Aging Neuroscience: Udall Center for Excellence in Parkinson Disease

Erika Augustine, MD, MS

on behalf of Ray Dorsey, MD, MBA

Associate Director, Center for Human Experimental Therapeutics

UNIVERSITY of ROCHESTER

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Center for Human Experimental Therapeutics

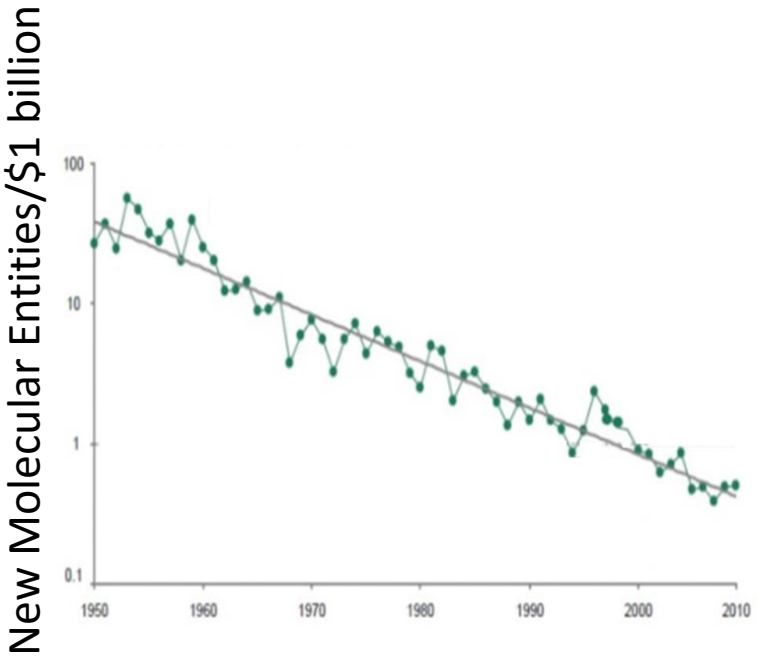
Vision: To enable anyone, anywhere, to participate in research, benefit from therapeutic advances, and receive care.

HEALTH AND TECHNOLOGY UNIT

CLINICAL TRIALS COORDINATION CENTER

CLINICAL MATERIALS SERVICES UNIT

Drug development productivity is declining; new methodological models are needed



Characteristic	20th Century	21st Century
Study design	Randomized, double-blind, parallel-group, placebo-controlled trial	Randomized, double-blind, parallel-group, placebo-controlled trial using adaptive designs
Study population	All comers with a given disease	Individuals selected based on phenotypic and genetic results
Study recruitment	Clinical practices	Global clinical trial registries and social networks organized by individuals affected by the disease
Trial visits	In person and audio calls	In person and audio and video calls
Data management	Paper and electronic forms	Electronic forms
Participant feedback	Limited, delayed	Almost universal, approximately real time
Outcome measures	Insensitive	Sensitive
	Episodic	Frequent or continuous
	Subjective	Objective
	Provider centered	Patient centered
	In clinic	Remote
	Unidimensional	Multidimensional

Source: JAMA Neurology 2015;72:582-8;
http://www.forbes.com/sites/matthewherper/2011/06/27/the-decline-of-pharmaceutical-researchmeasured-in-new-drugs-and-dollars/

Udall Centers define the causes of and discover improved treatments for Parkinson disease

Udall Centers – at a glance

Background: Funded by Morris K. Udall Parkinson's Disease Research Act of 1997 in honor of long-serving Representative Morris Udall, who had PD

Goal: "To rapidly advance synergistic, interdisciplinary research programs while serving as national leaders in PD research." Stated theme will "inform the etiology, pathogenesis, or **treatment** of PD"

