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?

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!
Continuous data from mobile sensors
Collect, process, analyse and add to clinical knowledge
Roche.com featuring Digital Biomarkers

The measure of you

Learn about digital biomarkers in health
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.
FLOODLIGHT study design
60 patients with MS, 20 controls

Site visit

Day

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

Muñoz et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana
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

Day

Mulero et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana
FLOODLIGHT study design

Site visit  Clinical/PRO rating scales  Active test

Week

Day

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

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)

Mulero et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana
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**

<table>
<thead>
<tr>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

**Daily**

- **1**
- **2**
- **3**
- **4**
- **5**
- **6**
- **7**

Mulero et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana
### FLOODLIGHT study design

<table>
<thead>
<tr>
<th>Day</th>
<th>Site visit</th>
<th>Clinical/PRO rating scales</th>
<th>Active test</th>
<th>Passive monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&quot;Gait Behaviour&quot;</td>
<td>&quot;Mobility Pattern&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Munro et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active tests</td>
<td>Active tests (excluding TMT)</td>
<td>TMT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Passive monitoring**

<table>
<thead>
<tr>
<th>Study week</th>
<th>Smartphone</th>
<th>Smartwatch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mulero et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana
Significant cross-sectional correlation at baseline of oral vs smartphone-based Symbol Digit Modalities Test

Number of correct responses
Spearman's correlation: 0.658, p-value < 0.0001 (n: 47)

Mulero et al. 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, May 24-27, Poster QL19, New Orleans, Louisiana
Smartphones allow for modernized and remote assessments
Example: pinching test “Squeeze a Shape”

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

Healthy controls n=15

Patients with MS with 9HPT ≥ 23.9s n=15

‡p<0.001

9HPT= 9-hole peg test;
MS= multiple sclerosis

Mulero et al. 2017 ECTRIMS-ACTRIMS Meeting, 25–28 October, Poster P1226, Paris, France
Smartphones allow for modernized and remote assessments

Example: 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)

T25FW
Speed spearman’s correlation: -0.57, p-value < 0.001 (n: 48)

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

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

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

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

Smartphone reported relapse onset (PRO)

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

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

**EDSS:** 3.5; **T25-FW:** 4.9s

**Screening visit** (patient skipped active test)

**Day in Month**

- **Smartphone** reported relapse onset (PRO)
- **12 week follow up**
  - **EDSS:** 3.5; **T25-FW:** 6.6s
- **Termination visit**
  - **EDSS:** 3.5; **T25-FW:** 10.3s

**SUIT 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 (SUIT) U-Turn speed distribution

Mulero et al. 2017 ECTRIMS-ACRIMS 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
FloodlightOpen.com was launched at AAN in April

http://ios.me/app/1365939494/floodlight-open
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

2. Agreement
Sensor data correlates with clinical scales

3. Augmentation
Sensor data provides novel insights beyond clinical scales

**Strong adherence** to active tests:
Participants did tests on average 3.5 days a week, including the gait test

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

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.

MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale
PIGD: Postural Instability / 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

Sit-to-stand transitions

Healthy control  Parkinson’s disease

STS transitions per hour

** **

Augmentation ✅
Parkinson’s disease case study
Continuous measurement picks up treatment effect fast and accurately

<table>
<thead>
<tr>
<th>Test:</th>
<th>Dexterity</th>
<th>Gait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature:</td>
<td>Tapping Time</td>
<td>Stride-Time</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
RG7935/PRX002 Ph1 Digital Biomarker analysis
First research article published in Movement Disorders
Acknowledgements

Roche

Aston University

prothena

McGill University

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

https://www.roche.com/careers
Doing now what patients need next