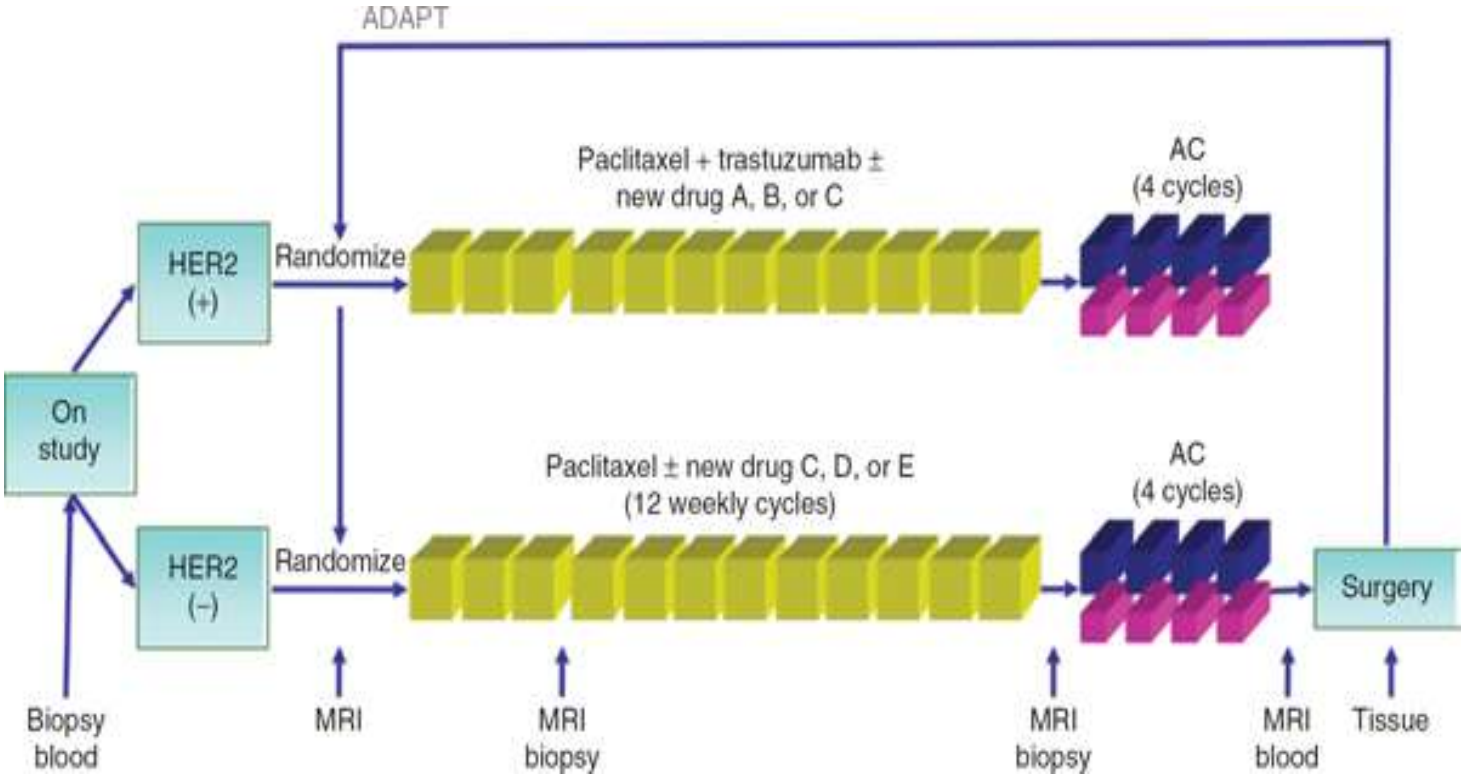
- Segmentation
- **Adaptation**
- Simulation and Disease modeling
- Remote Sensing and Automation

I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy



Clinical Pharmacology & Therapeutics
pages 97-100, 13 MAY 2009 DOI: 10.1038/clpt.2009.68