Centers: 9 nationwide

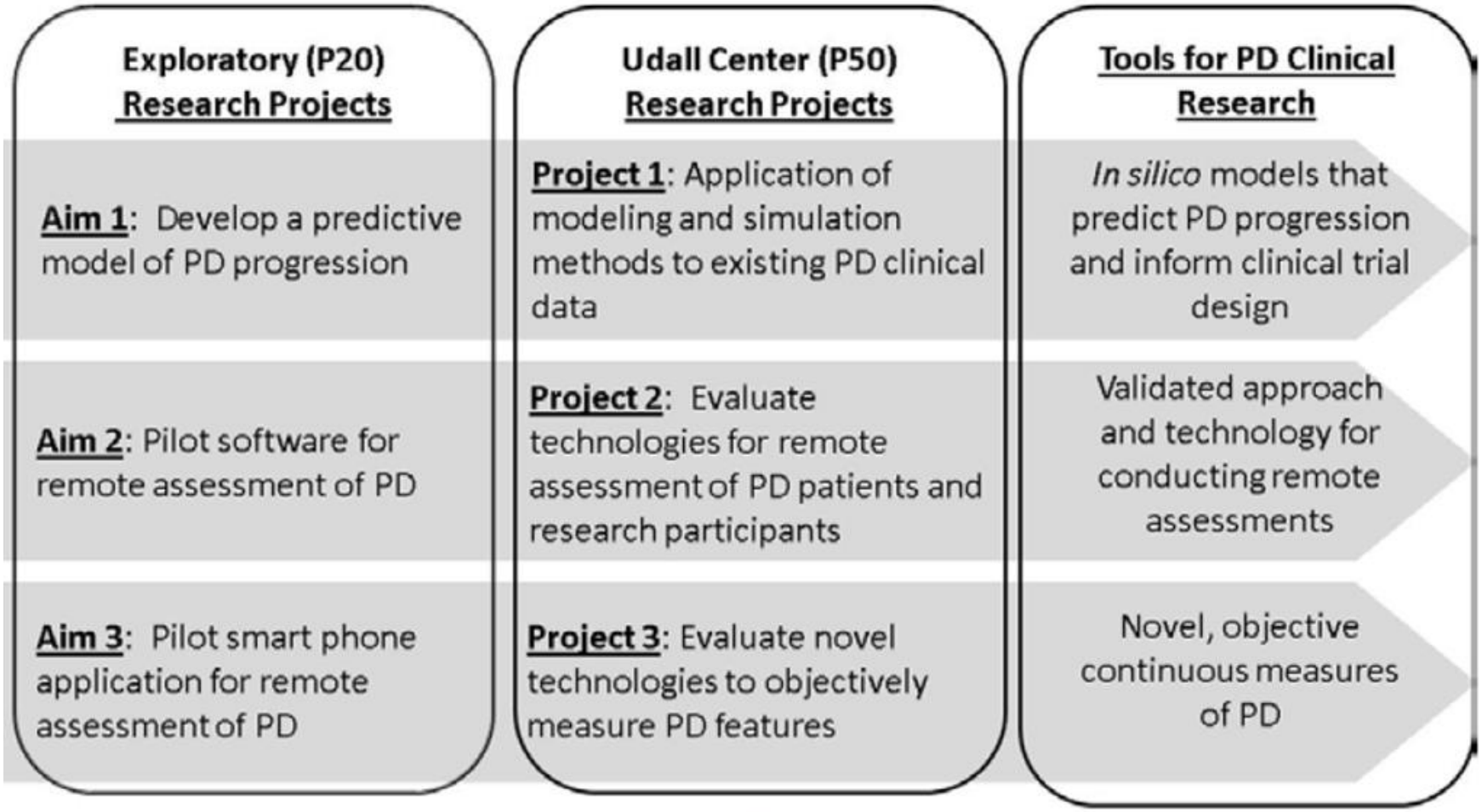
Required components:

- Administrative Core
- At least one integrated Research Core to support at least two research projects
- At least three Research Projects
- Mission statement
- Plan for periodic outreach activities
- Clinical research core if at least one Clinical Research Project is proposed

Source: RFA-NS-16-002

In the P20 planning grant, we outlined three research projects

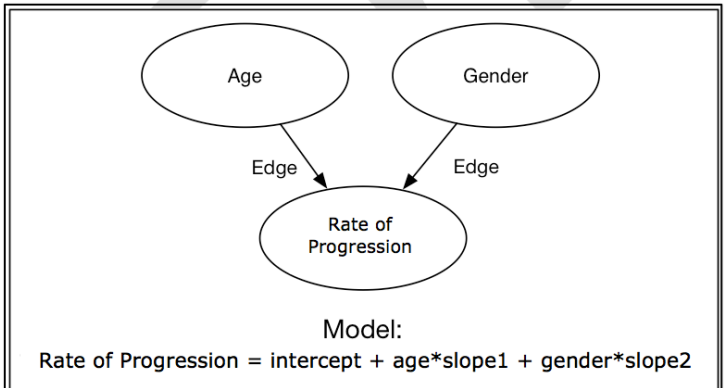
Proposed transition from P20 to Udall Center Research Projects



