
Digital Biomarker Development at Roche: How Mobile Technology Can Innovate Clinical Endpoints

*Luís Matos, Deployment Lead Digital Biomarkers
Washington, June 5, 2018*

Mobile sensors are already heavily used in other industries!

Where are they in clinical trials?

PLANES:

Minute-to-minute monitoring



Weather

Detailed weather sensors are more accurate than the National Weather Service, telling the airline when to prepare de-icers and delay and cancel flights.



Parts

Even a five degree temperature variation may indicate a part needs to be replaced.



Flight Plan

Keeping an eye on a plane's path from the ground, and alerting pilots of any anomalies.

“An engine alone... is likely to have as many as 5,000 elements monitored every second.”

Why «Digital» in Clinical Development?

Digital is new normal!



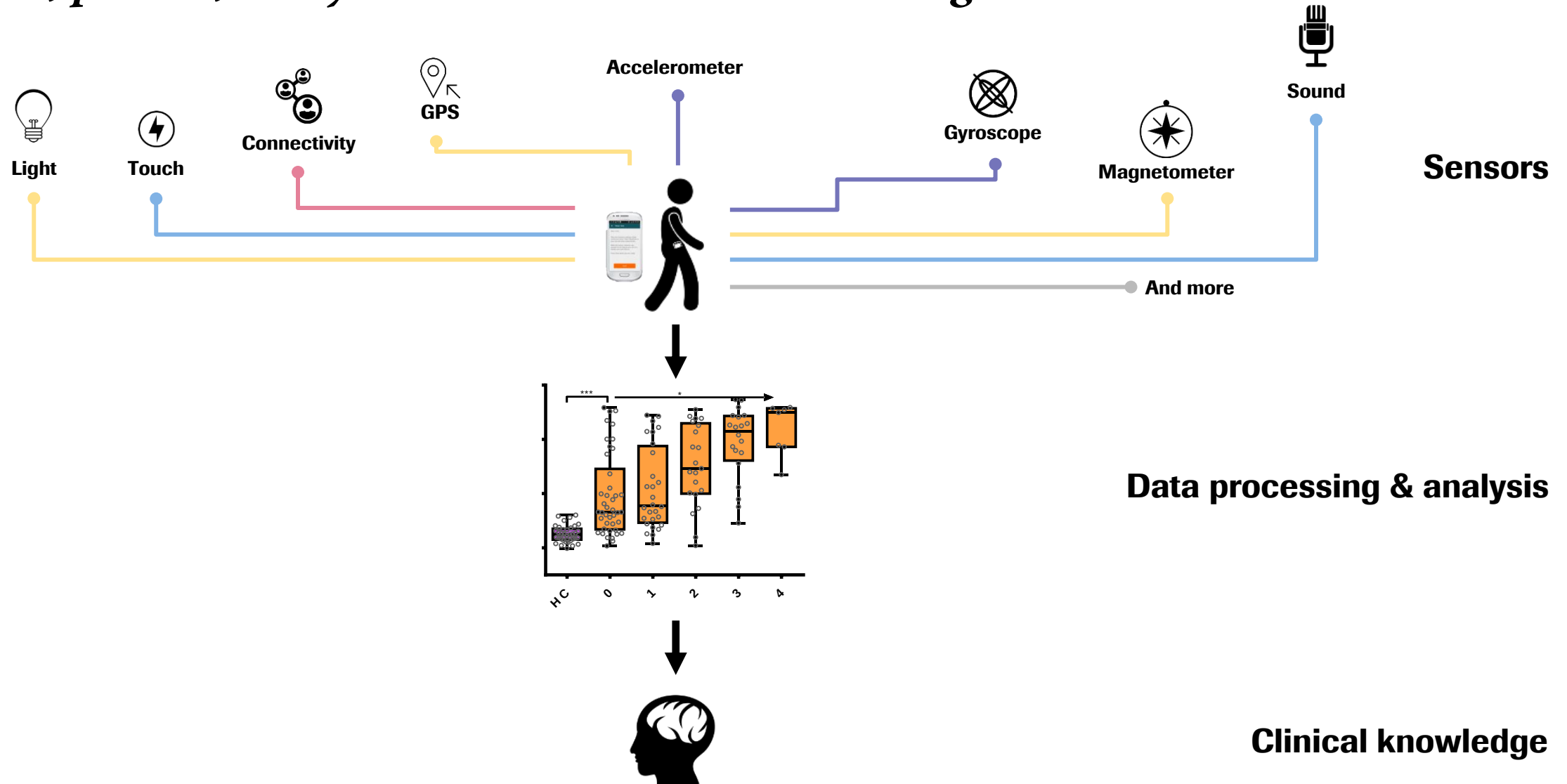
**Digital
Operational Efficiency**



**Digital
Translational Science**

Continuous data from mobile sensors

Collect, process, analyse and add to clinical knowledge



The measure of you

➤ Learn about digital biomarkers in health

Inside Roche



All 

Two case studies to show where we stand today at Roche



Multiple Sclerosis (MS)
Remote Monitoring

Distributed November 2016

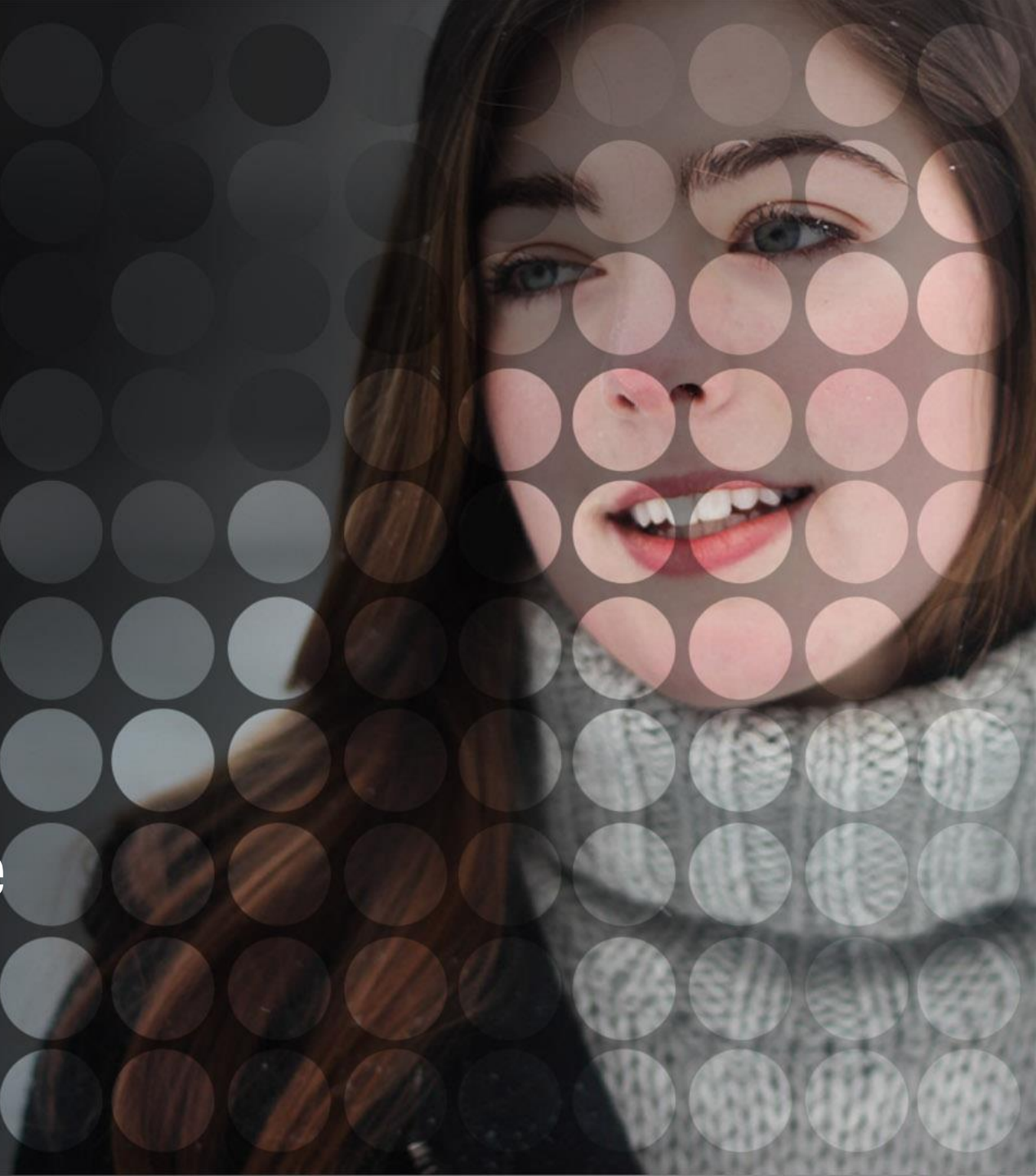


Parkinson's Disease (PD)
Remote Monitoring

Distributed February 2015

Floodlight

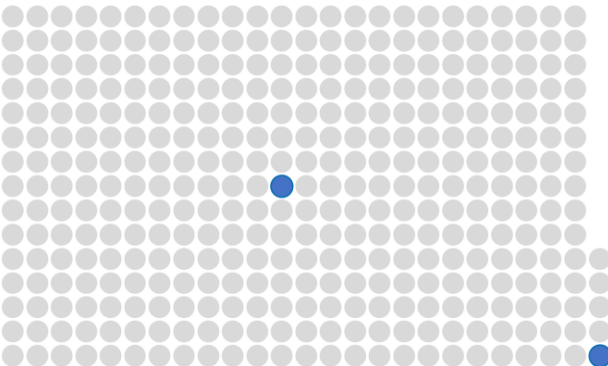
See beyond the surface



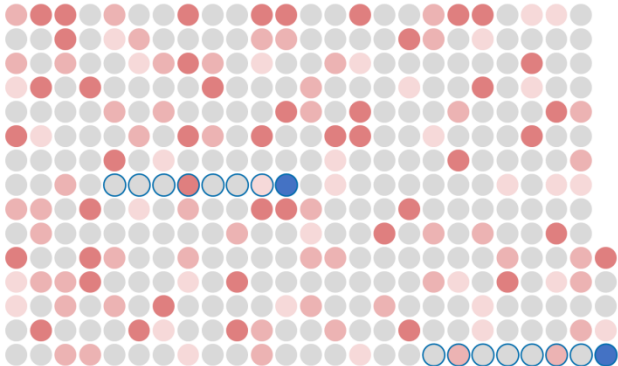
Identifying sub-clinical disease & progressing MS

365 days/year with active tests and passive monitoring

365 days in the life of a patient with MS: in current clinical practice a patient may only see their physician twice for around 10 minutes.

