Digital Biomarkers in Neurology

Digital Biomarkers Conference
March 31, 2016

Outline

- Rationale
- Smartphones in Parkinson disease
- Wearables in movement disorders
- Future

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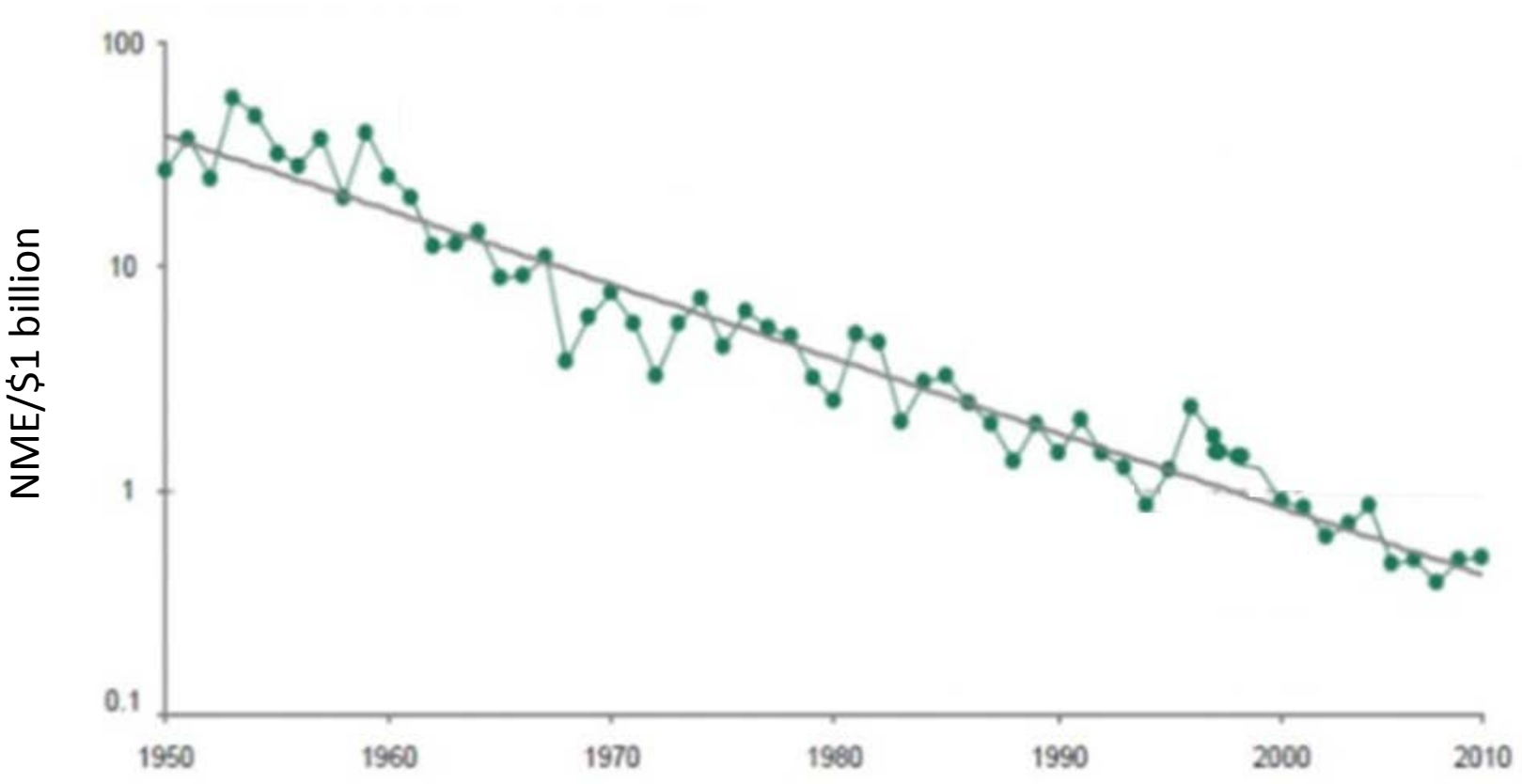
The productivity of the drug development industry continues to decline

New molecular entities per $1 billion in R&D (inflation adjusted), 1950-2010



Source: http://www.forbes.com/sites/matthewherper/2011/06/27/the-decline-of-pharmaceutical-researchmeasured-in-new-drugs-and-dollars/

In addition, many of our current outcome measures are subjective and sub-optimal

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

The field is limited by categorical, episodic, and subjective assessments

Assessment of motor function in Parkinson disease

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal:	No problems.
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.
2: Mild:	Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.
3: Moderate:	Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.

Source: Movement Disorders Society. United Parkinson Disease Rating Scale, 2008

These limitations have real consequences

Large trials terminated for futility in Parkinson disease and Huntington disease

September 11, 2013 Statement on the Termination of NET-PD LS-1 Study LS-1: 1700 patients with PD followed for up to 5 years
July 14, 2014 Announcement of 2CARE Early Study Closure 2 Care: 600 patients with HD followed for 5 years
September 8, 2014 Largest creatine clinical trial for Huntington's disease halted after 'futility' analysis CREST-E: 550 patients with HD followed for 4 years

Sources: http://parkinsontrial.ninds.nih.gov/netpd-LS1-study-termination.htm, http://www.ninds.nih.gov/disorders/clinical_trials/2CARE-Early-Study-Closure.htm, http://en.hdbuzz.net/181

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Mobile technologies can improve the way we measure disease

Pilot smartphone study in Parkinson disease

Figure 1. Picture of Android smartphone and software application.