Developing Predictive Models of PD Progression

- Reverse Engineering and Forward Simulation (REFS™) to generate prediction models for progression
  - Uses Bayesian inference, modeling directly from data without pre-specified hypotheses
  - Produces ensemble of models sampled from the Bayesian posterior

- Three outcomes (rate of progression) modeled separately
  - Motor (MDS-UPDRS Parts II and III)
  - Cognition (MoCA)
  - Functional and Behavioral (MDS-UPDRS Part I)



Predictors to be evaluated for the longitudinal endpoints of interest

Cohort	Clinical Variables	Genotyping	Endpoints
PD (Including SWEDD patients) N=241 Healthy Control N=109	**Demographics** Age, Gender, Race, Ethnicity, Education **Medical History** Family history of PD, PD medication use, Tremor-dominance, Primary affected side, REM sleep disorder **Baseline Clinical Tests** DatSCan imaging, Evidence of dopaminergic deficit (SWEDD flag), UPSIT **Baseline Levels of Disease Severity** Montreal Cognitive Assessment (MoCA), MDS-UPDRS **Baseline CSF Protein Tests** β-amyloid1-42, α-synuclein, Total tau, Phosphorylated tau181	**ImmunoChip** Illumina Infinium iSelect HD Custom Genotyping array	**Rate of decline across 3+ years of follow-up** Cognitive: Montreal Cognitive Assessment (MoCA) (N=345) Motor: MDS-UPDRS, Part II & III (N=333) Functional & Behavioral: MDS-UPDRS, Part I (N=333)

Testing the feasibility of Virtual Visits

Pilot randomized, controlled study of telemedicine for Parkinson disease

4 nursing home residents with PD

10 individuals from the local community with PD

3 telemedicine visits over 6 months

"Usual care" for 6 months

3 telemedicine visits over 6 months

Outcomes

Primary outcome

- Feasibility as measured by proportion of telemedicine visits completed as scheduled

Secondary outcomes

- Reliability and validity of the UPDRS motor examination
- Quality of life
- Patient satisfaction
- Motor performance
- Mood
- Cognition

Telemedicine visits were feasible
Remote assessment of the UPDRS was reliable
(remote v in-person ICC 0.78; test-retest remotely ICC 0.82)

Source: Pilot randomized controlled trial of telemedicine for individuals with Parkinson disease. International Congress of Parkinson's Disease and Movement Disorders. June 7-11, 2009.

A modified UPDRS conducted remotely is cross-sectionally and longitudinally valid