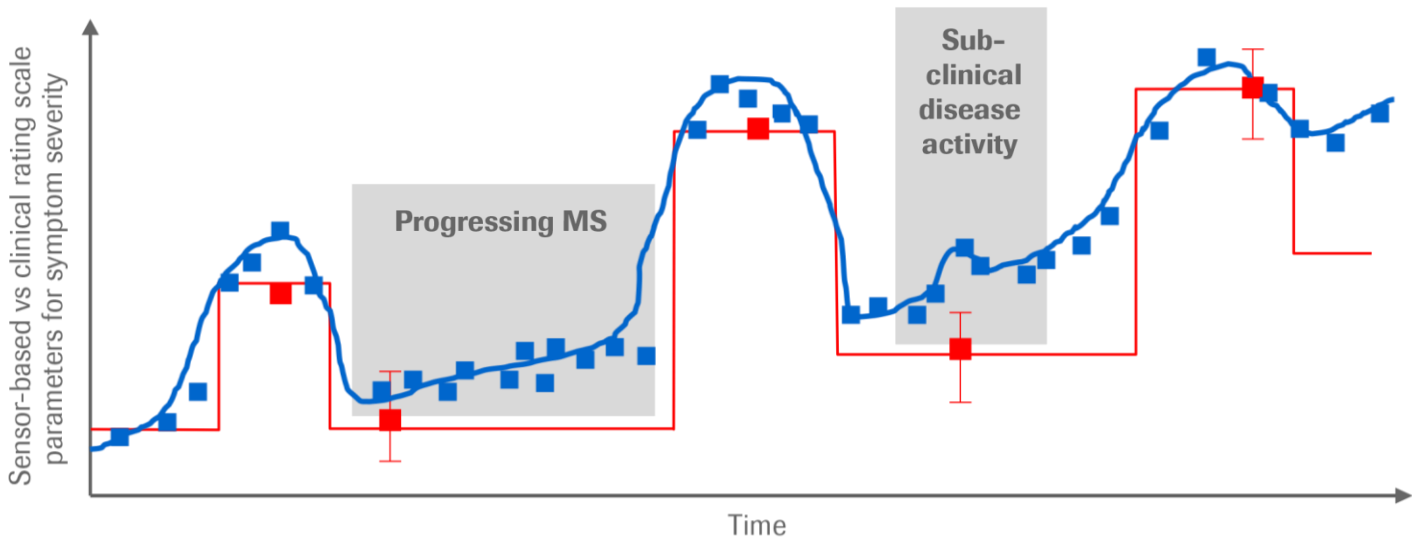


Remote monitoring promises to change this. Disease activity can be measured throughout the year, enabling better-informed treatment decisions.



Legend

- Day in the life of a patient with chronic stable symptoms
- Day with a **visit** to the clinic/physician
- Day with worsening **symptoms**
- Patients' **recall period**

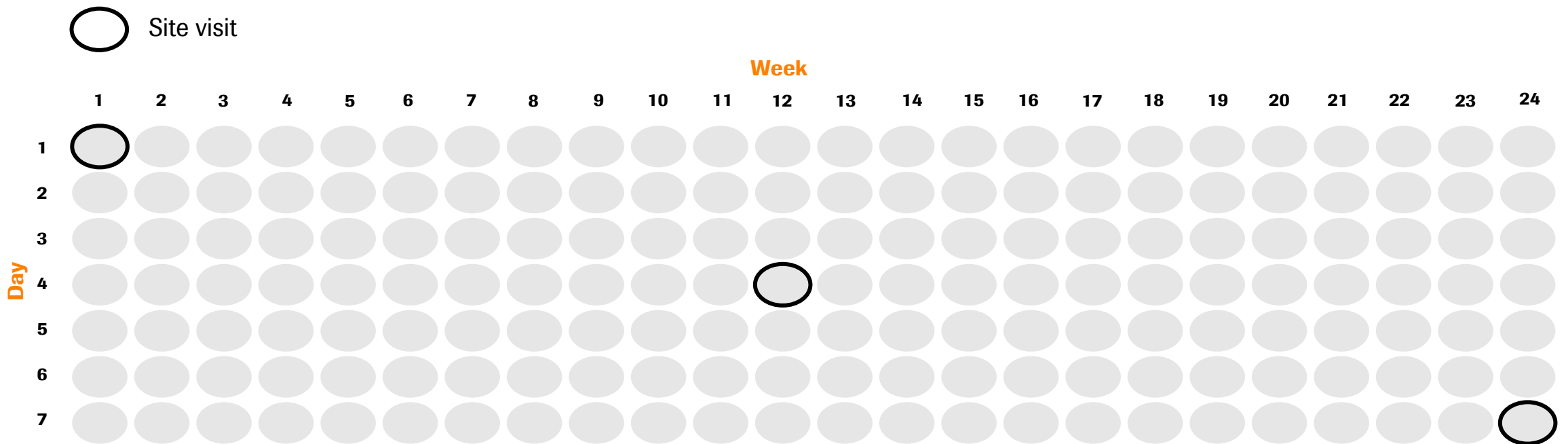


- EDSS course
- Disease course
- Sensor** outcomes
- Precision of **Sensor** parameters
- In-clinic outcomes
- Precision of in-clinic assessments

*Routine clinical assessments, not including MRI

FLOODLIGHT study design

60 patients with MS, 20 controls



FLOODLIGHT study design



Timed 25-Foot Walk (T25-FW)



Berg Balance Scale (BBS)



Nine hole peg test (9HPT)



Oral Symbol Digit Modalities Test (SDMT)



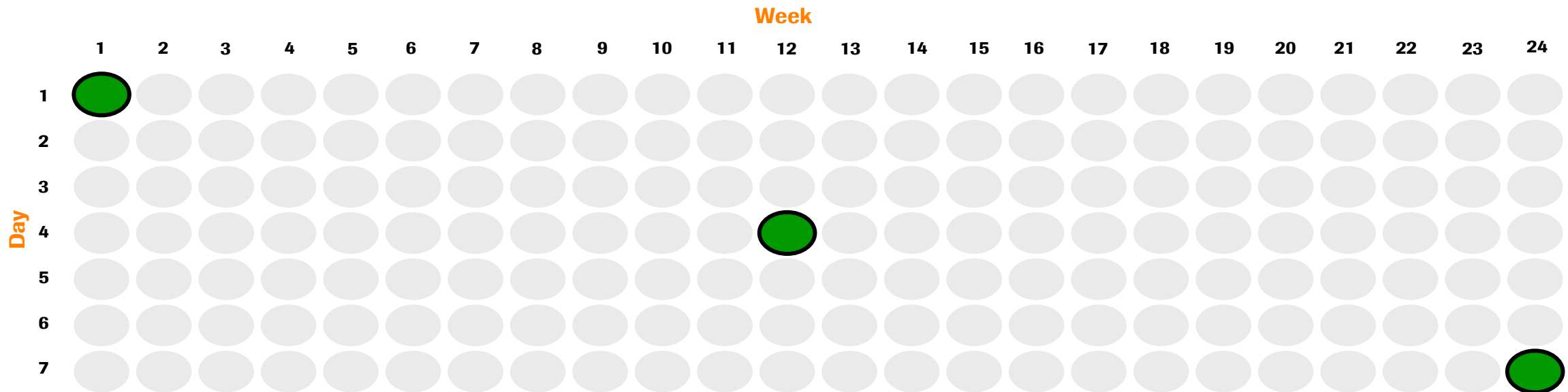
Various Clinical/PRO Rating Scales



Site visit



Clinical/PRO rating scales



FLOODLIGHT study design



Daily Mood Question (DMQ)



Symptom Tracker (ST)



Multiple Sclerosis Impact Scale (MSIS)-29



Symbol Digit Modalities Test (SDMT)



Pinching Test



Draw a Shape Test



Static Balance Test (SBT)



Five U-Turn Test (5UTT)



Two-Minute Walk Test (2MWT)



Site visit



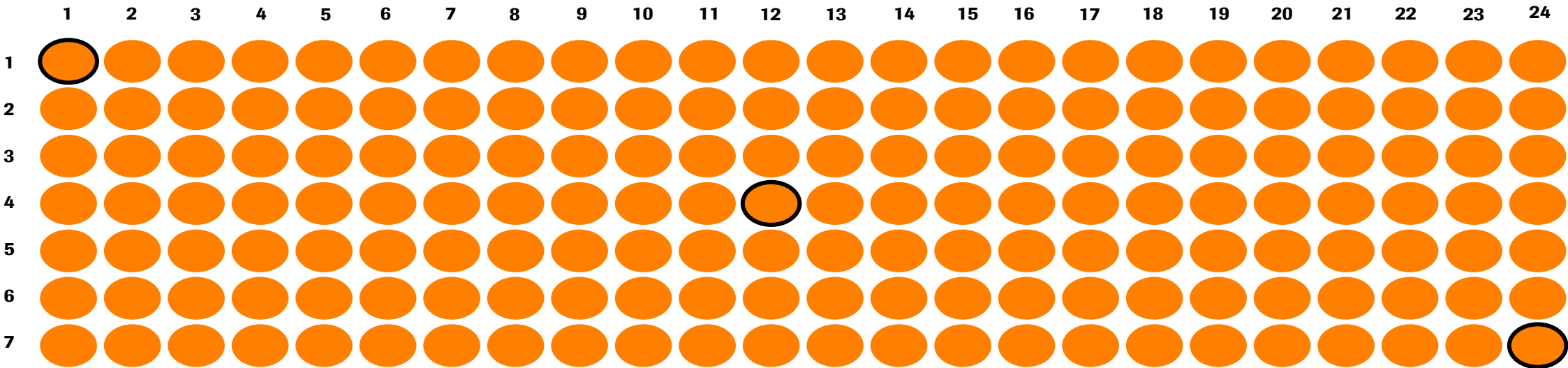
Clinical/PRO rating scales



Active test

Week

Day



FLOODLIGHT study design



Daily Mood Question (DMQ)



Symptom Tracker (ST)



Multiple Sclerosis Impact Scale (MSIS)-29



Symbol Digit Modalities Test (SDMT)



Pinching Test



Draw a Shape Test



Static Balance Test (SBT)



Five U-Turn Test (5UTT)