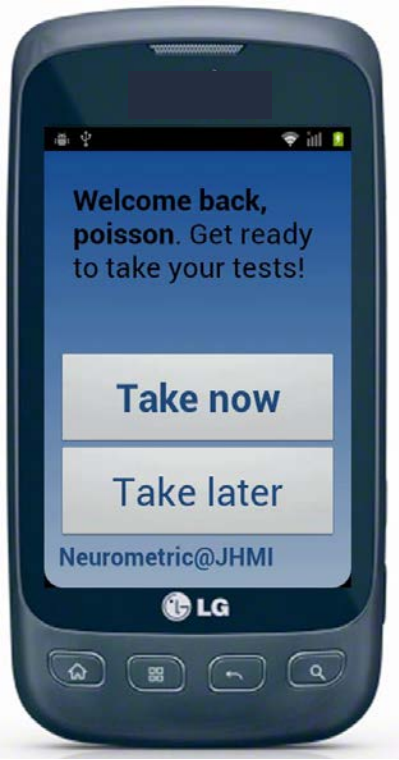
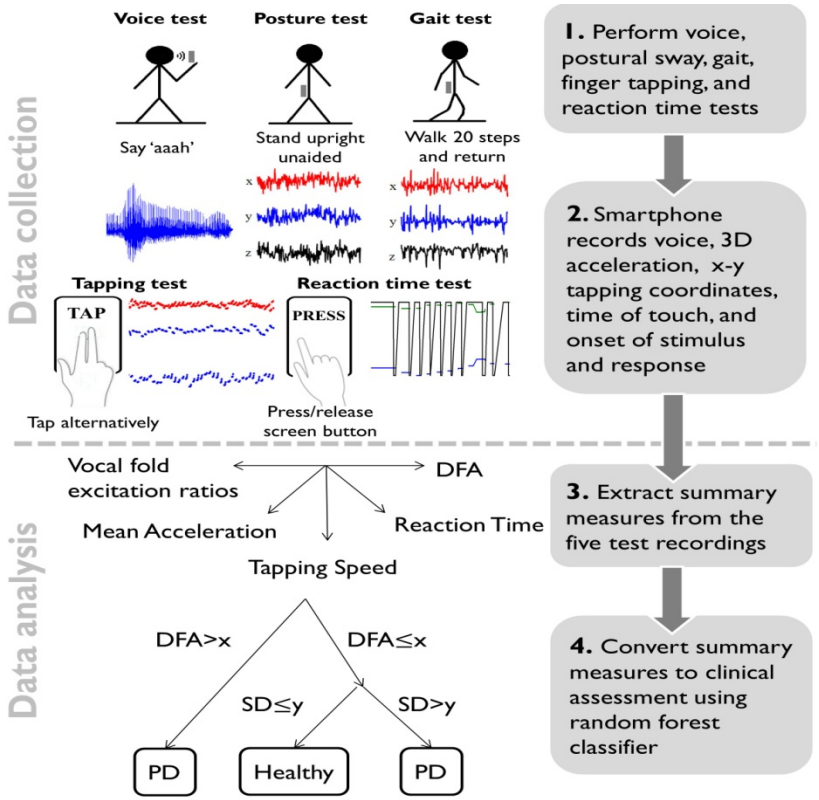


Figure 2. Procedure for collecting voice recordings (sustained vowel 'aaah'), finger tapping coordinates and the time of touch, acceleration time traces during gait, and postural sway tests along with the major steps in the data analysis