I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

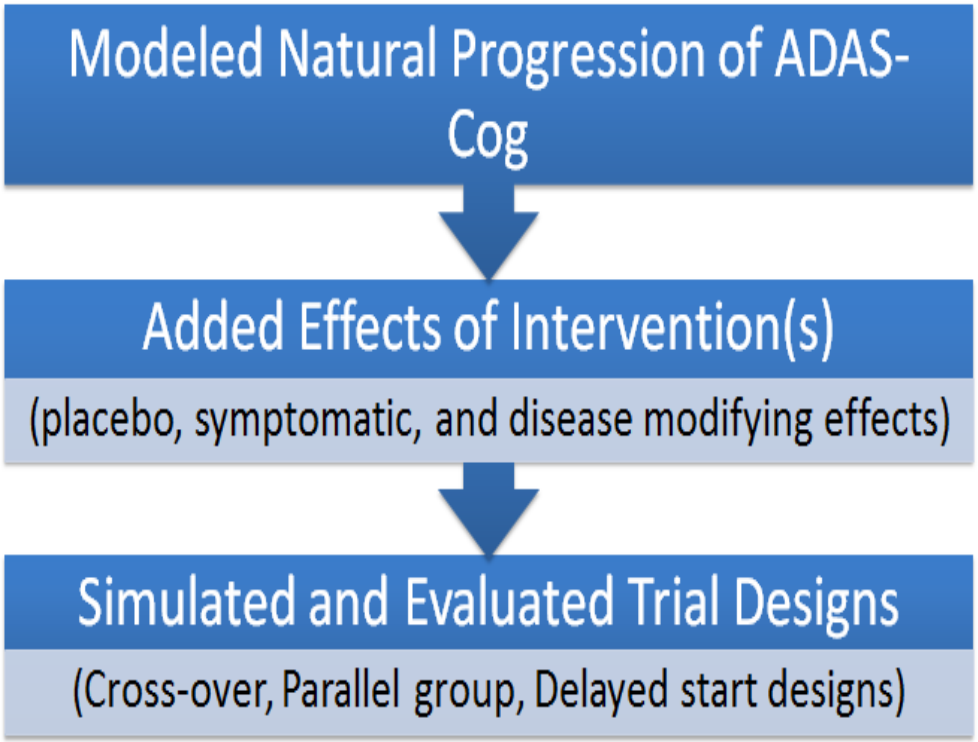


Clinical Pharmacology & Therapeutics
pages 97-100, 13 MAY 2009 DOI: 10.1038/clpt.2009.68

- Segmentation
- Adaptation
- **Simulation and Disease modeling**
- Remote Sensing and Automation

A quantitative model to track cognitive changes in mild-to-moderate Alzheimer's Disease