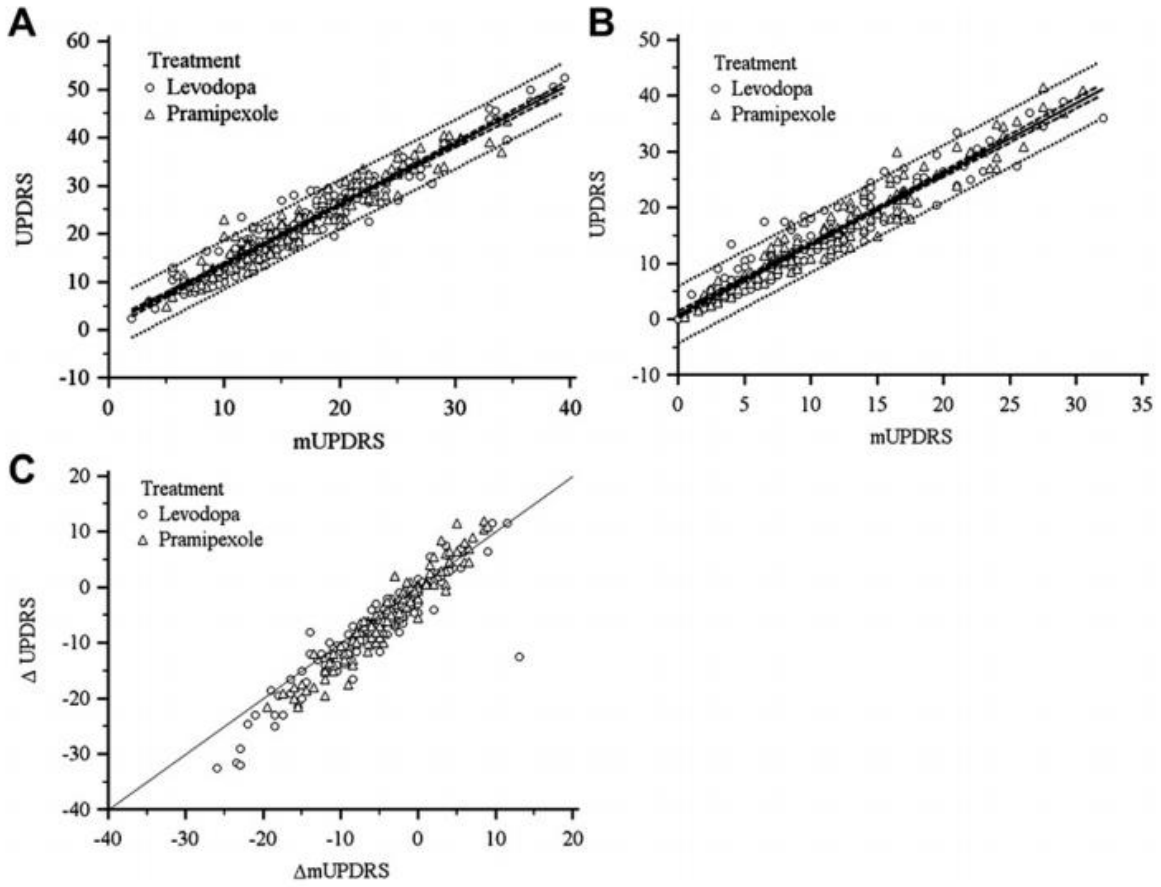


Fig. 1. Scatter plots for (A) modified motor UPDRS (mUPDRS) versus standard motor UPDRS at baseline, (B) mUPDRS versus UPDRS at 2-year follow-up, and (C) change from baseline to 2-year follow-up for mUPDRS versus UPDRS. Solid lines represent best-fit linear regression line (plots A and B) and line of identity (plot C). For plots A and B, dashed line represents 95% confidence interval and dotted line represents 95% prediction interval about the best-fit line.

Parkinsonism Relat Disord. 2013 Feb; 19(2): 218–221.

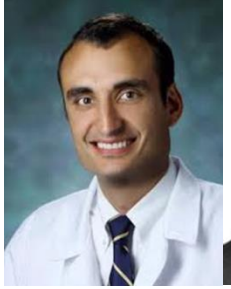
REACT-PD Study Design

- Observational study assessing feasibility of conducting virtual research visits in a subset of individuals with early PD participating in an ongoing clinical trial (STEADY-PD III)
- 40 participants in STEADY-PD III who consented to be contacted for future research will be enrolled and followed for up to 12 months
- Virtual Research visits to occur within 4 weeks *after* in-person clinical trial visit
- Virtual research visits will collect the same data as is collected at the corresponding in-person visit and include:

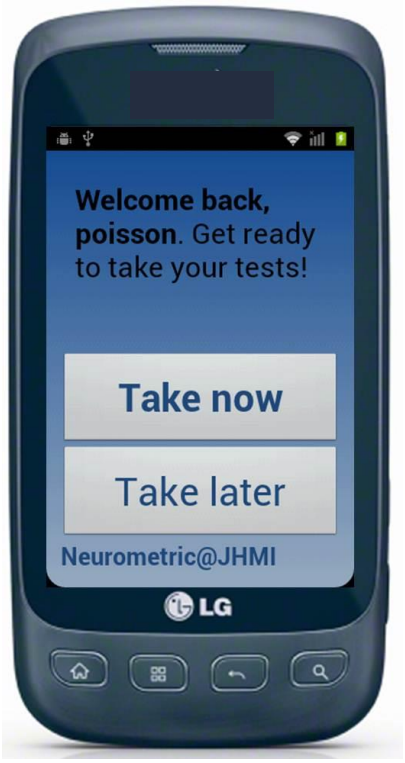
Every Visit	Annual Visit Only
UPDRS I-IV*	MDS UPDRS
Hoen and Yahr	MoCA
Schwab and England ADL	PDQ-39
C-SSRS	
Concomitant medications	
Evaluate need for therapy	
Participant/investigator surveys	