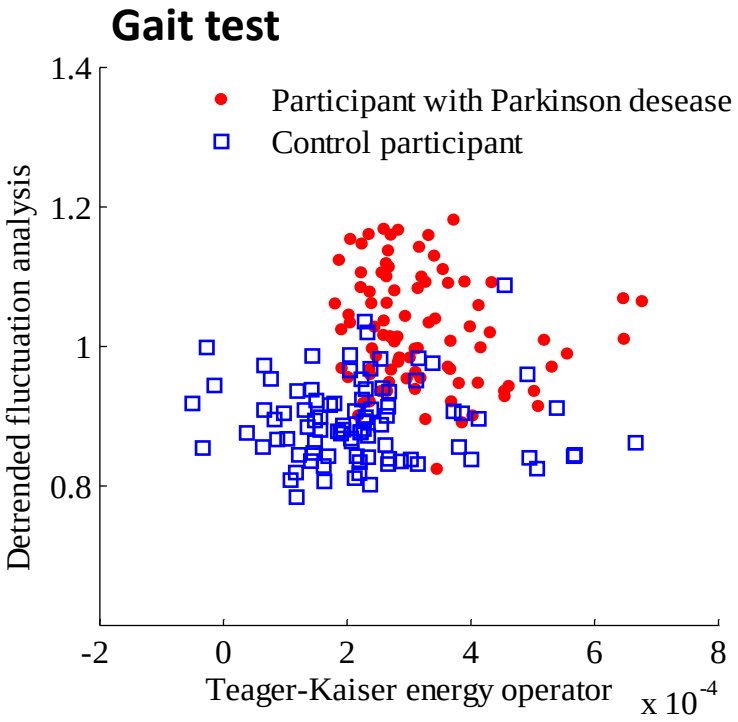


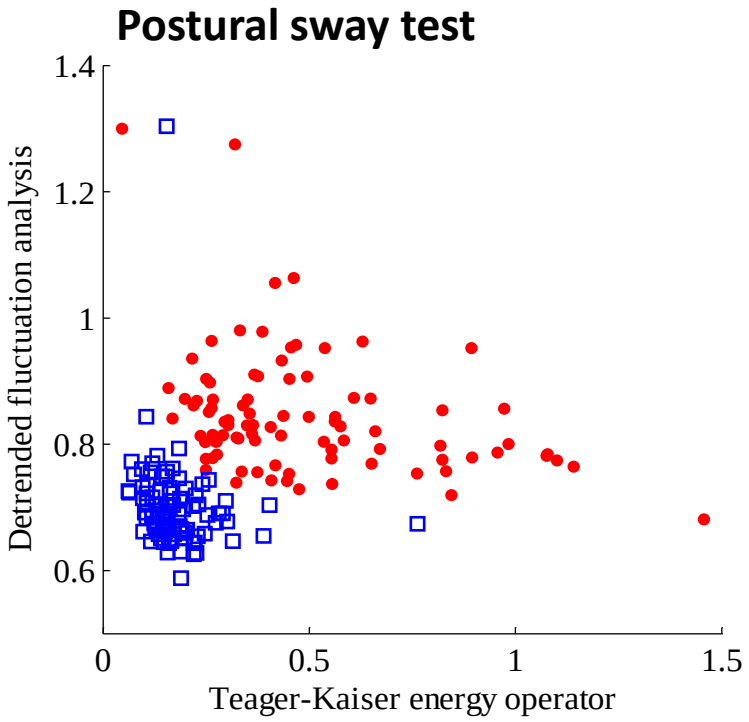
Abbreviations: 3D = three dimensional; DFA = detrended fluctuation analysis; PD = Parkinson disease; SD = standard deviation; TKEO = Teager-Kaiser energy operator