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Site visit



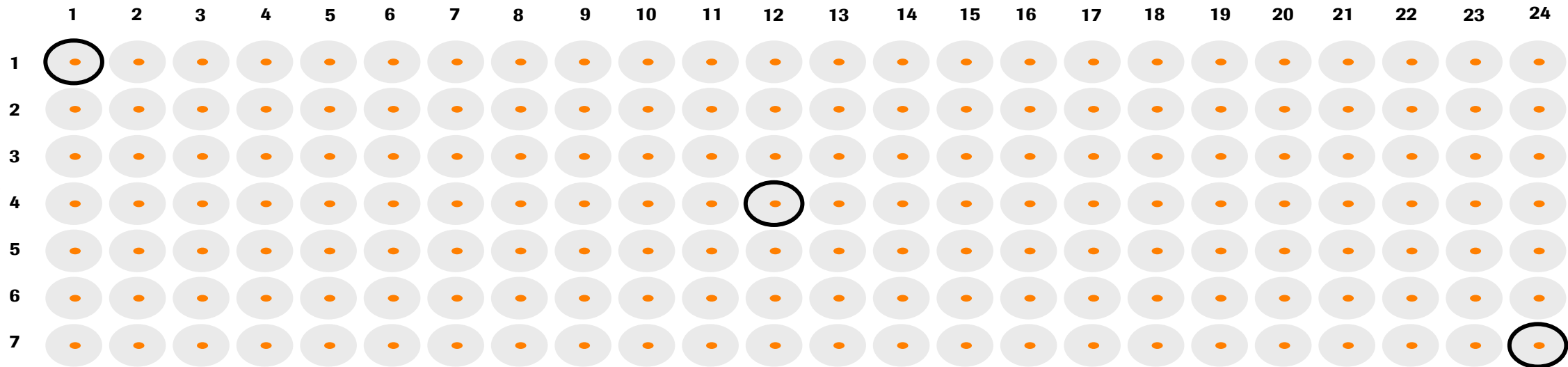
Clinical/PRO rating scales



Active test

Week

Day



FLOODLIGHT study design



Gait Behaviour



Mobility Pattern



Site visit



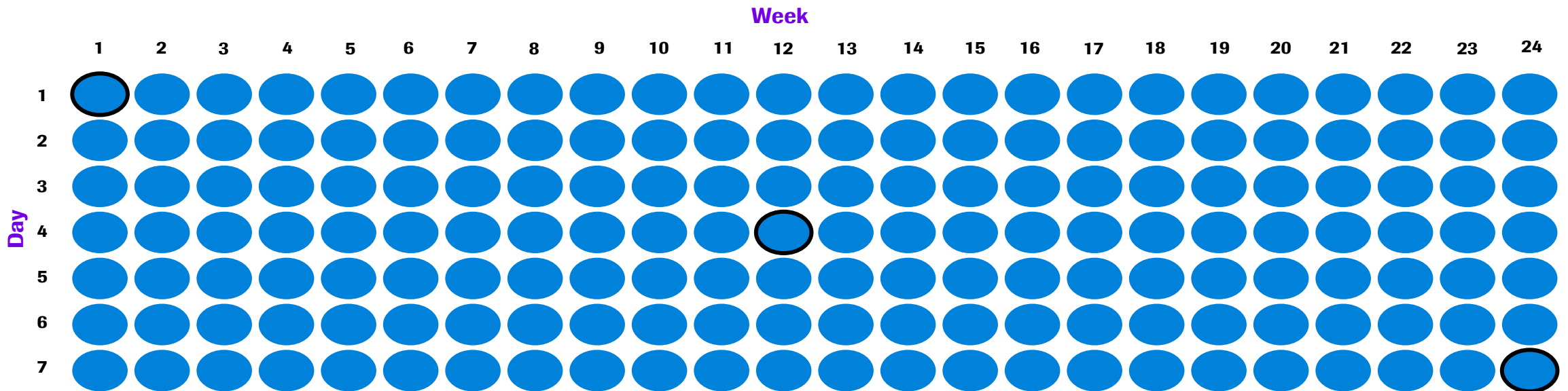
Clinical/PRO rating scales



Active test



Passive monitoring



Three pillars of our Digital Biomarker analysis

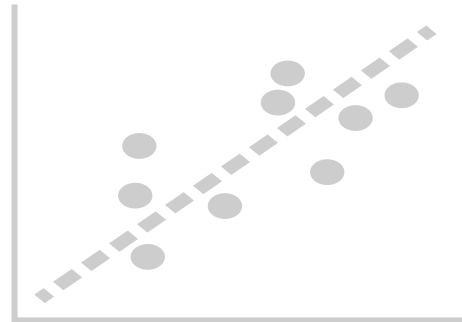
1. Adherence

Patients collect data regularly



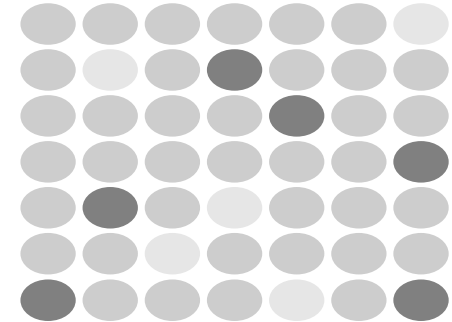
2. Agreement

Sensor data correlates with clinical scales



3. Augmentation

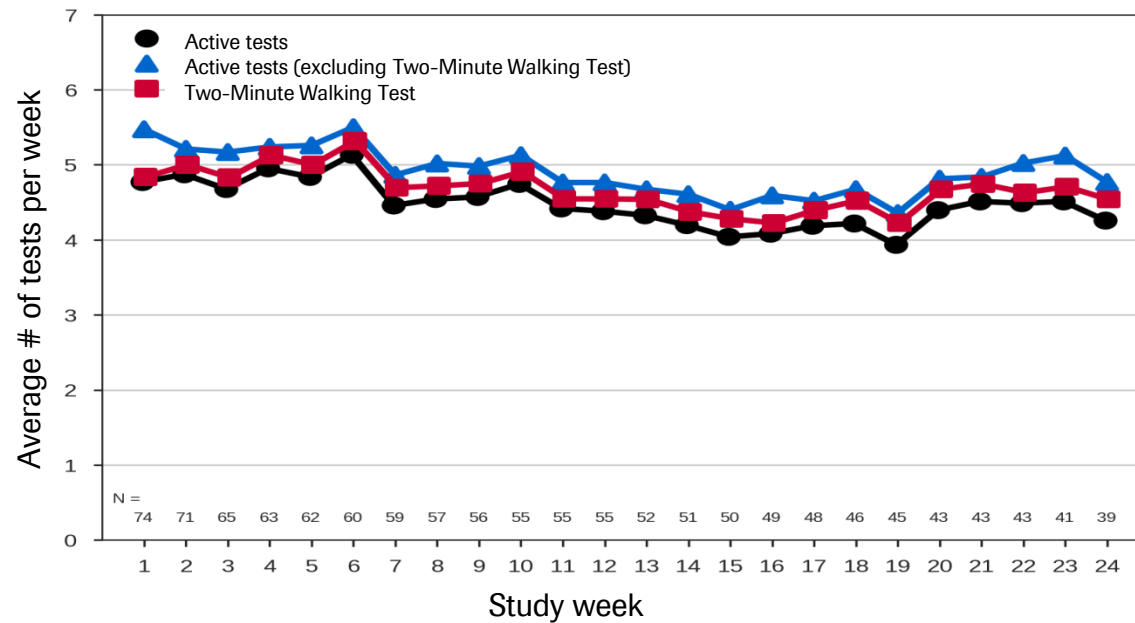
Sensor data provides novel insights beyond clinical scales



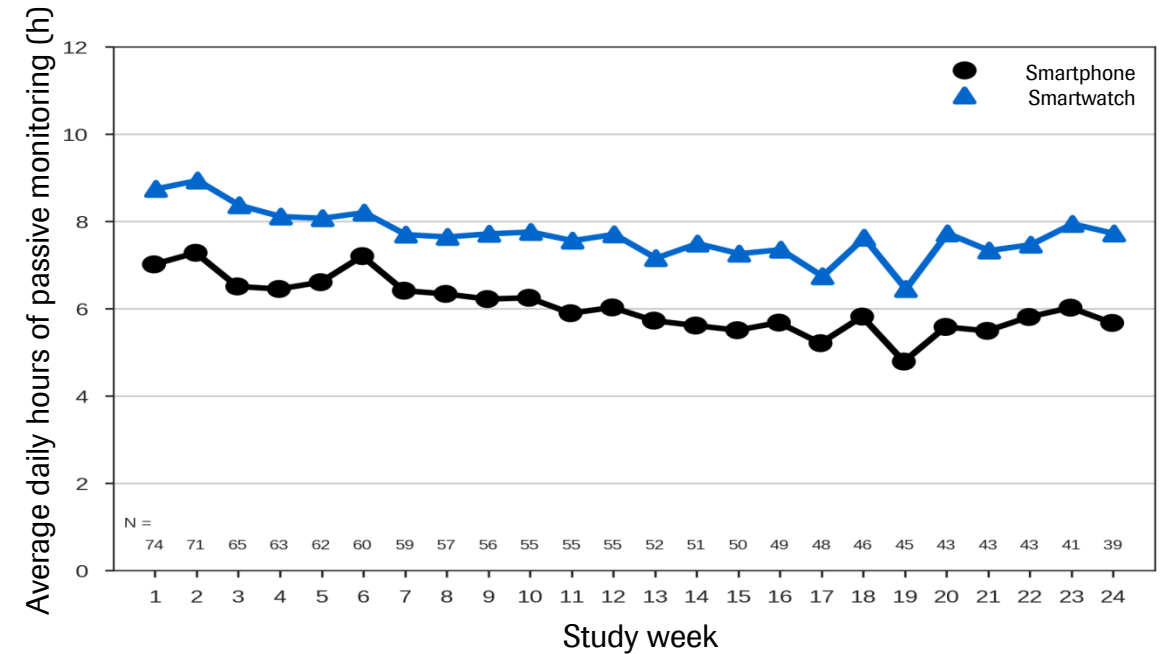
Adherence to active tests and passive monitoring is good and stable over 24 weeks



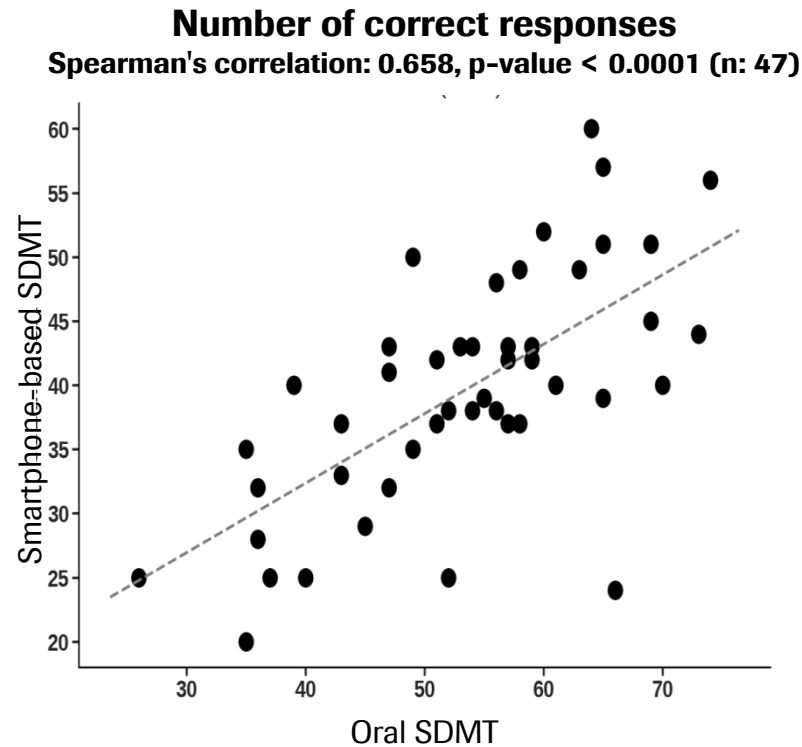
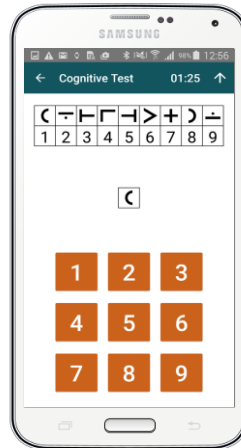
Active tests