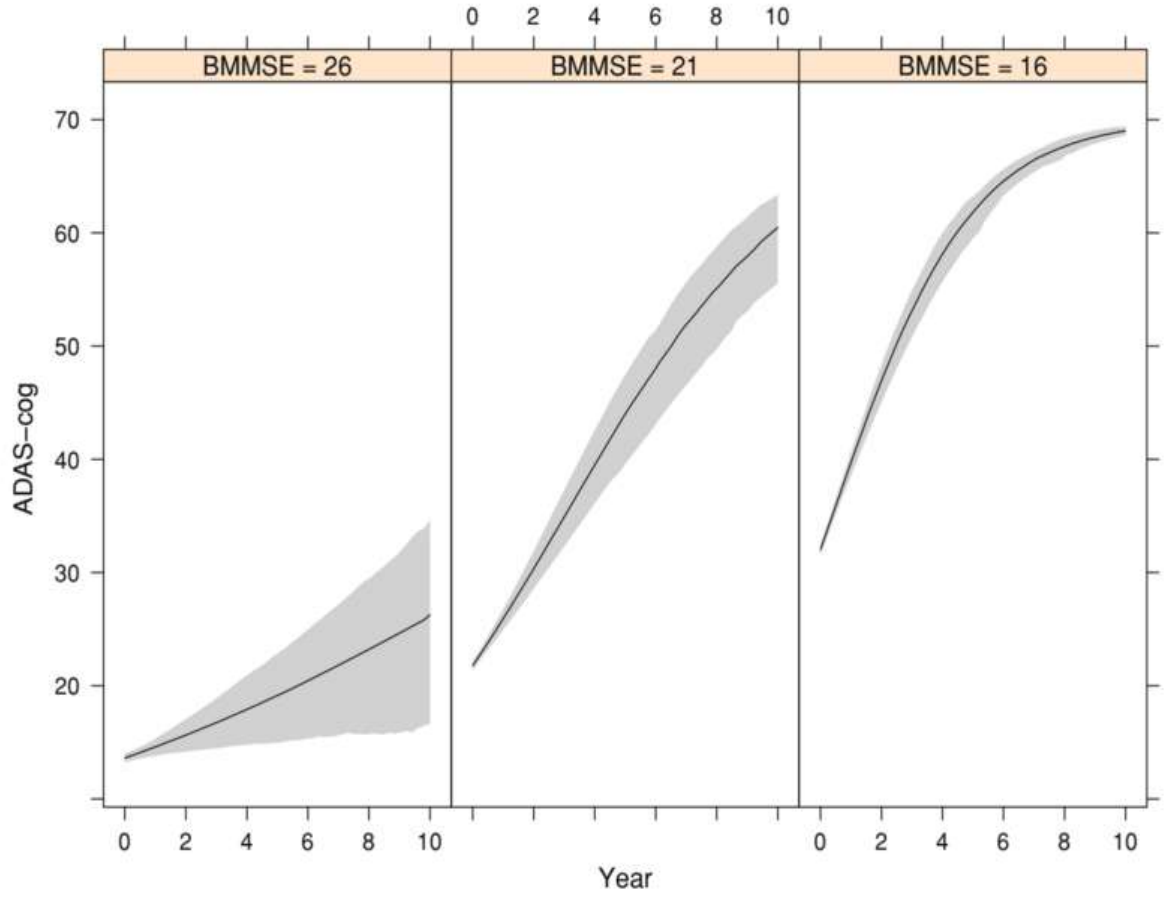
The model described disease progression, drug effects, dropout rates, placebo effect, and sources of variability



Deemed by the Food and Drug Administration as "fit for purpose" and the European Medicines Agency as "suitable for qualification"