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

Smartphones can distinguish those with Parkinson disease from those without

Gait and posture tests in Parkinson disease

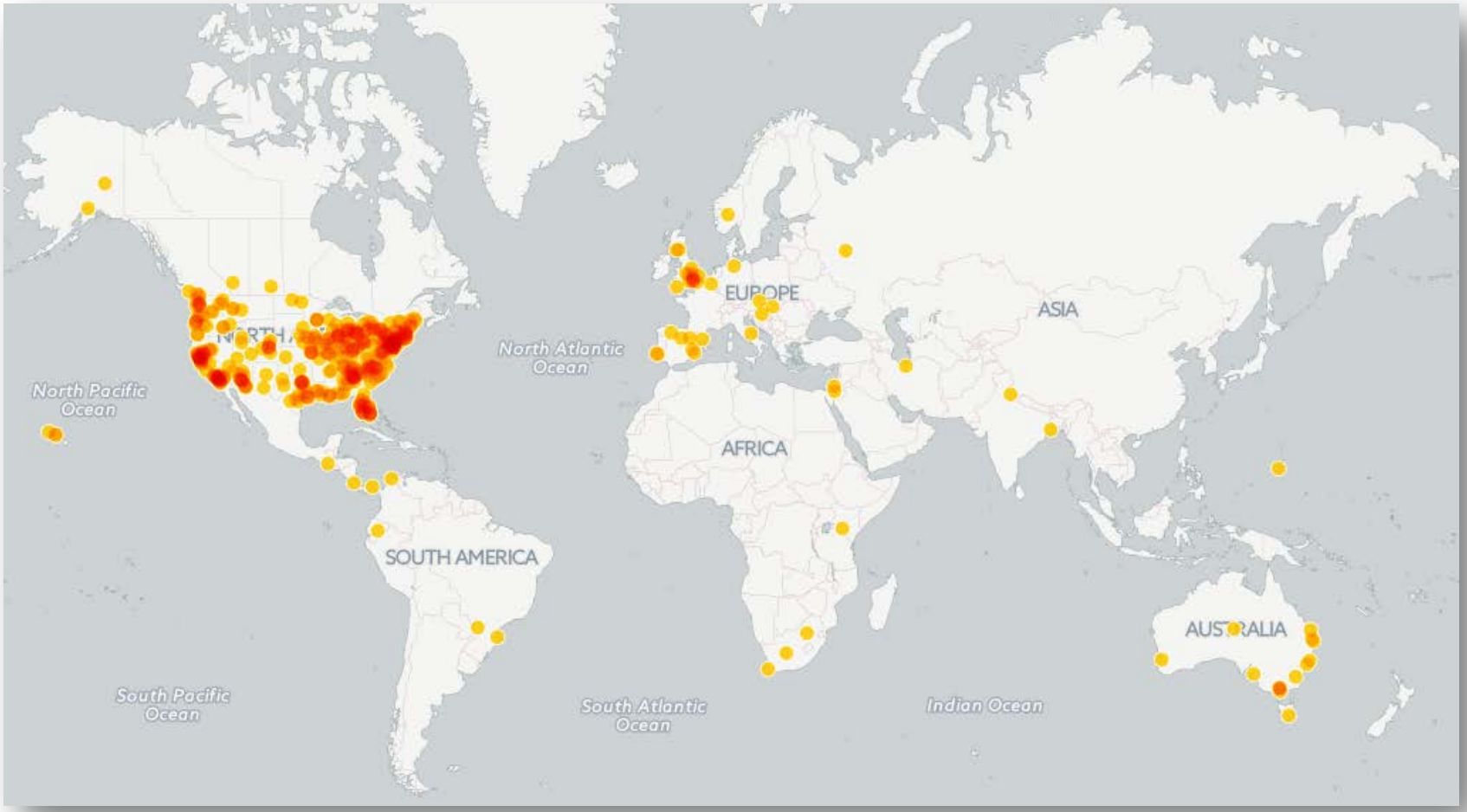




Source: Parkinsonism and Related Disorders 2015

New measures enable research to be conducted at unprecedented scale and scope

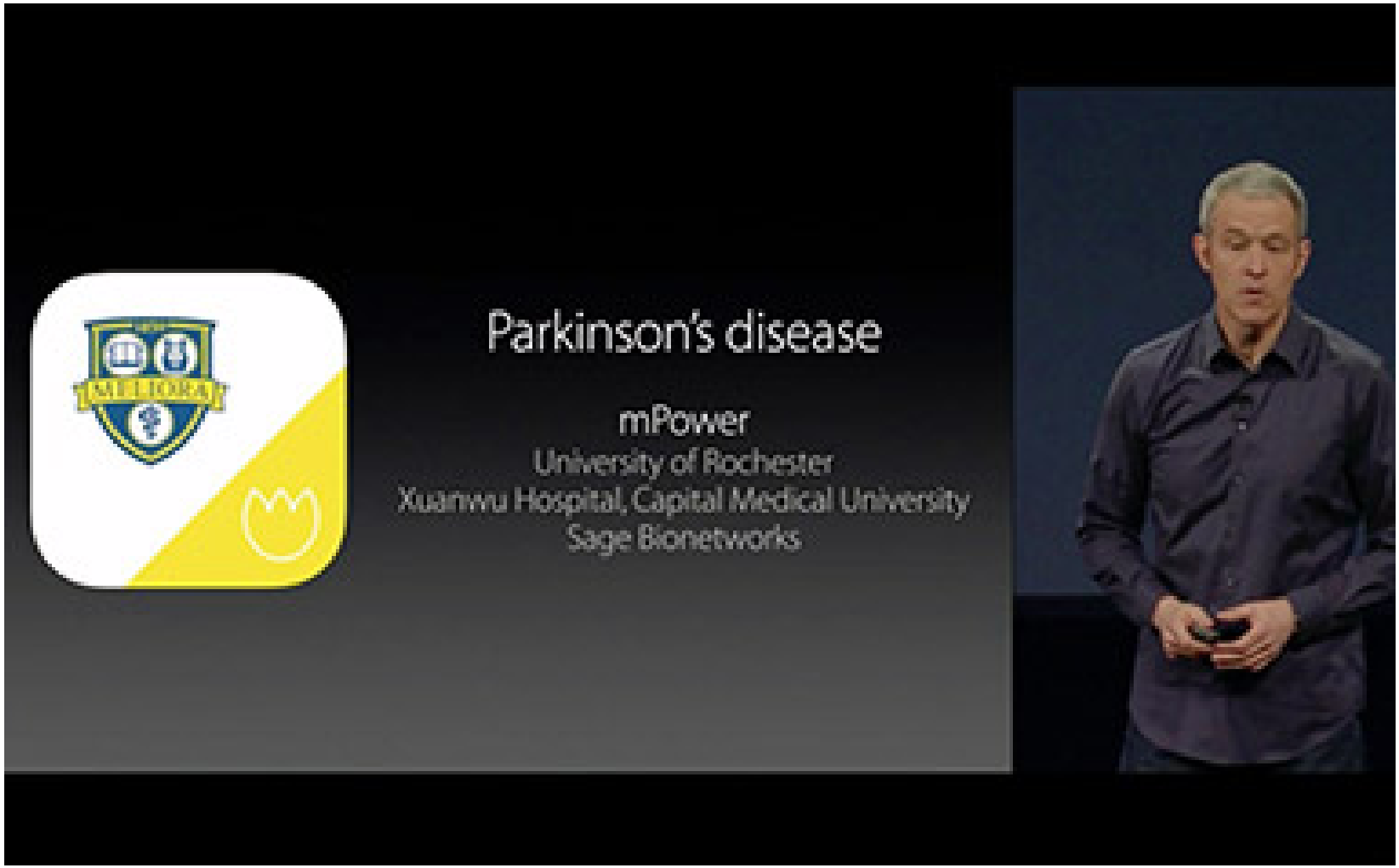
Geographical representation of study participants (N = 1000)



Source: Smartphone PD

Last year Apple announced the release of smartphone applications for medical research

mPower smartphone application for Parkinson disease (N = 15,000)

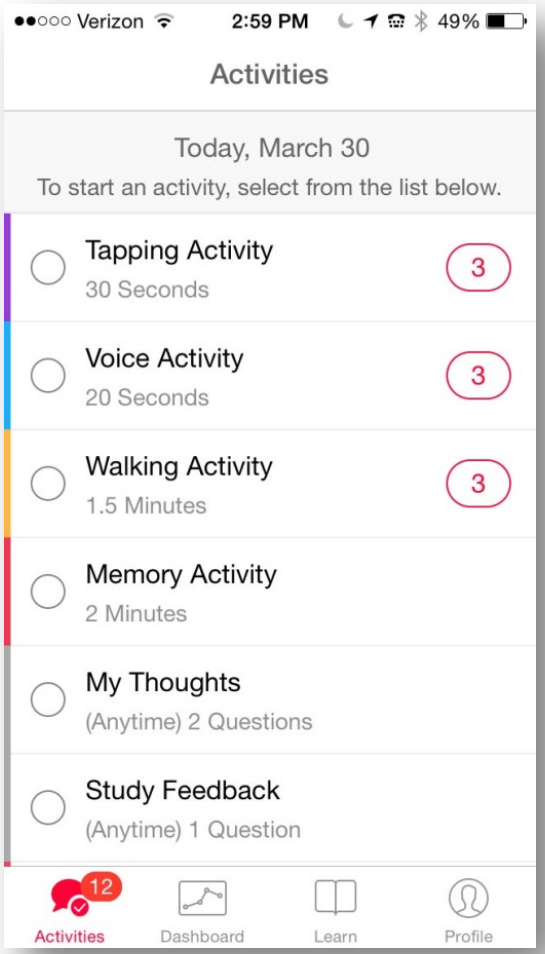


Researchers are leveraging these apps to reach large populations

Condition	Name of the app (lead organization)	Participants enrolled as of 10/5/15	Functionality of the app
Asthma	Asthma Health (Mount Sinai)	7,770	• Surveys • Structured tasks, including electronic diary of symptoms and triggers • Passive monitoring of activity and local air quality • Daily maintenance medication reminders • Educational information
Breast cancer	Share the Journey (Sage Bionetworks)	2,508	• Surveys to assess cognitive changes, changes in mood, fatigue, sleep patterns and exercise • Randomization to daily expressive diary and exercise motivation • Passive monitoring of movement, exercise and typing patterns • Educational information
Cardiovascular disease	My Heart Counts (Stanford)	44,841	• Surveys • Passive monitoring of physical activity through phone or wearables • Structured tasks, including assessments of fitness and guideline-based-cardiovascular risk scores
Diabetes	GlucoSuccess (Massachusetts General Hospital)	5,595	• Surveys on sleep, diabetes care, quality of life • Blood glucose tracking (from device or manual entry) • Food logging • Passive monitoring of physical activity through phone or wearables • Insights relating users' blood glucose levels with health behaviors
Parkinson disease	mPower (Sage Bionetworks)	15,340	• Surveys • Structured tasks, including assessments of voice, motor speed, memory, gait, and posture • Passive monitoring of activity and mobility