Passive monitoring



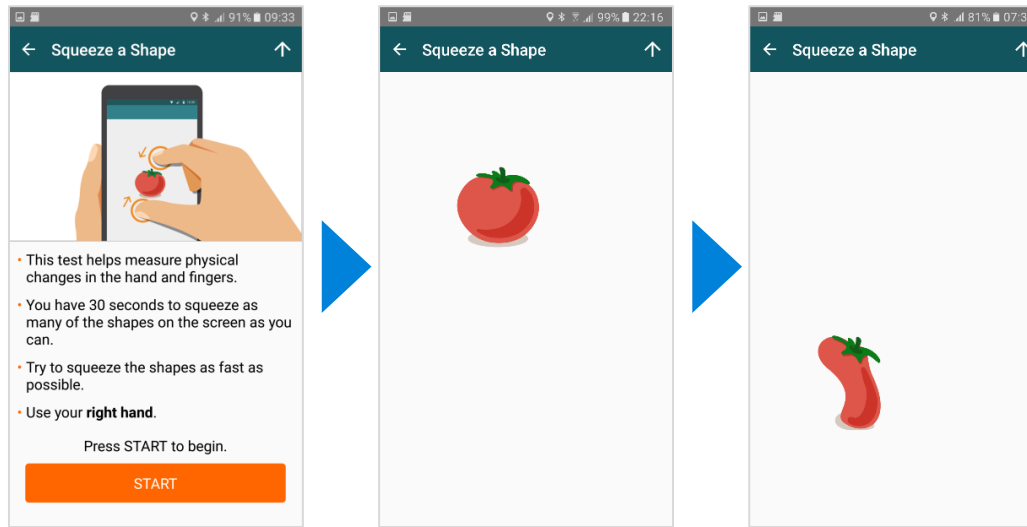
Significant cross-sectional correlation at baseline of oral vs smartphone-based Symbol Digit Modalities Test



Smartphones allow for modernized and remote assessments

Example: pinching test “Squeeze a Shape”

Smartphone-based task



Clinical anchor



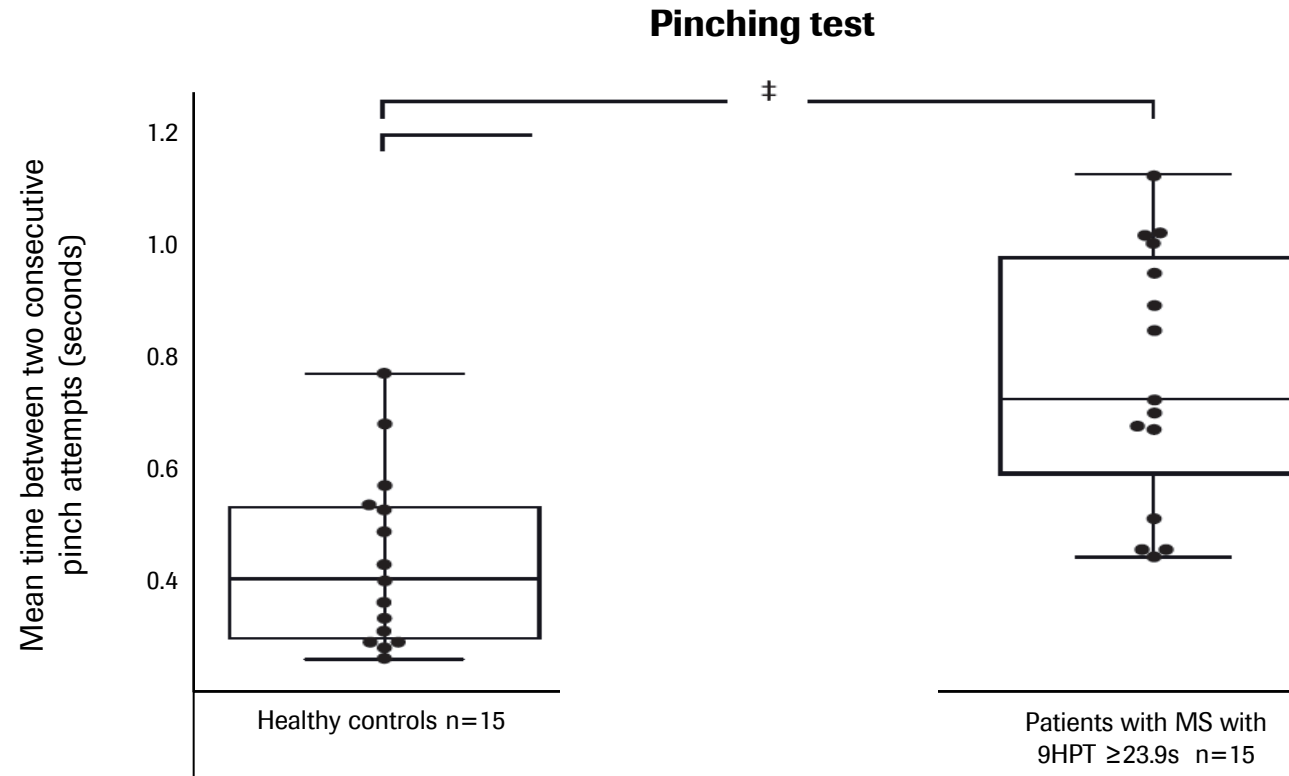
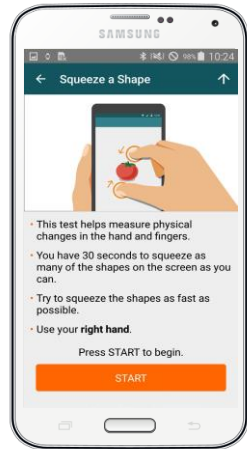
Test rationale:

- To assess fine distal motor manipulation (gripping & grasping, muscle weakness), motor control and impaired hand-eye coordination

Patients are asked to:

- Pinch tomatoes as fast as possible for 30 seconds

Pinching test discriminates healthy controls from MS patients with normal hand/arm function

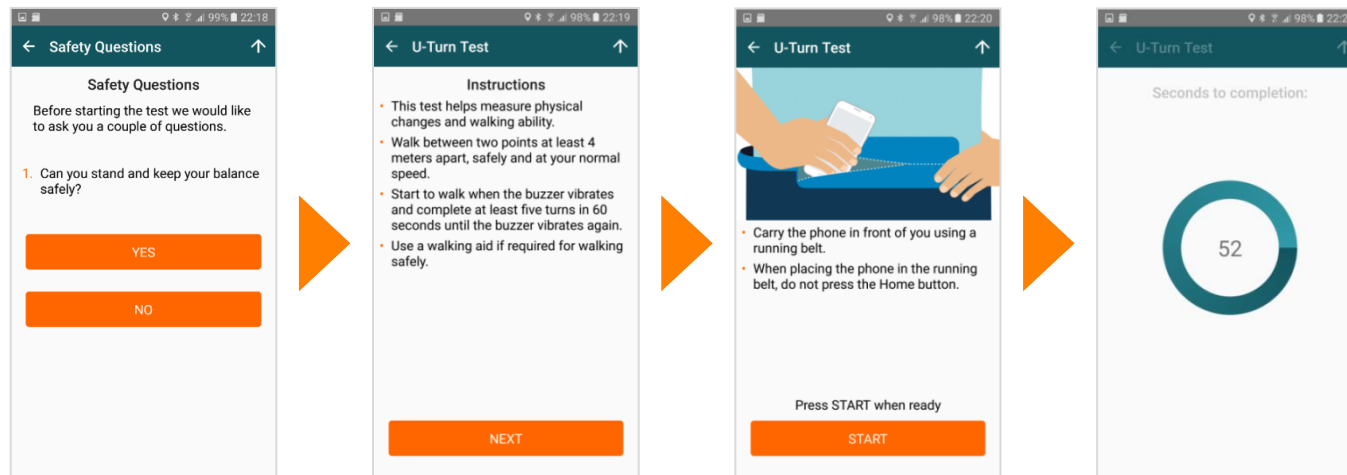


‡ p<0.001
 9HPT= 9-hole peg test;
 MS= multiple sclerosis

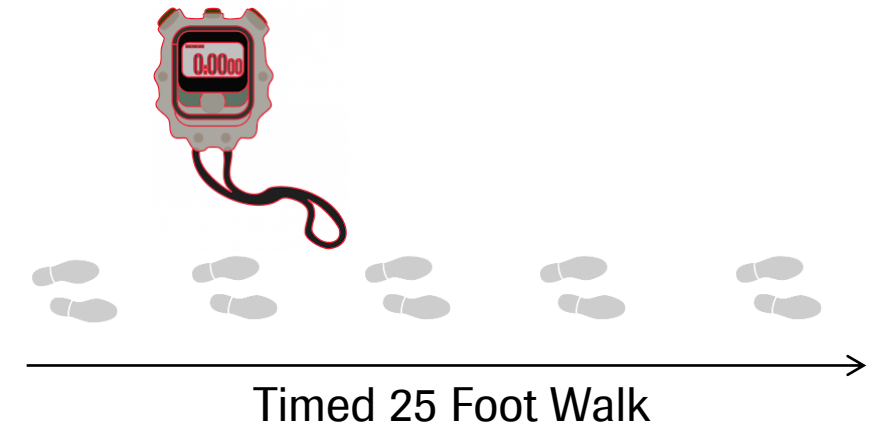
Smartphones allow for modernized and remote assessments

Example: Turning speed in “5 U-Turn Test” (5UTT)