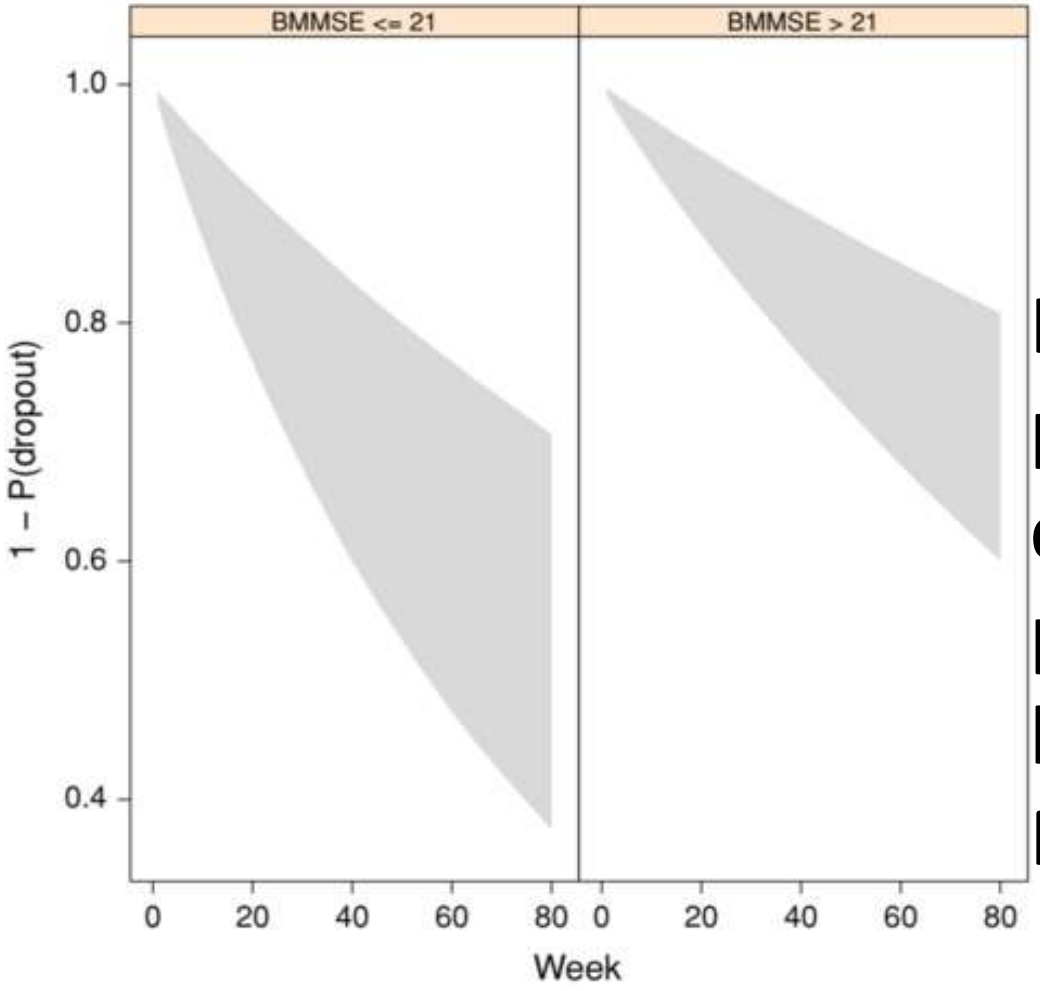
Corrigan B. CAMD M&S Workshop 2013

Covariate effects that accounted for baseline severity of cognition (baseline Mini Mental Status Examination), *APOE* genotype status, and baseline age as predictors of progression rate



More rapid progression with lower baseline MMSE

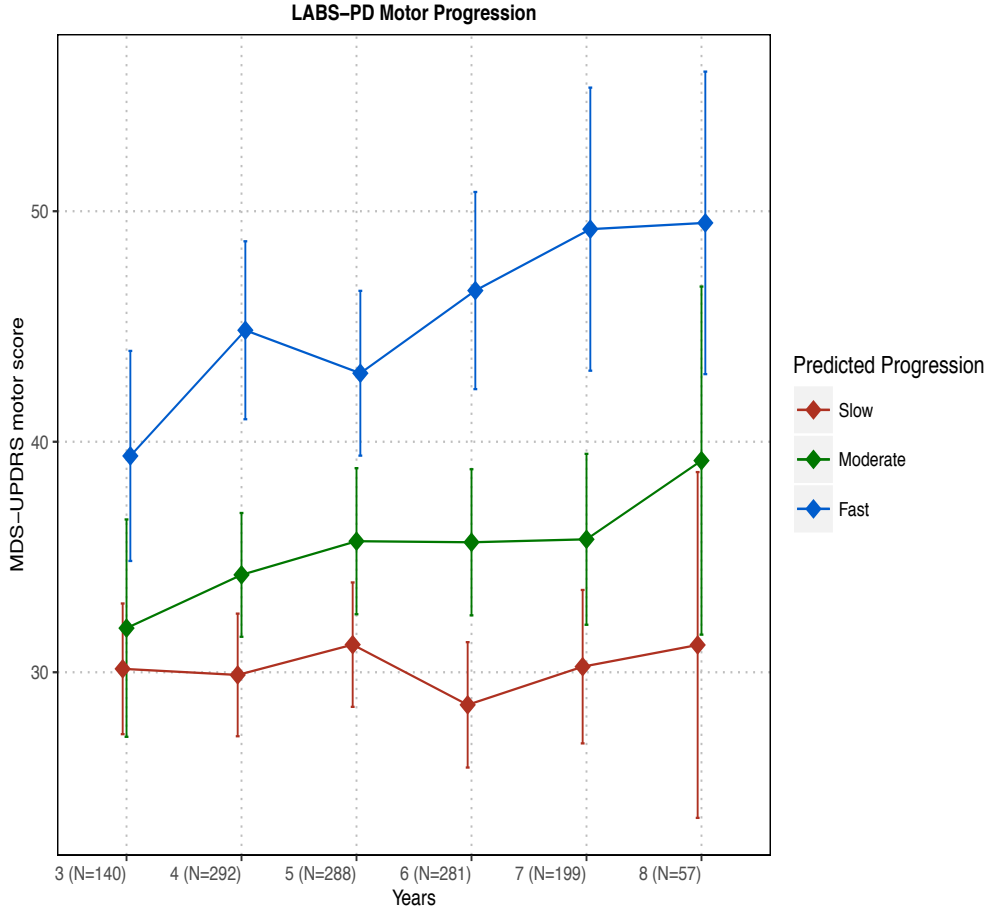
The use of baseline age and baseline cognitive severity as covariates on the hazard of drop-out