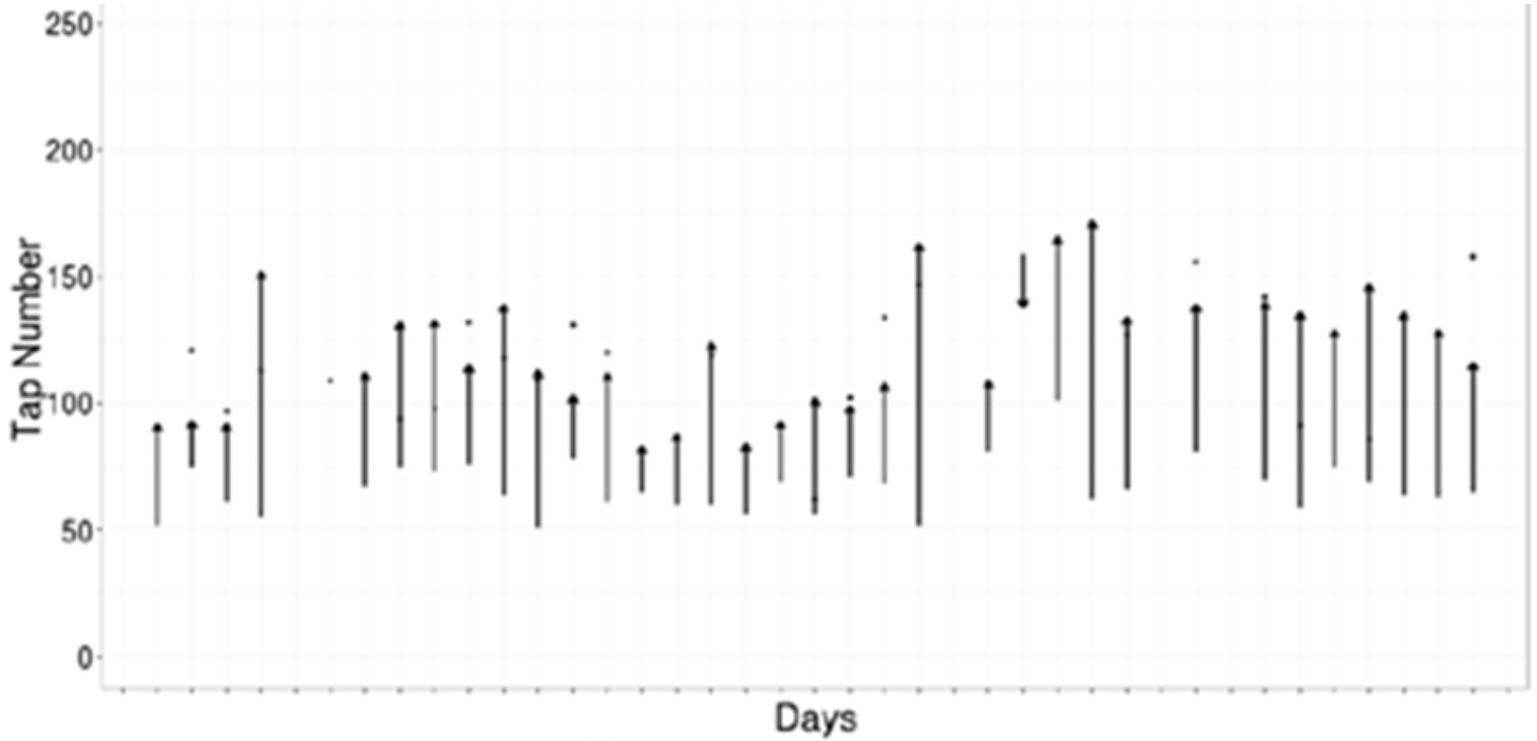
Source: Academic Medicine (in press)

Smartphone research apps contain surveys, structured tests, and passive monitoring



These apps can detect responses from 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

Pharmaceutical companies are now incorporating such devices into their early stage development efforts

Roche app measures Parkinson's disease fluctuations

"This could be the first time that such an app has been used to measure disease and symptom severity in a medicine development program in Parkinson's disease."

Source: http://www.roche.com/media/store/roche_stories/roche-stories-2015-08-10.htm

Last week Apple released CareKit, enabling patients and clinicians to better understand their health through data

User feedback on the mPower app

Source: http://www.apple.com/researchkit/

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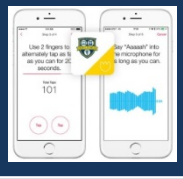
In addition to smartphones, other novel sensors can measure disease