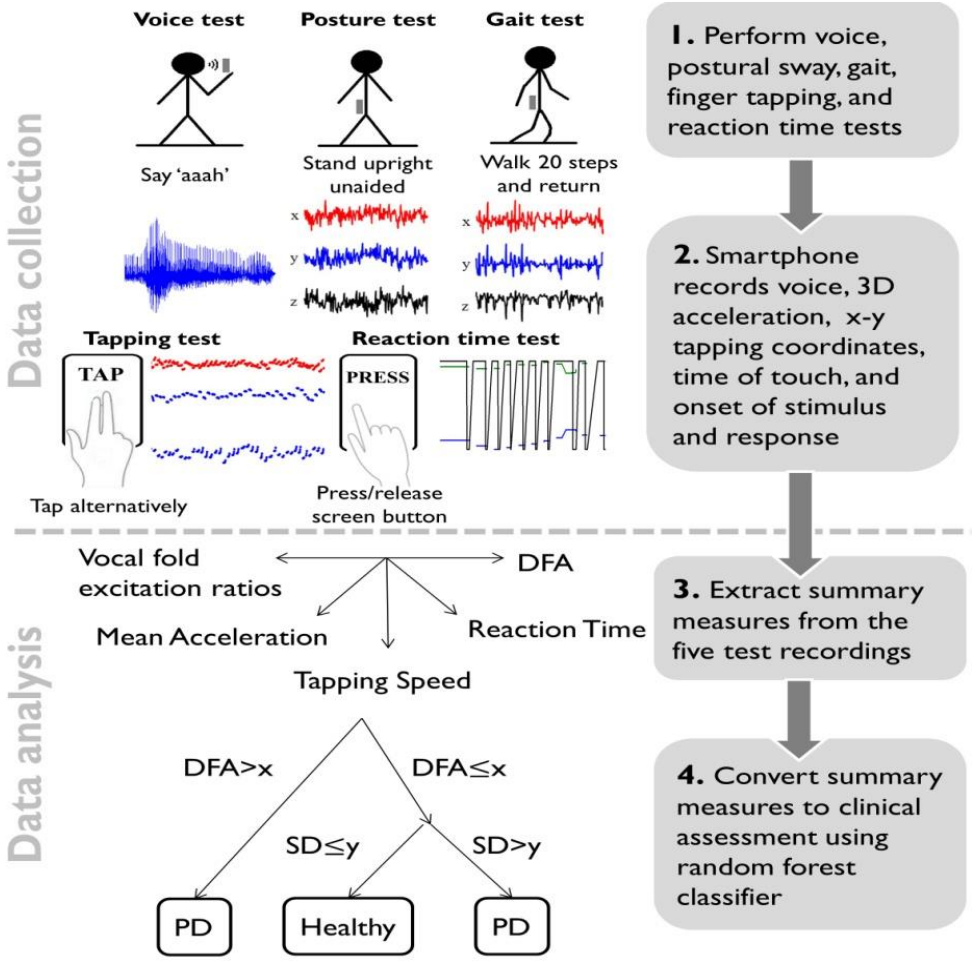
*Primary outcome measure of STEADY-PDIII