Higher probability of drop-out in patients with lower baseline MMSE

We can unequivocally identify patients with rapid PD progress

Observed MDS-UPDRS Motor Progressions Separated by Model-Predicted Baseline Progression Categories



Movement disorders have external manifestations that smartphones can assess

Figure 1: Picture of Android smartphone and software application.

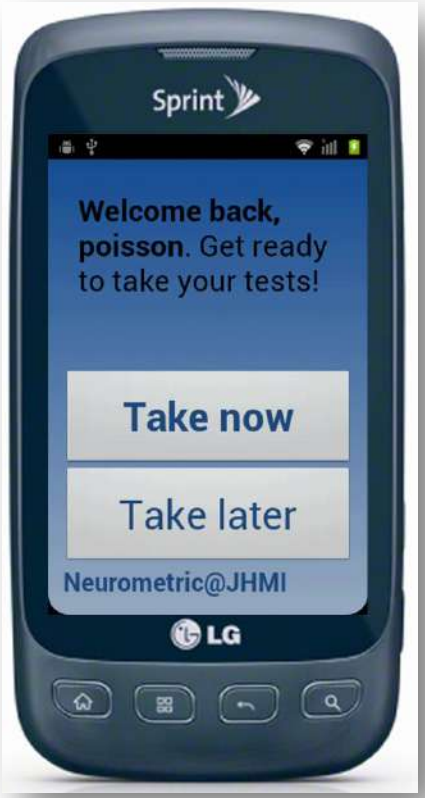
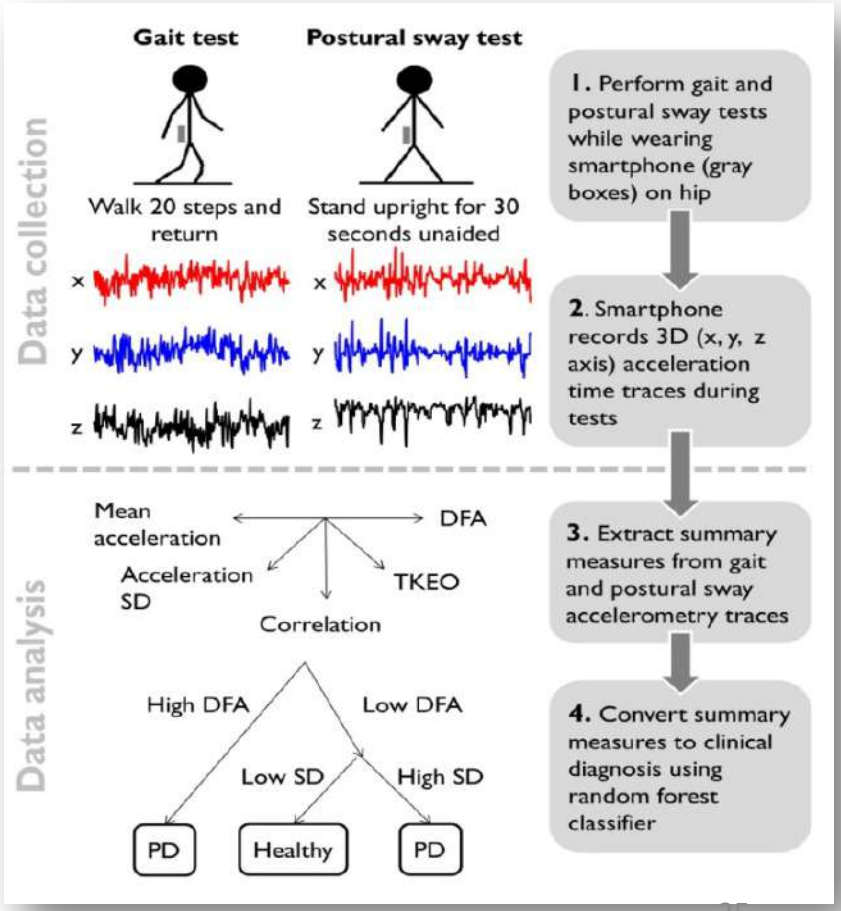


