Towards scientific validated digital biomarkers measured by patient's own smart devices:
cases studies from Parkinson's disease and Multiple Sclerosis

Christian Gossens, PhD, MBA, Global Head Digital Biomarkers, Roche pRED
ISCTM Autumn 2018 Conference, Marina Del Rey, 15 October 2018
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

Data processing & analysis

Clinical knowledge

Sensors

Connectivity

GPS

Sound

Light

Touch

Accelerometer

Gyroscope

Magnetometer

HC0 1 2 3 4

-1

0

1

2

3

4

And more

HC 0 1 2 3 4

-1

0

1

2

* ***

****
Two case studies

Parkinson's Disease (PD)
Remote Monitoring

Distributed February 2015

Multiple Sclerosis (MS)
Remote Monitoring

Distributed November 2016
RG7935/PRX002 Ph1 Parkinson’s disease case study
44 subjects completed daily assessments for 6 months, starting Feb. 2015
Active Test Example 1: Gait

*How does the incoming data look like?*

---

**Active Tests**

<table>
<thead>
<tr>
<th>Voice</th>
<th>Tremor</th>
<th>Dexterity</th>
<th>Bradykinesia: Lower Body</th>
</tr>
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<tbody>
<tr>
<td>Phonation</td>
<td>Rest</td>
<td>Postural</td>
<td>Tapping</td>
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</tbody>
</table>

**Passive Monitoring**

- Motor behavior in everyday life
- Gait
- Mobility
Accelerometer and gyroscope data from Gait test

Illustrative example
Active Test Example 2: Balance

How sensitive are sensors in a normal Smartphone?

Active Tests

<table>
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</table>

Passive Monitoring

Motor behavior in everyday life

<table>
<thead>
<tr>
<th>Gait</th>
<th>Mobility</th>
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</table>

Test 2 of 6
Stand upright and without support, with the phone close to your hip (e.g. in your pocket or in a fanny pack).

When the buzzer vibrates, stand unaided until the buzzer vibrates a second time.

Press Start to begin.
Balance: Visualizing sway

Illustrative example

“Healthy” tester: not much sway

Patient: a lot of sway
Sensor measures correlate with clinical gold standard (MDS-UPDRS)

**Example: Rest Tremor**

![Graph showing correlation between sensor data feature and physician rating for Rest Tremor (MDS-UPDRS)]
Frequent sampling enabled measurement of symptoms before/after sporadic clinic visits

‘We only see a snapshot of a patient’s clinical status during the exam – there is so much more we would need to know.’ (Investigator)

Sensor data feature (mean over 2 weeks)

Physician rating for Rest Tremor (MDS-UPDRS)
Sensors detect significant rest tremor in patients clinically scored as having no tremor (‘0’)

Heightened sensitivity to motor symptoms will help measure progression, especially in prodromal patients.
**Parkinson’s disease case study**

*Continuous measurement picks up treatment effect fast and accurately*

**Test:** Dexterity

<table>
<thead>
<tr>
<th>Feature</th>
<th>Tapping Time</th>
<th>Stride-Time</th>
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<tbody>
<tr>
<td><strong>p-value</strong></td>
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</table>
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

<table>
<thead>
<tr>
<th>Daily Active Tests</th>
<th>Tremor</th>
<th>Brady-kinesia</th>
<th>Rigidity/Postural Instability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy control</td>
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<tr>
<td>Parkinson’s disease</td>
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</table>

Sit-to-stand transitions per hour

Healthy control
Parkinson’s disease

Augmentation

Passive Monitoring
Motor behavior in everyday life
Gait Mobility

Diagram showing sit-to-stand transitions per hour for healthy control and Parkinson’s disease.
RG7935/PRX002 Ph1 Digital Biomarker analysis
First research article published in Movement Disorders
Acknowledgements
The Roche PD Mobile Application V2 was just presented at MDS 2018 meeting (Hongkong, October 6)