Smartphone-based task



Clinical anchor



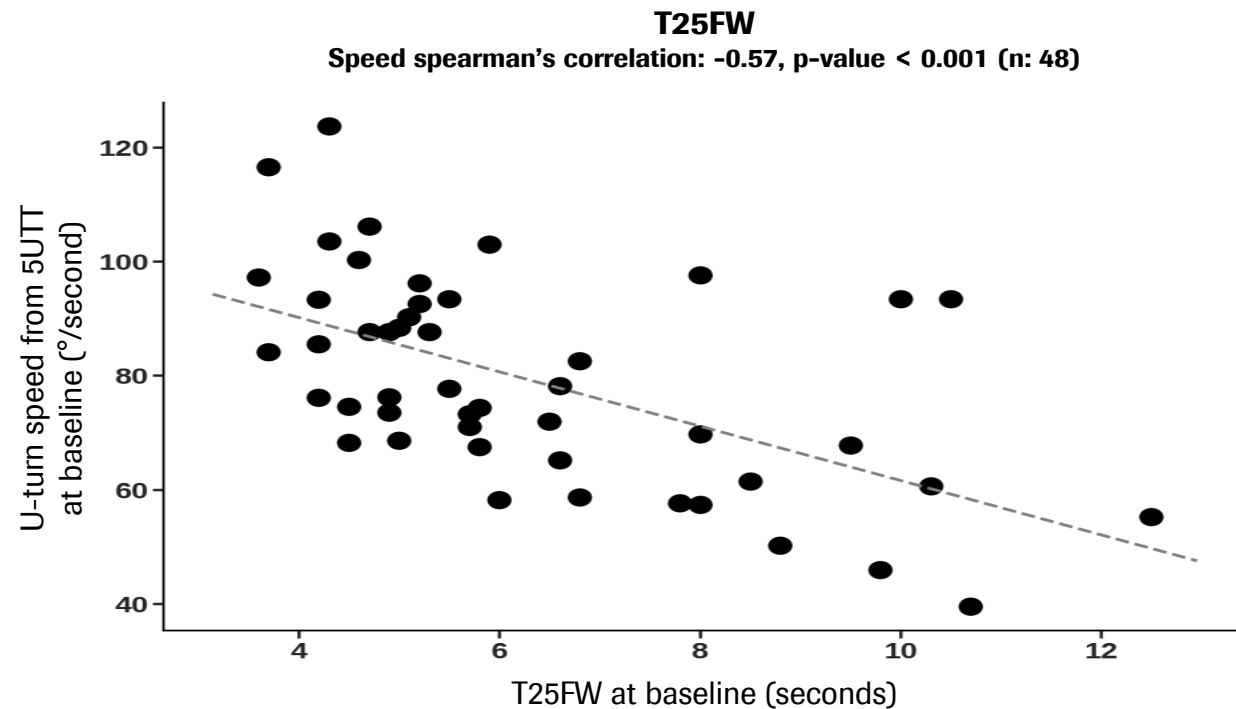
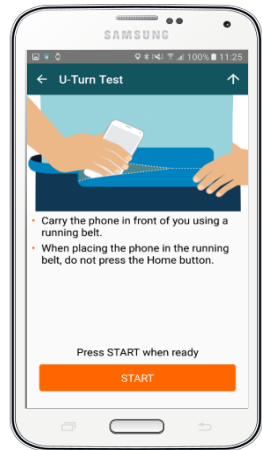
Test rationale:

- U-Turns can be used to assess certain features of gait and balance
- Smartphone and smartwatch sensors can measure change step counts, speed and asymmetry during U-Turns

Patients are asked to:

- Do at least 5 U-turns while walking between two points

Turning speed in U-turns while walking correlates with Timed 25-Foot Walk Test at baseline (and also with Expanded Disability Status Scale)



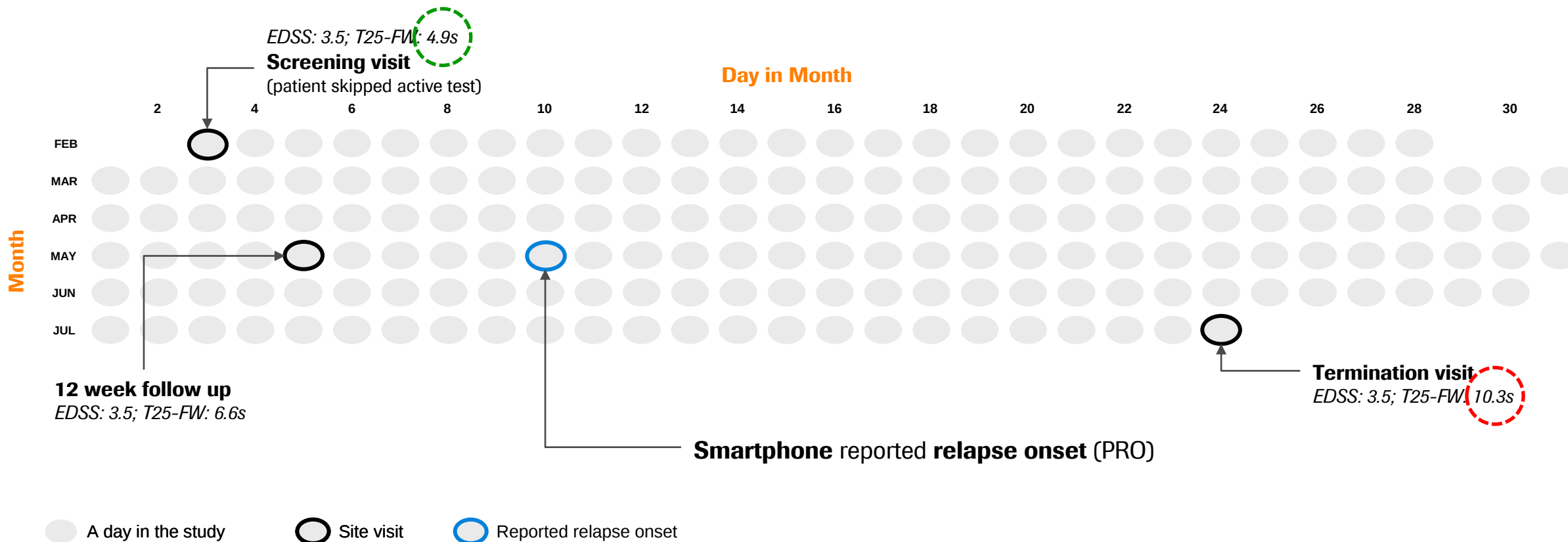
T25-FW: Timed 25 Foot Walk

Mulero et al. 2017 Congress of the European Academy of Neurology, June 25-27, e-Poster EP2169, Amsterdam, The Netherlands

Mulero et al. 2017 ECTRIMS-ECTRIMS Meeting, 25-28 October, Poster P1226, Paris, France

Augmentation:

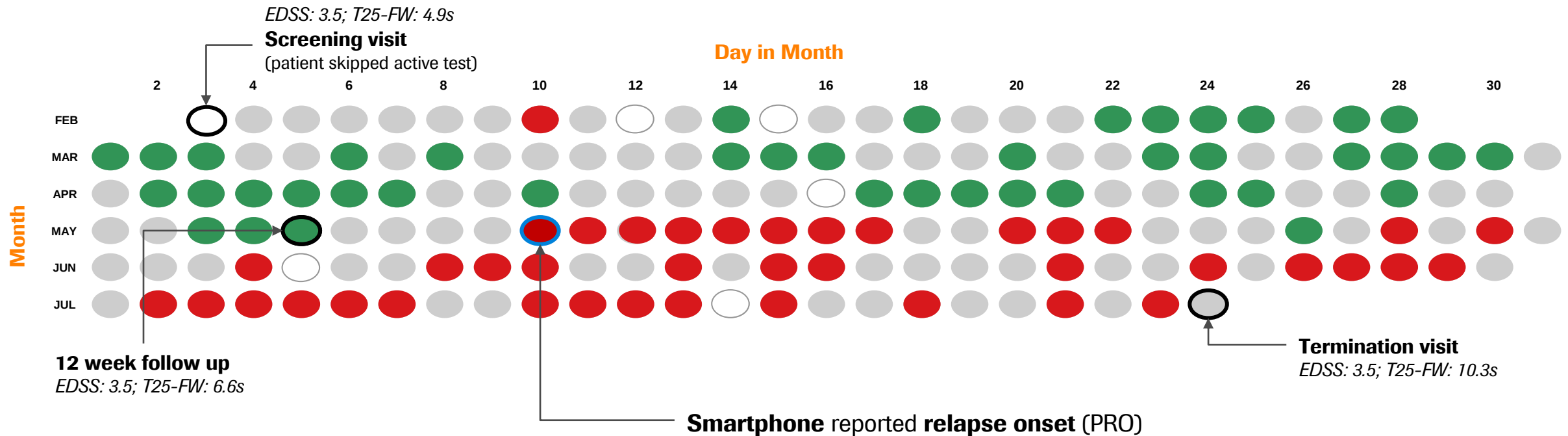
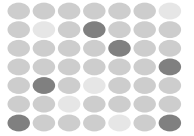
An example journey of a patient with MS in the FLOODLIGHT trial



EDSS: Expanded Disability Status Scale
T25-FW: Timed 25 Foot Walk

Augmentation:

An example journey of a patient with MS in the FLOODLIGHT trial



5UTT U-Turn speed Performance (°/second)*

● Good (> 79.4)
 ● Average (67.3 < x ≤ 79.4)
 ● Poor (≤ 67.3)
 ○ Test not performed

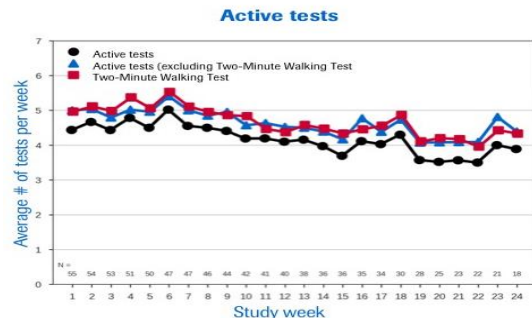
* Performance based on patient's 5 U-Turn Test (5UTT) U-Turn speed distribution

Mulero et al. 2017ECTRIMS-ECTRIMS Meeting, 25–28 October, Poster P1226, Paris, France

FLOODLIGHT Digital Biomarker analysis from adherence to augmentation

1. Adherence

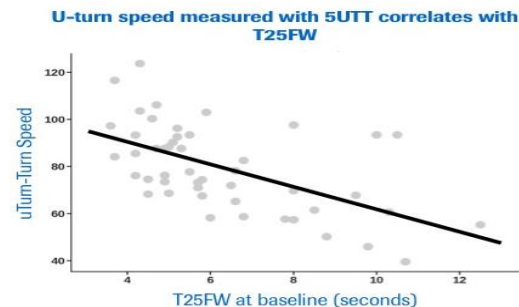
Patients collect data regularly



Strong adherence to active tests measured as proportion of study weeks with at least three days of completed testing

2. Agreement

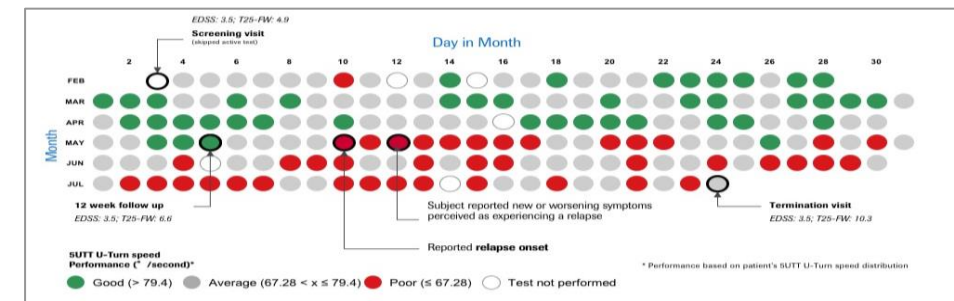
Sensor data correlates with clinical scales