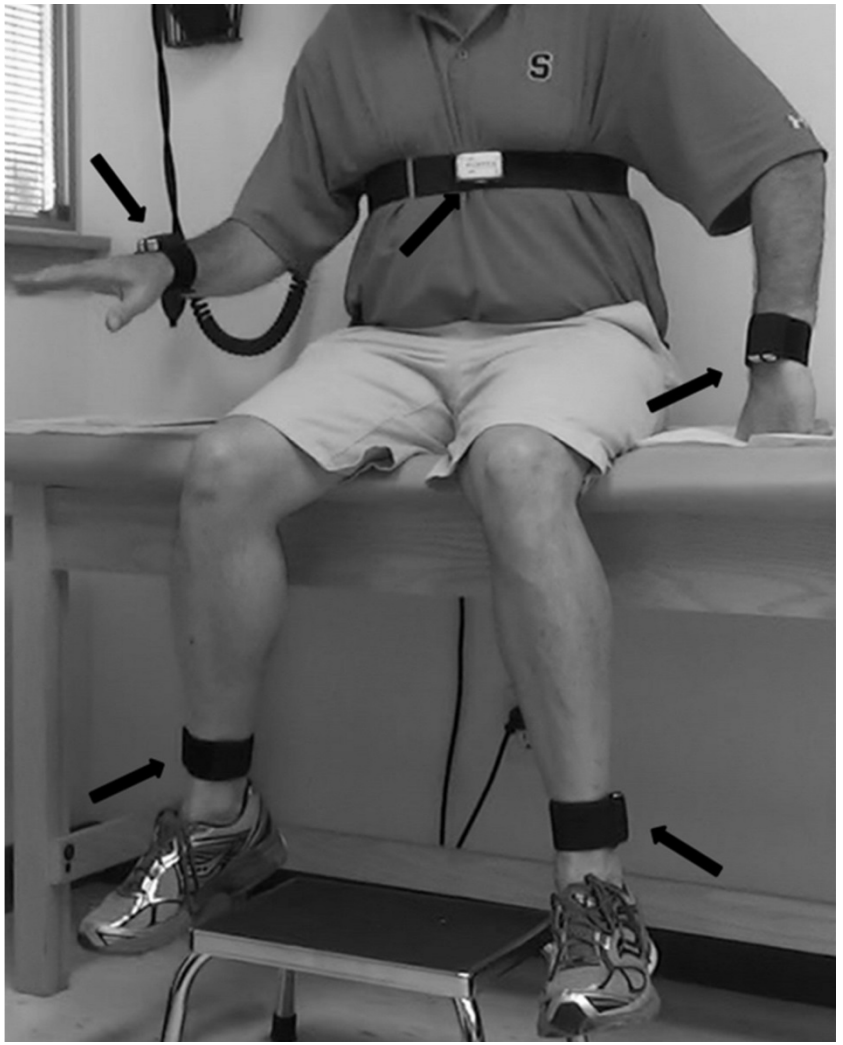
Technology	Example	Benefits	Limitations
Portables	Smartphones 	• Readily accessible • Continuous evaluation • Multidimensional evaluation	• Requires in-person validation • Need smartphone • Concern over privacy
Remote monitoring	Kinesia HomeView 	• FDA cleared device • Perform high frequency evaluations in home	• Limited to use in home • Requires hardware • Episodic evaluation
Wearables	PKG Data logger 	• FDA cleared device • Well positioned to assess tremor	• Provides narrow window of observation • Requires person to wear it • Limited functionality at present
Implantables	DBS neurostimulators 	• Opportunity for closed loop feedback • Individualize care based on individual activity	• Requires surgery • Only applies to small proportion of patients

Sources: http://glneurotech.com/kinesia/products/homeview/, http://www.medtronic.com/patients/parkinsons-disease/therapy/, http://www.globalkineticscorporation.com/, http://parkinsonmpower.org/, http://www.ncbi.nlm.nih.gov/pubmed

We conducted a pilot study of wearable sensors in Huntington disease

Pilot study

- 15 individuals with Huntington disease and five unaffected family members
- Individuals wore five sensors (one for chest and one for each limb) in clinic and for one day at home
- Wore chest sensor at home for an additional six days
- Objective was to assess feasibility and ability to differentiate those with Huntington disease from controls
- Sponsored by Auspex/Teva Pharmaceuticals; sensors from BioSensics



Source: Andrzejewski KL, Dowling AV, Stamler D et al. Wearable sensors in Huntington disease: a pilot study. (under review)

We found significant differences in gait in the clinic and more differences at home