Figure 2: Procedure for collecting voice recordings, finger tapping, and passive sensor data from gait and postural sway test

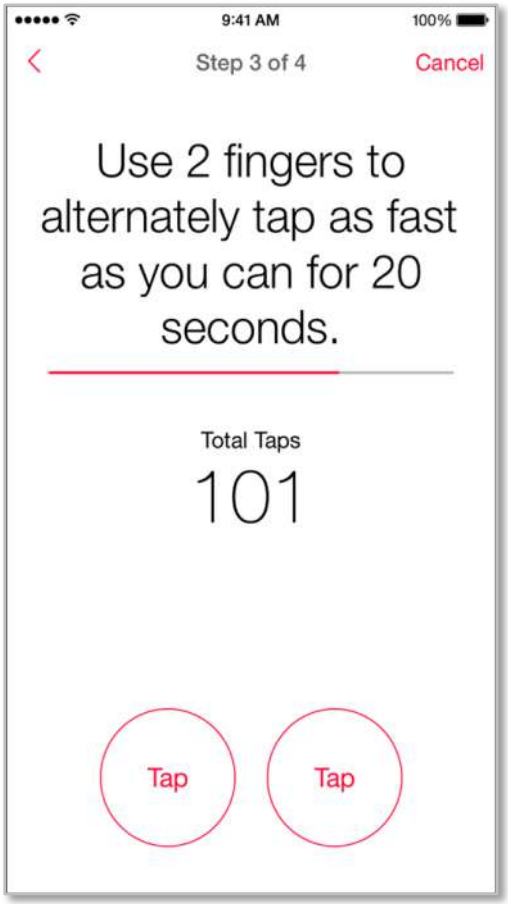


Source: Parkinsonism & Related Disorders, http://dx.doi.org/10.1016/j.parkreldis.2015.02.026.