U-turn speed measured with the 5UTT showed **significant correlation with the T25FW**

3. Augmentation

Sensor data provides novel insights beyond clinical scales



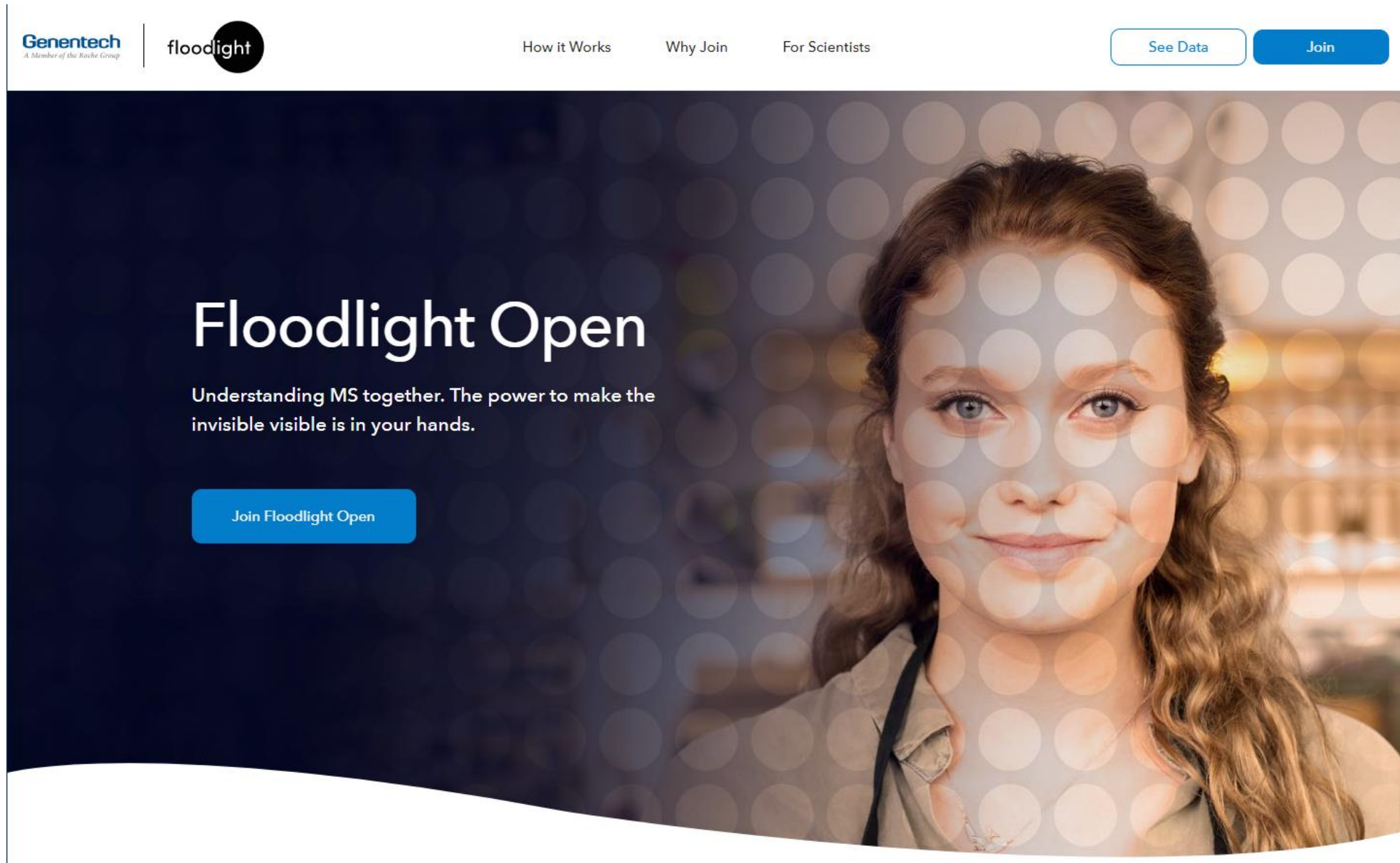
5UTT able to detect relapse between clinic visits. Relapse was **not reported** by the patient to the physician **at the next clinic visit**

Acknowledgements

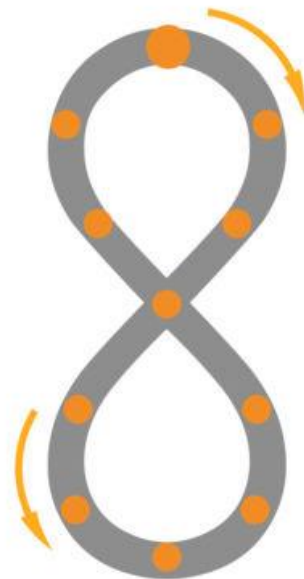
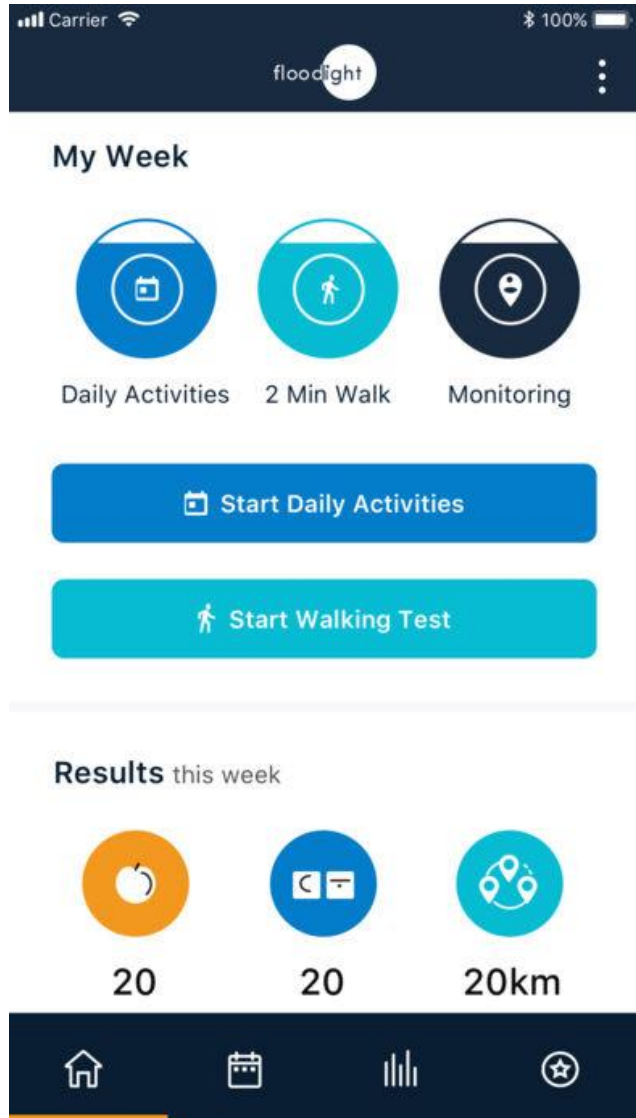


FloodlightOpen.com was launched at AAN in April

Roche



FloodlightOpen.com was launched at AAN in April



Squeeze a Tomato

Squeeze as many tomatoes as possible by pinching them between your thumb and index finger.

START

? Instructions



U-turn Task

Walk between 2 points 4 metres apart. Complete at least 5 turns in 60 seconds.

START

? Instructions

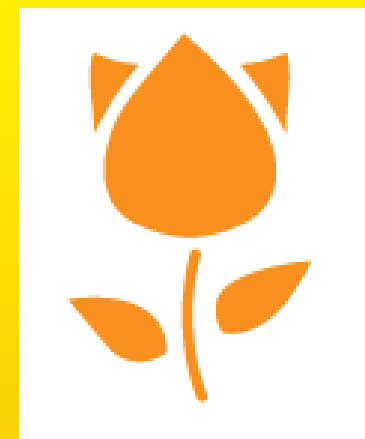
Doing now what patients need next

Two case studies to show where we stand today at Roche



Multiple Sclerosis (MS)
Remote Monitoring

Distributed November 2016

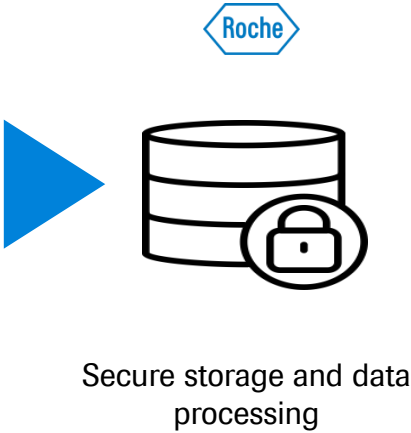
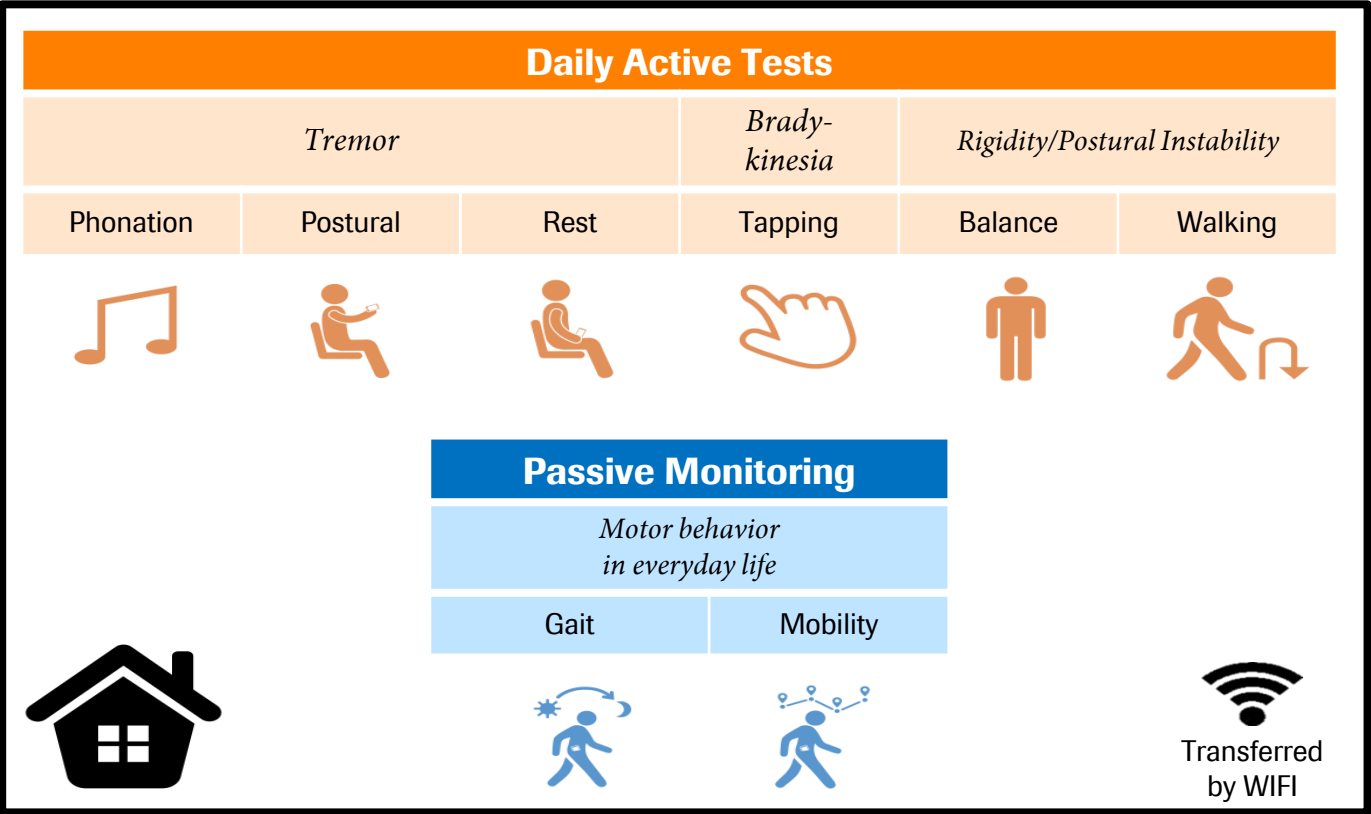
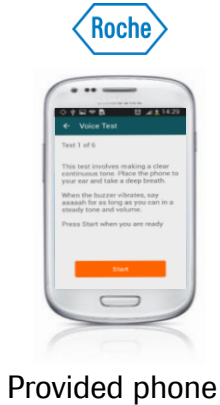