<table>
<thead>
<tr>
<th>ACTIVE TESTS</th>
<th>PASSIVE MONITORING</th>
<th>IN–CLINIC TESTS</th>
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</thead>
<tbody>
<tr>
<td><strong>Bradykinesia</strong></td>
<td>Bradykinesia and Activities of Daily Living</td>
<td>Balance</td>
</tr>
<tr>
<td>Draw A Shape</td>
<td>Gait</td>
<td>Daily</td>
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<tr>
<td>Dexterity</td>
<td>Arm Swing &amp; Tremor</td>
<td>Daily</td>
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<tr>
<td>Hand Tensing</td>
<td>Mobility &amp; Sociability</td>
<td>Daily</td>
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<tr>
<td><strong>Tremor/Bradykinesia</strong></td>
<td>Timed Up &amp; Go</td>
<td>At selected visits</td>
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<tr>
<td>Speech</td>
<td>Cognitive Test (SDMT)</td>
<td>At selected visits</td>
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<tr>
<td>Phonation</td>
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<td>Postural Tremor</td>
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<td>Rest Tremor</td>
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<td>U-Turn</td>
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<td>Alternating</td>
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<tr>
<td><strong>Rigidity/Postural Instability</strong></td>
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<tr>
<td>Bradykinesia Days (Every 2nd Day)</td>
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<td><strong>Cognition</strong></td>
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<td><strong>In–Clinic Tests</strong></td>
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<td>Daily</td>
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<td>Fortnightly</td>
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Two case studies

Parkinson’s Disease (PD)
Remote Monitoring

*Distributed February 2015*

Multiple Sclerosis (MS)
Remote Monitoring

*Distributed November 2016*
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

Sensor-based vs clinical rating scale parameters for symptom severity

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

Site visit

Week

Day
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

Week

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Day

1 2 3 4 5 6 7

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**FLOODLIGHT study design**

- **Site visit**
- **Clinical/PRO rating scales**
- **Active test**

<table>
<thead>
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<th>Week</th>
<th>Day</th>
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*Munro et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana*
# FLOODLIGHT study design

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<td>Clinical/PRO rating scales</td>
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**Site visit**
- Day 1

**Clinical/PRO rating scales**
- Days 4, 5, 6, 7

**Active test**
- Days 1, 2, 4, 7

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FLOODLIGHT study design

Gait Behaviour
Mobility Pattern

Site visit  Clinical/PRO rating scales  Active test  Passive monitoring

Week

Day

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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

<table>
<thead>
<tr>
<th>Study week</th>
<th>Active tests</th>
<th>Active tests (excluding Two-Minute Walking Test)</th>
<th>Two-Minute Walking Test</th>
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<tr>
<td>1-2</td>
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<td>23-24</td>
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<td>4-5</td>
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</table>

### Passive monitoring

<table>
<thead>
<tr>
<th>Study week</th>
<th>Smartphone</th>
<th>Smartwatch</th>
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<tbody>
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<td>3-4</td>
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Smartphones allow for modernized and remote assessments

**Example 1: Pinching test “Squeeze a Shape”**

**Smartphone-based task**

- This test helps measure physical changes in the hands and fingers.
- You have 30 seconds to squeeze as many of the shapes on the screen as you can.
- Try to squeeze the shapes as fast as you can.

**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

Montalban et al. 2018 ECTRIMS Meeting, 10–12 October, Berlin, Germany

‡ p<0.001; * p<0.05
9HPT= 9-hole peg test;
MS= multiple sclerosis
Smartphones allow for modernized and remote assessments

Example 2: Turning speed in “5 U-Turn Test” (5UTT)

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)

Montalban et al. 2018 ECTRIMS Meeting, 10–12 October, Berlin, Germany
Augmentation:
An example journey of a patient with MS in the FLOODLIGHT trial

- **Screening visit** (patient skipped active test)
  - EDSS: 3.5; T25-FW: 4.9s

- **12 week follow up**
  - EDSS: 3.5; T25-FW: 6.6s

- **Smartphone reported relapse onset (PRO)**
  - EDSS: 3.5; T25-FW: 10.3s

- **Termination visit**
  - EDSS: 3.5; T25-FW: 10.3s

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

Mulero et al. 2017 ECTRIMS-ACRIMS Meeting, 25–28 October, Poster P1226, Paris, France
Augmentation: An example journey of a patient with MS in the FLOODLIGHT trial

Screening visit (patient skipped active test)  
EDSS: 3.5; T25-FW: 4.9s

12 week follow up  
EDSS: 3.5; T25-FW: 6.6s

Termination visit  
EDSS: 3.5; T25-FW: 10.3s

Smartphone reported relapse onset (PRO)

SUTT 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 (SUTT) U-Turn speed distribution

Mulero et al. 2017 ECTRIMS-ACTRIMS Meeting, 25–28 October, Poster P1226, Paris, France
Acknowledgements
Digital Biomarkers rapidly built into clinical research programs

- Parkinson’s disease (Phase 1, Feb 2015)
- Multiple Sclerosis (Floodlight, 2016)
- Parkinson’s disease (Phase 2, 2017)
- Spinal Muscular Atrophy
- Huntington’s disease (2018+)

Phase II study of Anti-Amyloid Antibody in Early Parkinson’s Disease

BP39529

PASADENA

Press START to begin.
Working with the community to build sets of robust digital outcome measures

Parkinson’s disease

Multiple Sclerosis

https://floodlightopen.com
FDA launched Program to apply Digital Health to Drugs

• “... We’re also working to ... develop digital biomarkers as drug development tools.”