Analysis of gait features during walking test in clinic and at home*

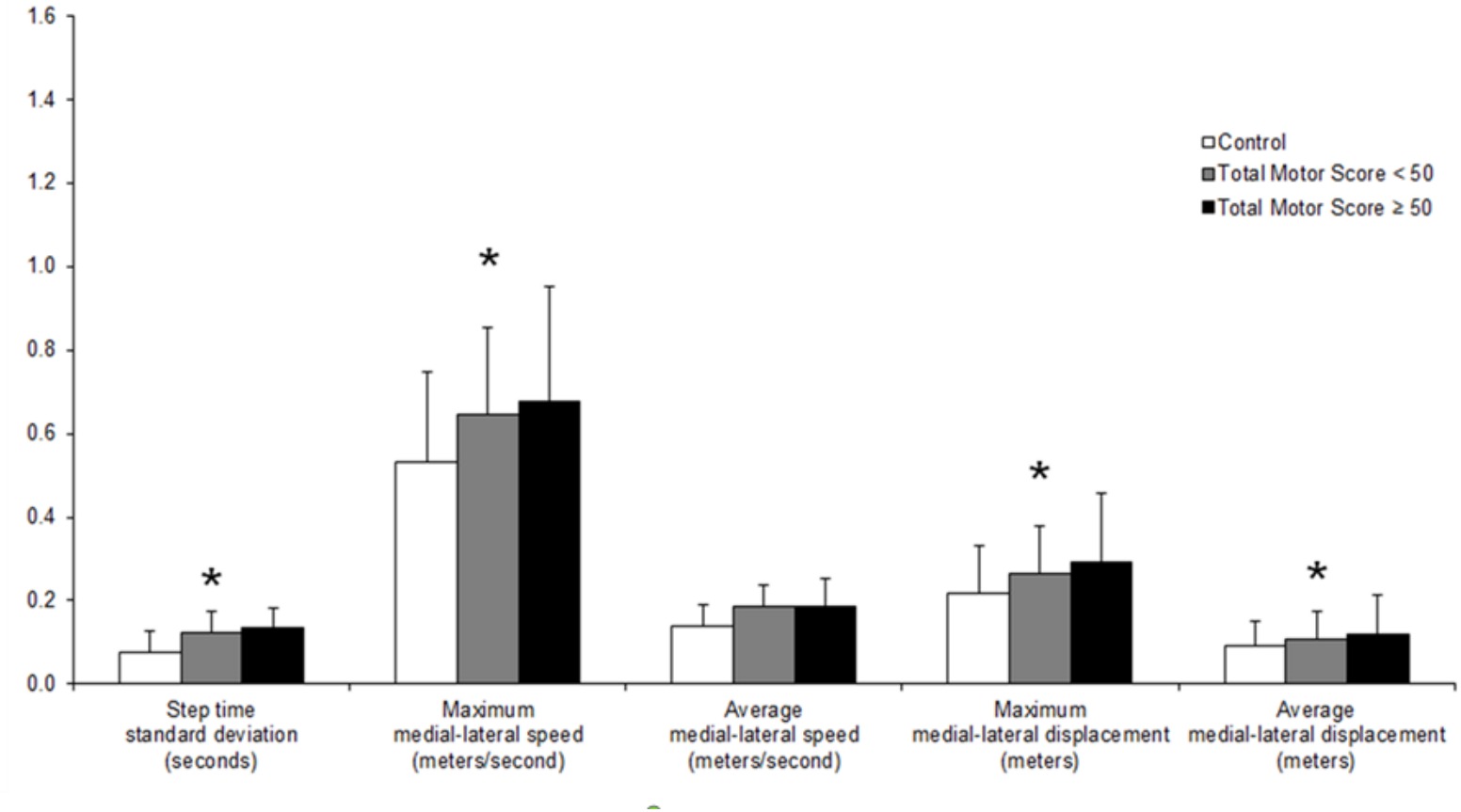
	In Clinic			At Home		
Feature	Control (n = 5)	HD (n = 15)	p-value	Control (n = 7812)	HD (n = 6987)	p-value
Step time standard deviation (seconds)	0.03 ± 0.01	0.12 ± 0.04	<0.0001*	0.08 ± 0.05	0.13 ± 0.05	<0.0001*
Maximum medial-lateral speed (meters/second)	0.46 ± 0.08	0.59 ± 0.15	0.091	0.53 ± 0.22	0.66 ± 0.23	<0.0001*
Average medial-lateral speed (meters/second)	0.12 ± 0.02	0.18 ± 0.07	0.059	0.14 ± 0.05	0.19 ± 0.06	<0.0001*
Maximum medial-lateral displacement (meters)	0.14 ± 0.04	0.21 ± 0.11	0.179	0.22 ± 0.11	0.27 ± 0.13	<0.0001*
Average medial-lateral displacement (meters)	0.06 ± 0.03	0.09 ± 0.06	0.386	0.09 ± 0.06	0.11 ± 0.08	<0.0001*

* Walking test was the Timed Up and Go test

Source: Andrzejewski KL, Dowling AV, Stamler D et al. Wearable sensors in Huntington disease: a pilot study. (under review)

The data from the wearable sensors correlated with traditional clinical rating scales

Analysis of gait features by total motor score**



* p<0.001

** Total motor score is a standard clinician-rated assessment of movement disorder in Huntington disease

Source: Andrzejewski KL, Dowling AV, Stamler D et al. Wearable sensors in Huntington disease: a pilot study. (under review)

We are launching a pilot study to evaluate state of the art sensors for multiple neurological disorders

MC10 BioStampRC

Sensor-MD Overview:

- We are enrolling 40 participants
  - 10 with Parkinson disase
  - 10 with Huntington disease
  - 10 with Prodromal Huntington disease
  - 10 without a movement disorder
- Participants will wear sensors on their 1) trunk; 2) arms; and 3) legs
- Aims of the study:
  - Feasibility
  - Ability to differentiate between groups
  - Ability to detect pharmacological response to treatment
  - Ability to generate novel insights

Source: http://www.mc10inc.com/our-products/biostamprc

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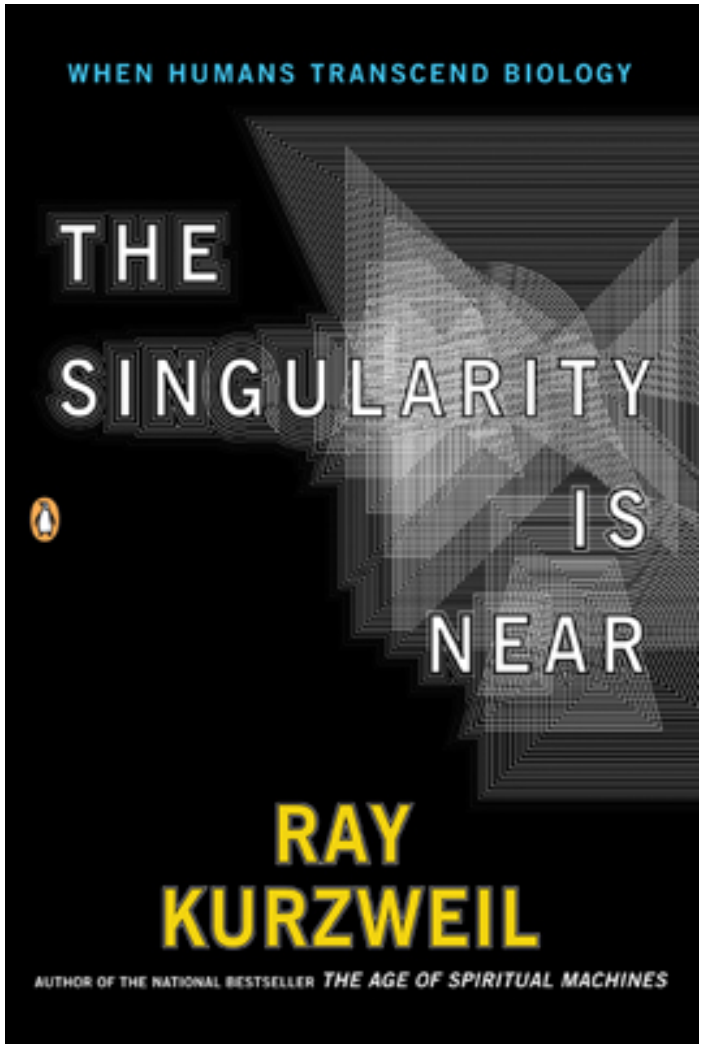
Improvements in human technology and knowledge happen exponentially not linearly