Parkinson's Disease (PD)
Remote Monitoring

Distributed February 2015

RG7935/PRX002 Ph1 Parkinson's disease case study

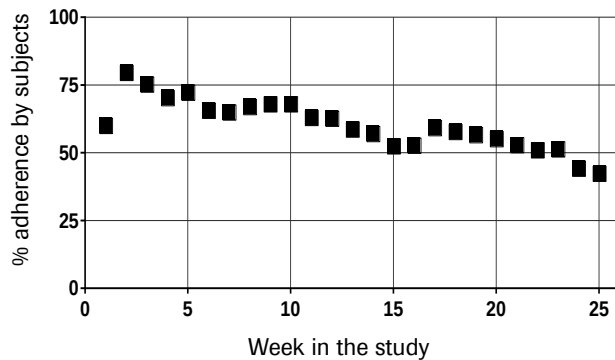
44 subjects completed daily assessments for 6 months, starting Feb. 2015



RG7935/PRX002 Ph1 Digital Biomarker analysis from adherence to augmentation

1. Adherence

Patients collect data regularly

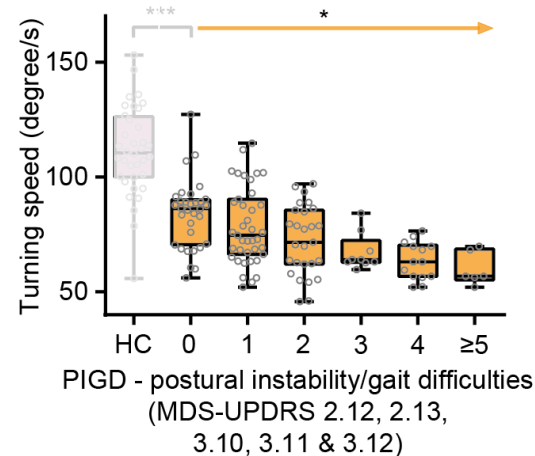


Strong adherence to active tests:

Participants did tests on average 3.5 days a week, including the gait test

2. Agreement

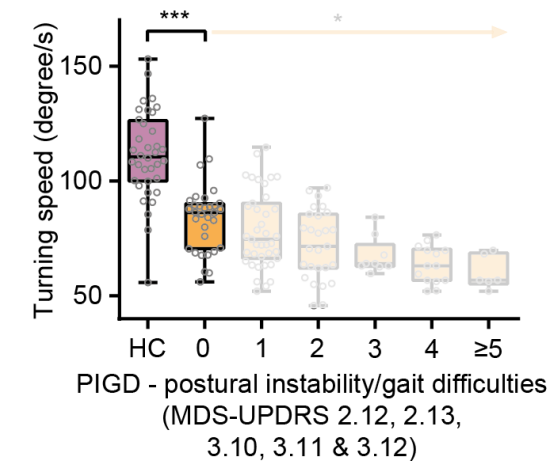
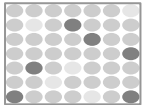
Sensor data correlates with clinical scales



Turn speed measured with gait test showed **significant correlation with the PIGD score**

3. Augmentation

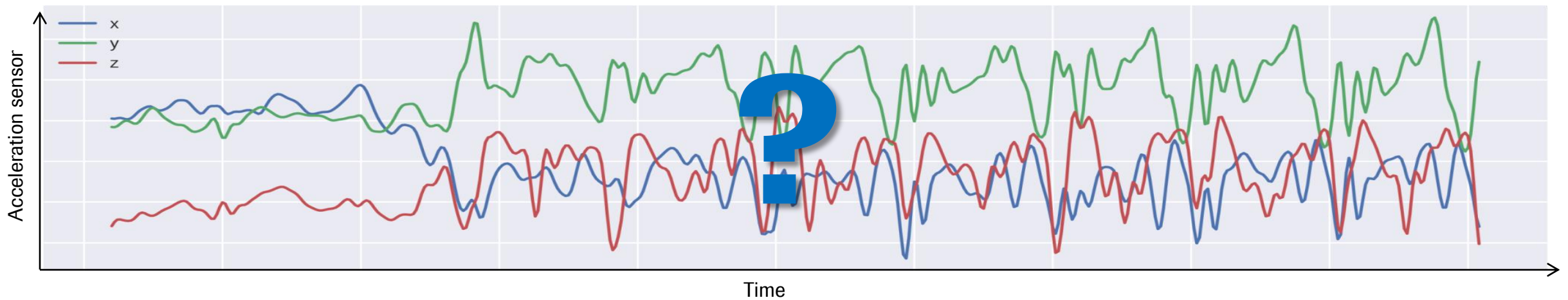
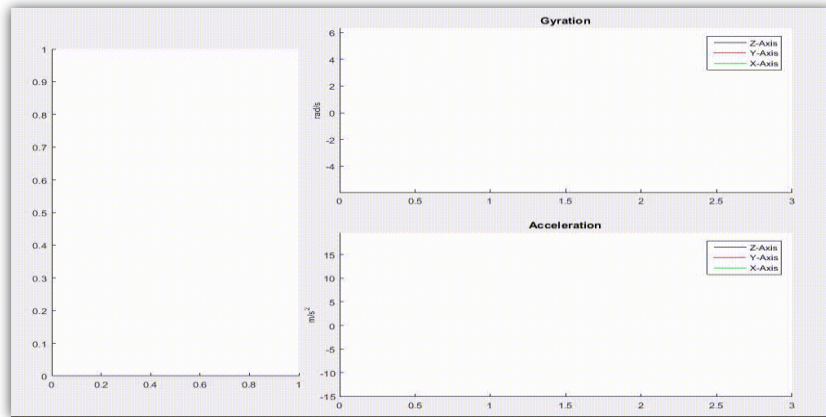
Sensor data provides novel insights beyond clinical scales



Turn speed for healthy controls was **significantly faster** than PD patients scored '0' (= normal) by physician in the MDS-UPDRS items related to postural instability and gait difficulties.

Unlocking insights from passive monitoring data

Routinely using machine learning and high-performance computing to extract unprecedented insights



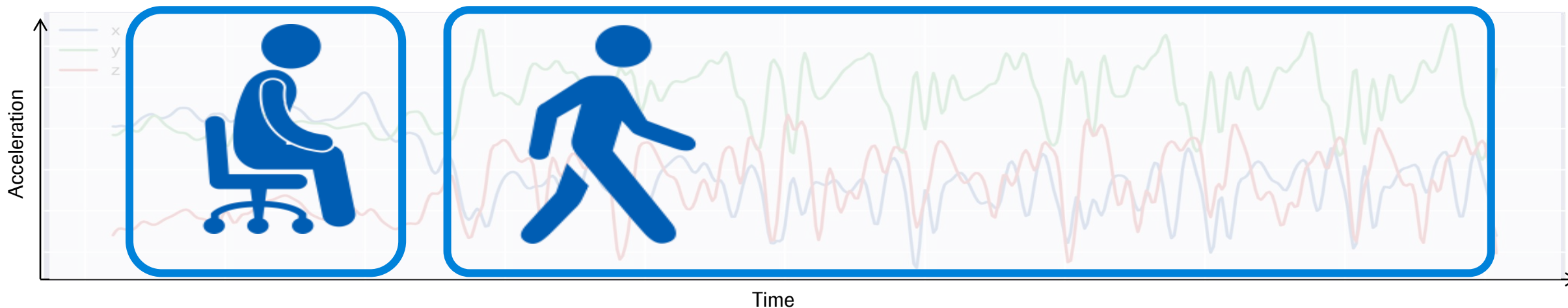
Unlocking insights from passive monitoring data

Routinely using machine learning and high-performance computing to extract unprecedented insights

Trained with 50 hours of activity data
(categorized datasets)



90 mins
to process
1'200 GB



Measuring effects of disease on everyday motor behavior

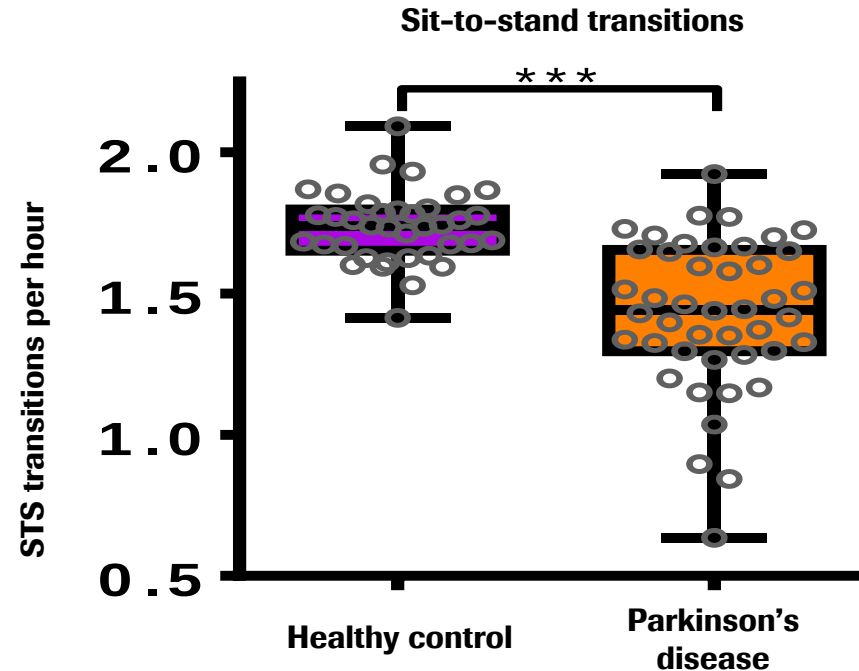
Activity in daily life outside the clinic:

Parkinson's patients differ from controls

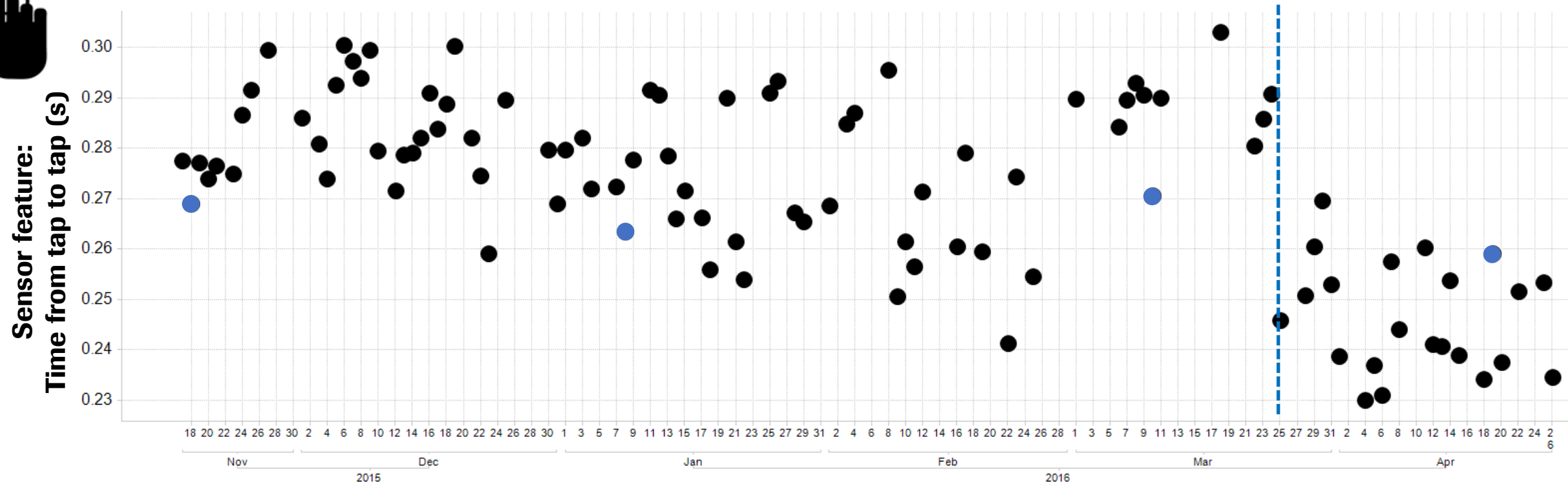
Augmentation

Daily Active Tests					
Tremor			Bradykinesia	Rigidity/Postural Instability	
Phonation	Postural	Rest	Tapping	Balance	Walking

Passive Monitoring	
Motor behavior in everyday life	
Gait	Mobility



Continuous measurement picks up treatment effect fast and accurately



Test:	Dexterity	Gait
Feature:	Tapping Time	Stride-Time
p-value	<0.001	<0.001

RG7935/PRX002 Ph1 Digital Biomarker analysis

First research article published in Movement Disorders

RESEARCH ARTICLE

Evaluation of Smartphone-Based Testing to Generate Exploratory Outcome Measures in a Phase 1 Parkinson's Disease Clinical Trial

Florian Lipinski, PhD,¹ Kirsten L. Taylor, PhD,¹ Timothy Kichenmann, MSc,¹ Detlef Wolf, MSc,¹ Alf Scotland, MSc,¹ Jens Schjodt-Erikson, PhD,¹ Wei-Yi Cheng, PhD,¹ Ignacio Fernandez-Garcia, PhD,¹ Juliane Sidbourg-Polster, PhD,¹ Liping Jin, MD,¹ Jay Solis, BS,² Lynne Versella, MA,² Frank Boess, PhD,¹ Martin Koller, MD,² Michael Grundman, MD,^{2,3} Andreas U. Monsch, PhD,⁴ Ronald B. Postuma, MD,⁵ Anirvan Ghosh, PhD,¹ Thomas Kromer, PhD,¹ Christian Czech, PhD,¹ Christian Gossens, PhD,^{1,4} and Michael Lindemann, PhD¹

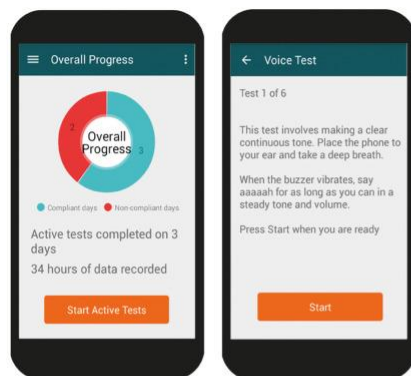
¹Roche Pharma Research and Early Development, pRED Informatics, Pharmaceutical Sciences, Clinical Pharmacology, and Neuroscience, Ophthalmology, and New Disease Discovery and Translational Area, Roche Innovation Center Basel, F. Hoffmann–La Roche Ltd., Basel, Switzerland

²ProPhase Biosciences Inc., South San Francisco, California, USA

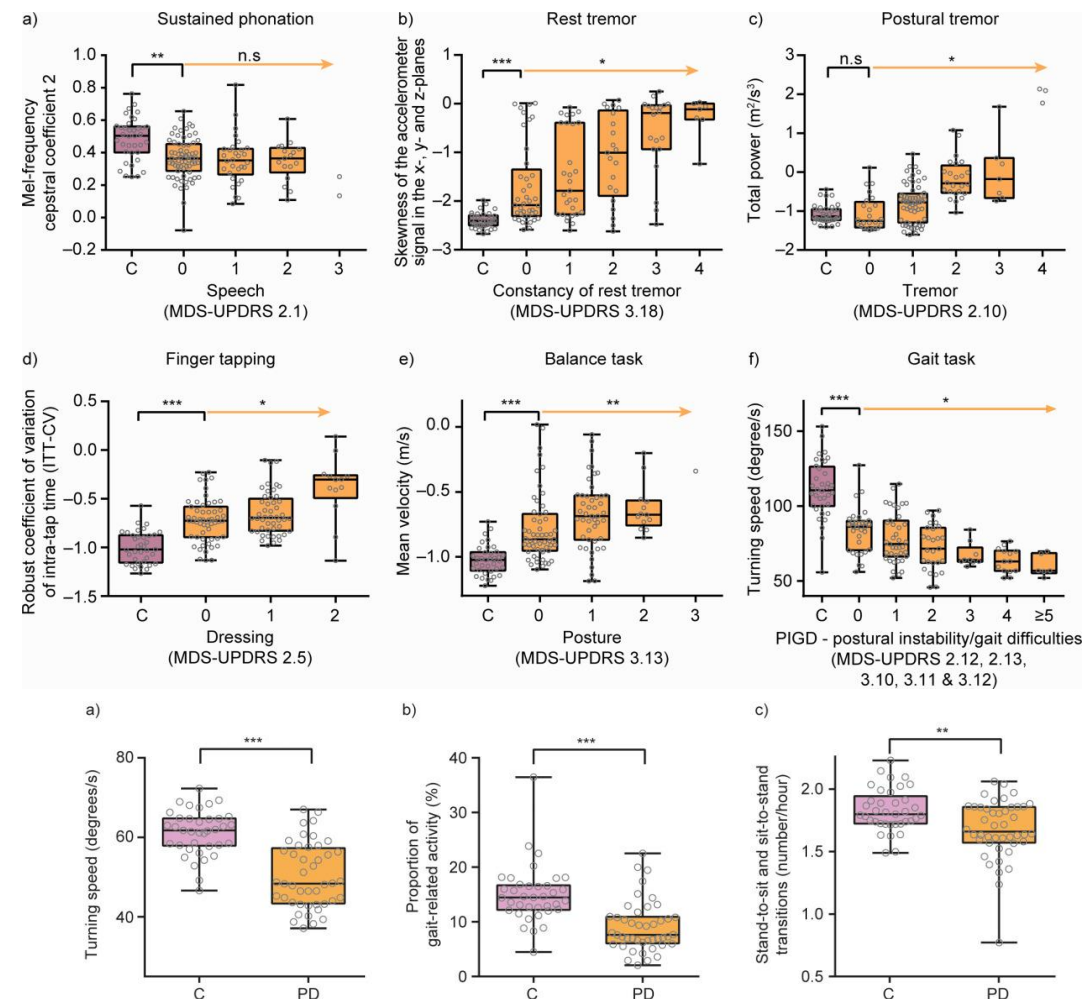
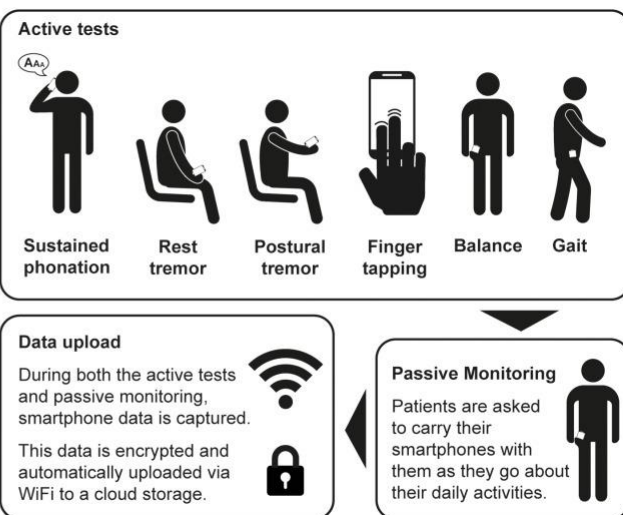
³Global R&D Partners, LLC, San Diego, California, USA

⁴Felix Platter Hospital, University Center for Medicine of Aging, Memory Clinic, Basel, Switzerland; University of Basel, Faculty of Psychology, Basel, Switzerland

⁵Department of Neurology, McGill University, Montreal General Hospital, Montreal, Quebec, Canada



Manufacturer, model: Samsung, Galaxy S3 mini.
Battery life: 7h (due to sensor usage).
Sensors (sampling frequencies): accelerometer and gyroscope (66 Hz $\pm$ 10 Hz); magnetometer (66 $\pm$ 7 Hz); microphone (44.1 kHz).



Acknowledgements



felixplatter*spital*

We are hiring!



- Digital Biomarker Neurodegeneration & Movement Disorder Technology Lead
- Digital Biomarker Neurodevelopment & Psychiatric Disorder Technology Lead
- Digital Biomarker Clinical Operations Lead
- Software Product Manager
- Mobile Solution Software Architect
- Digital Biomarker Data Analysis Lead
- Data Scientists
- Mobile App Development Lead

Menu Search Careers

DE Roche

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Graduates at Roche



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Doing now what patients need next