• “... to enable these opportunities, we need clear policies for how the review and validation of digital health tools can be baked into drug development programs.”

https://www.fda.gov/NewsEvents/Speeches/ucm605697.htm
Doing now what patients need next
Deep Learning-Based Human Activity Recognition for Continuous Activity and Gesture Monitoring for Schizophrenia Patients with Negative Symptoms

Daniel Umbricht1, Wei-Yi Cheng2, Florian Lipsmeier1, Atieh Bandadian1, Paul Tamburrini1, Michael Lindemann1,2

1 Roche Innovation Center Basel, P. Hoffmann-La Roche Ltd, Basel, Switzerland 2 Roche Innovation Center New York, Roche TCRG Inc, New York, USA 3 Baden-Württemberg Cooperative State University, Leonberg, Germany

1 Corresponding authors

1. Introduction
- Diminished expression and affectation are two key factors of the negative symptoms of schizophrenia. Among them, affectation represents the critical component that drives functional outcome [1].
- Quantitative and continuous monitoring of behavior and symptoms associated with negative symptoms of schizophrenia has been a challenge in clinical trials.
- Recent development in wearable sensor technology provides new opportunities to tackle these problems.
- However, to connect the sensor data with clinical observations and measures of motivated behavior still requires development of advanced analytics and real-world validations.

2. Trial design and data collection
- Thirty-three schizophrenia patients with moderate negative symptoms were recruited in a 5-week cross-over proof-of-concept study (Roche study EP290904, Table 1).
- Of these, 31 patients were provided with a GeneActiv© wrist-worn accelerometer device to record activity data for 15 weeks.
- Motivation behavior was assessed with an effort choice task (Fig 1a) [2], 2% of high effort choices was the outcome measure.
- Negative symptoms were rated with the Brief Negative Symptom Scale (BNSS) and Positive and Negative Syndrome Scale (PANSS).
- The activity device recorded the acceleration of wrist movement at 30Hz.
- Patient adherence was acceptable. Median collected monitoring data per patient was 1,988 hours (about 11 weeks) of 7,4% (Fig 1a).
- For all analyses activity data obtained over the last 5 days of the placebo period and assessments at the end of the placebo period were used.

3. Human Activity Recognition (HAR) and Gesture Feature Derivation
- We trained a 9-layer convolutional recurrent neural network (Fig 2a) using two public annotated data sets containing wrist-worn accelerometer data to infer the subject’s activities [3][4].
- The trained human activity recognition (HAR) model was tested with hold-out validation data and internally collected sensor data from previous studies [5].
- More than 89% of accuracy to separate the ambulatory (walking, standing, cycling) from stationary activities (sitting, standing, lying down, hand work) was achieved (Fig 2b).
- From the predicted activities we derived for each patient the activity ratio (= the total active time divided by the monitoring time).
- We further inferred the gesture events and gesture features based on the activities and acceleration signal using an empirically defined threshold on an accelerometer signal from the wrist [5].

4. Activity ratio correlates with high effort choice
- The activity ratio was significantly correlated with the % high effort choice at the end of the placebo period (Spearman r = 0.58, P value = 0.01, Fig 3), indicating an association of avolition and lower activity in daily life.

5. Gesture features correlate with BNSS
- The median daily gesture counts were negatively correlated with BNSS total score (Spearman r = -0.44, P value = 0.03, Fig 4a) at the end of placebo period, specifically with the diminished expression sub-score at the end of placebo period (Spearman r = -0.42, P value = 0.03, Fig 4b).
- Gesture features correlated with BNSS total score and diminished expression sub-score (Table 2).

6. Discussion and Outlook
- The results demonstrate the feasibility of using wrist-worn activity for continuously monitoring clinically-relevant behavior in a clinical trial setting.
- Activity and gesture features derived from a human activity recognition model were associated with motivated behavior and expressive deficits, respectively, supporting the validity of activity and gesture-based digital biomarkers for negative symptoms.
- The activity and gesture features derived from human activity recognition model shows promise to be used as biomarker for drug development.

References
Doing now what patients need next