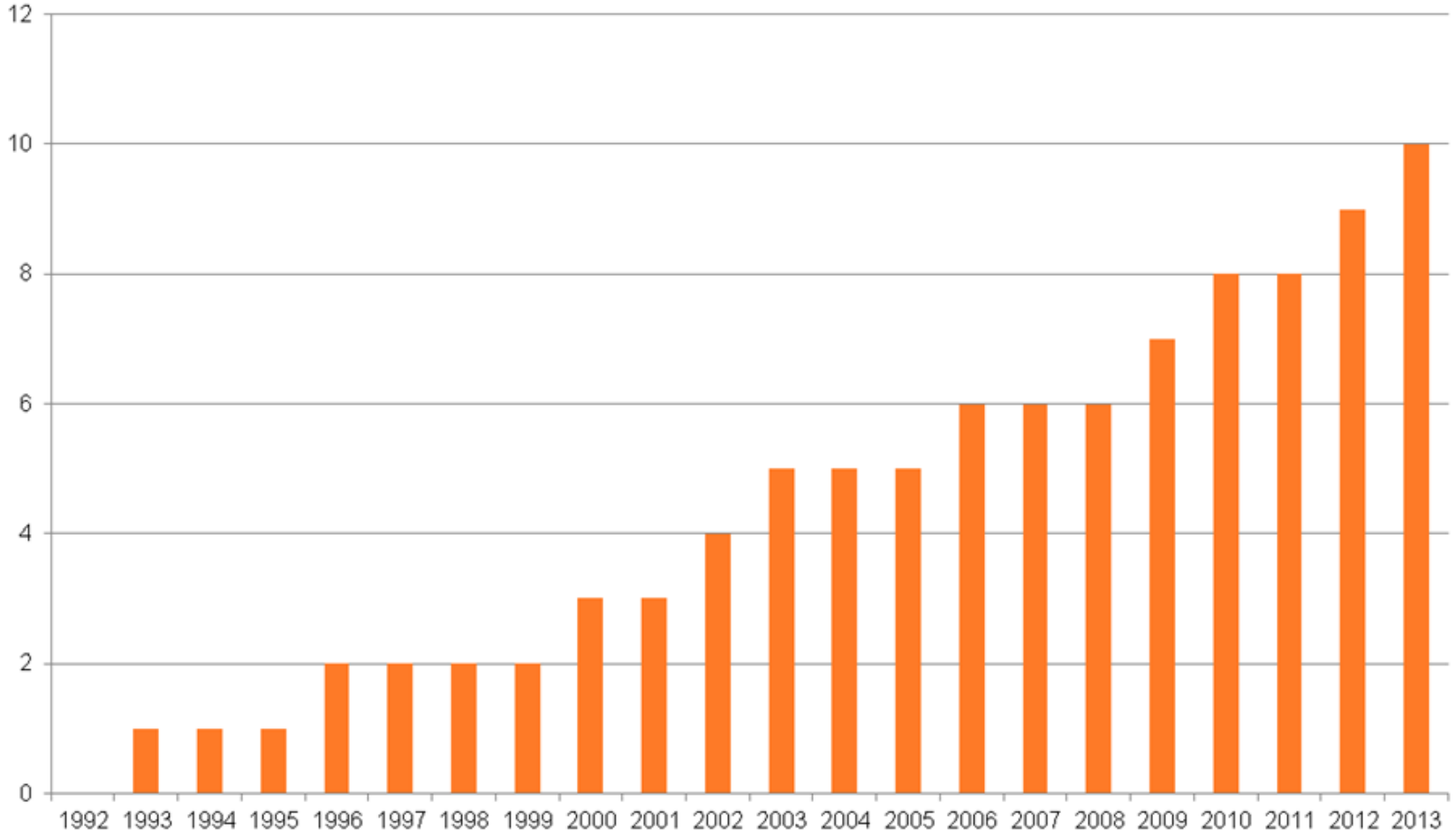
Law of accelerating returns

"Technology, particularly the pace of technological change, advances (at least) exponentially, not linearly, and has been doing so since the advent of technology, indeed since the advent of evolution on Earth. … The returns of an evolutionary process increase exponentially over time … [As] a particular evolutionary process becomes more effective, greater resources are deployed toward the further progress of that process."

Sources: Kurzweil, Ray (2005). *The Singularity is Near*. New York: Viking Books; http://www.kurzweilai.net/the-law-of-accelerating-returns

With objective measures in place, we can advance development of novel therapies rapidly

Number of FDA-approved therapies for multiple sclerosis, 1992-2013



Source: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx

We are beginning to see the potential of digital biomarkers

Digital biomarker as primary outcome measure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

METHODS

In this multicenter, double-blind, crossover study, 110 patients with heart failure and a preserved ejection fraction were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate (from 30 mg to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. The primary end point was the daily activity level, quantified as the average daily accelerometer units during the 120-mg phase, as assessed by patient-worn accelerometers. Secondary end points included hours of activity per day during the 120-mg phase, daily accelerometer units during all three dose regimens, quality-of-life scores, 6-minute walk distance, and levels of N-terminal pro–brain natriuretic peptide (NT-proBNP).

Source: N Engl J Med 2015; 373:2314-2324