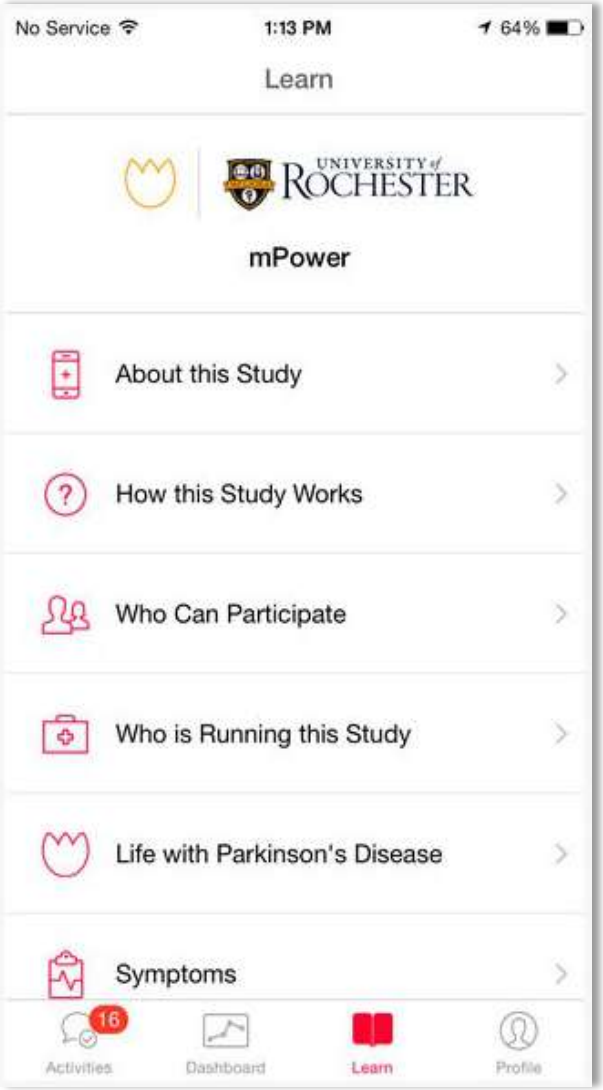
In March 2015 Apple announced the release of smartphone applications for medical research

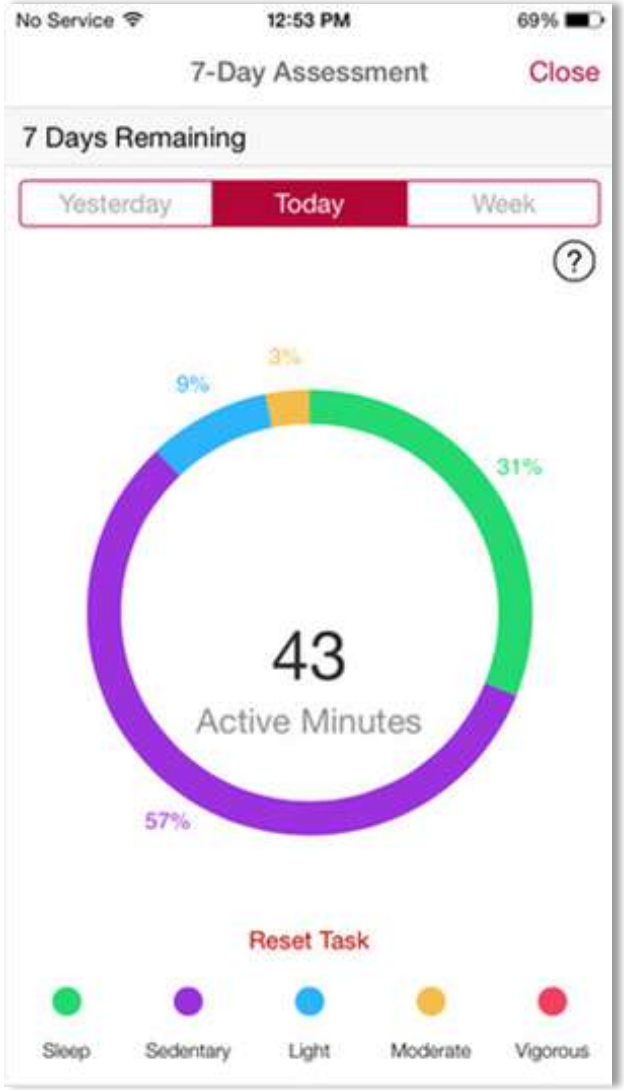
mPower smartphone application for Parkinson disease

mPower includes surveys, structured tests of cognition, speech, speeded taps, speed and gait



This technology is currently being used in clinical trials to capture objective measures of Parkinson disease





Will new Methods help?

Our track record is not efficient or effective, yet…

We need to at least attempt something new

There is strong support from regulators (US)

We have additional resources to guide Complex Innovative Designs, including large natural history cohorts, increased biological and imaging data, and existing trial collaborations.

Sensor/dense data may provide actionable information earlier than traditional methods of data collection

While the methods are yet unproven in PD, the success in Oncology is encouraging, and we should Innovate!