Software applications for remote measurement



Pilot smartphone study in Parkinson disease



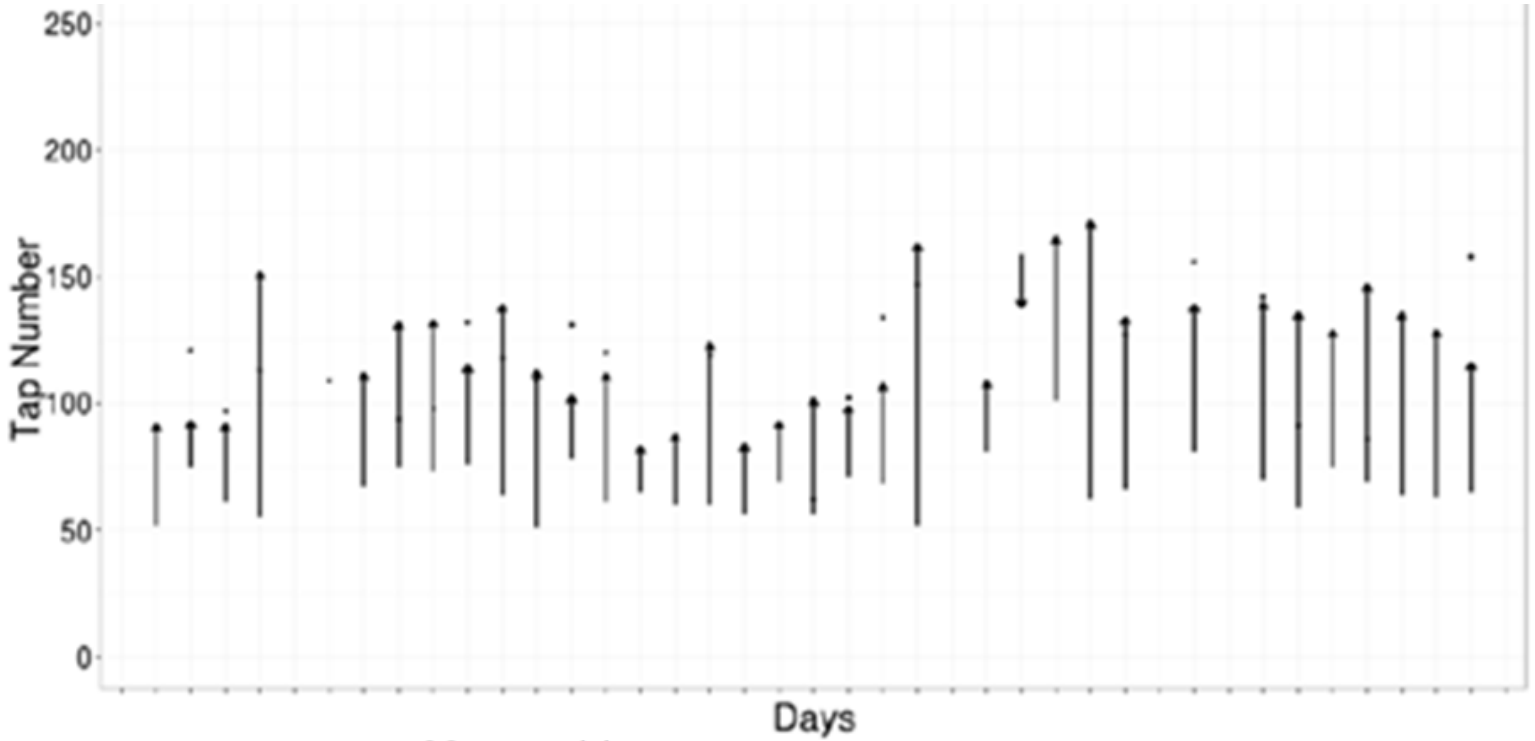


DFA = detrended fluctuation analysis; TKEO = Teager-Kaiser energy operator

Source: Parkinsonism & Related Disorders 2015 Jun;21(6):650-3

These apps can detect responses from dopaminergic medications

Tapping frequency in individual with PD before and after medication



62 year old man
2009 Onset of Symptoms / Start meds
Mean change: 51 taps
Max change: 111 taps
Min change: -21 taps

Source: Sage Bionetworks

Progress and Future Directions

Developing predictive models of PD progression

- Platform for integrated trial datasets
- Identifying influential factors in disease progression
- Validation with external datasets

Testing the feasibility of virtual visits

- Incorporation into trials (STEADY-PD)
- Independent sample – evaluate influence on recruitment, retention

Developing and testing applications for remote measurement

- Incorporate applications into trials (SURE-PD3)
- Pilot wearable sensors for outcome quantification

Future: Incorporate these approaches as a standard in therapeutic development and expand to new disease models