Roche Pharma Day 2019

Digitalisation & Personalised Health Care (PHC)

Bryn Roberts | Global Head of Operations & Informatics, pRED
Introduction

FAIR Data

Examples

Summary
Introduction to Digital and PHC @Roche

FAIR Data

Examples

Summary
Roche is part of a dynamic healthcare ecosystem
Undergoing and anticipating a high degree of digital transformation and disruption
Drivers and enablers of digital transformation
Creating opportunities across the pharma value chain

<table>
<thead>
<tr>
<th>Data</th>
<th>Technology</th>
<th>Compute</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Scale, variety, complexity</td>
<td>• Sensors, wearables, mobile</td>
<td></td>
</tr>
<tr>
<td>• Real world, real time</td>
<td>• Connected app ecosystem</td>
<td></td>
</tr>
<tr>
<td>• FAIR-ification</td>
<td>• IOT, blockchain, cloud</td>
<td></td>
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<tr>
<td></td>
<td>• High performance compute</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Machine learning</td>
<td></td>
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<tr>
<td></td>
<td>• Deep learning</td>
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</tbody>
</table>

Digital talent
Digitalisation is transforming Roche’s entire Pharma value chain

Deliver the right treatment to the right patient at the right time

Pre-clinic → Clinical Development → Registration → Access → Production & Supply → Diagnosis → Treatment

- Meaningful data at scale (MDAS)
- Genomics
- Real world data (RWD)
- Digital biomarkers
- Artificial Intelligence (AI)
- NAVIFY®
- Decision support
- Consumer ecosystems

- Quality «Big» data
- Positive impact on Pharma business
- Leveraging data through analytics
Pharma digital strategic priorities

Research & development
Accelerate and de-risk early-stage assets in research via automation, modelling and AI technologies, e.g. for:
- Better target selection
- Automated compound profiling and selection
- De novo compound design

More effective and faster clinical trials in development via integrating clinical and real-world datasets and AI technologies, e.g. for:
- Improved outcomes and enhanced data quality
- Lower cost and operational efficiency
- Faster time to market for new products

Production & supply chain
Blockbuster drugs
Targeted medicines
Individualised treatment

Medicine augmentation
Today
Future
Digitally-enabled therapeutic decisions
Digitally-enabled behaviour change
Digital biomarkers
Introduction

**FAIR Data** *are the foundation for digital transformation*

Examples

Summary
Meaningful data at scale (MDAS)
Integrate complementary, longitudinal data at scale

Enable understanding of patient and disease heterogeneity and its relevance to clinical outcome at unprecedented resolution
Realising the value of MDAS
These data must be Findable, Accessible, Interoperable and Reusable
FAIR Data @Roche

EDIS project: taking clinical data FAIRness & insights to a new level

- **Enhanced Data and Insight Sharing (EDIS)**
- Accessibility and integration of clinical trial data assets, previously siloed or left with CROs
- Capability development, e.g.
  - Roche Data Commons architecture
  - Roche Terminology Service and data standards
  - Curation capability
- Deliverables, e.g.
  - Datamarts for CIT, ASD, Asthma...
  - Data workflows and citizenship policies
- Our CEO is personally sponsoring and supporting these initiatives
Introduction

FAIR Data

Examples of transformative digital use cases

Summary
4 examples of transformative digital use cases
Across different therapeutic areas, modalities and pipeline phases

1. **Molecule discovery and optimization**
   Leveraging AI (machine learning)…

2. **Utilizing clinic-genomic RWD in Oncology trials**
   External control arms and patient selection

3. **Deep image analysis in Ophthalmology**
   Leveraging AI (deep learning)…

4. **Digital biomarkers in Neuroscience**
   Mobile, wearables and AI for real-world relevance
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Bacterial phenotypic profiling

Predicting mechanism of novel antibiotic candidate molecules

High content screening assay with sub-lethal compound concentrations

Multi-parametric fingerprints

Multi-class probabilistic predictions

The Random Forest algorithm provides robust, fast and interpretable classification of reference compounds and similarity probabilistic predictions of test compounds

Predicting VH–VL domain orientation for antibodies
Preserving original antibody properties during antibody engineering from models based only on sequence information

Relative orientation of the VH and VL domains codetermines the topology of the antigen-binding site

VH-VL=variable heavy-variable light; Prediction of VH–VL domain orientation for antibody variable domain modeling Bujotzek A. et al. 2015, Proteins 83, 681–695
Predicting VH–VL mAb domain orientation from primary sequences

Preserving original antibody properties during antibody engineering from models based on sequence information

- Extract mAb sequences and crystal structures from public and internal data sets
- Describe orientation by 5 angles & C length
- Train Random Forest classifier to predict angles from sequence
- Test on independent dataset
- Roche classifier outperforms other methods
- Now part of the mAb engineering workflow in LMR

VH-VL=variable heavy-variable light; LMR=large molecule research; Prediction of VH–VL domain orientation for antibody variable domain modeling Bujotzek A, et al. 2015, Proteins 83, 681-695
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Flatiron data as external control - Alecensa payer dossiers

Accelerated access in 20+ countries by more than 1 year

Alecensa was associated with significantly prolonged OS compared to Ceritinib in the real world and ASCEND 2 trial

- Overall survival analysis comparing Alecensa Ph II data with real world external control to demonstrate value of Alecensa relative to standard of care for patients with ALK+ metastatic non-small cell lung cancer

CI=confidence interval; HR=hazard ratio; NR=not reached; OS=overall survival; RWD=real world data; Davies, J. et al. 2018 Journal of Comparative Effectiveness Research
• RWD allow fast tracking of changes in the standard of care as new treatments enter clinical utility
• Understanding current treatment patterns allows for improved trial design in on-going development programs
Identifying patients with poor prognosis

**Reporting directly to Roche Group CEO**

- Identification of patients with rapidly progressing disease
- Characterisation of their tumor genomic profiles
- Roche invention and patenting* of an improved progression prediction algorithm (RoPro) using AI (deep learning)
  - RoPro is used to improve clinical trial design, e.g. to support dose selection in CD20 TCB studies

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**Flatiron-FMI clinic-genomic data enabled:**

- Identification of patients with rapidly progressing disease
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*“Roche Prognostic Score (RoPro) for overall survival”*
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Prediction of optical coherence tomography measures of diabetic macular thickening from color fundus photographs

Input data from Phase 3 DME studies

Central Subfield Thickness (CST) or Central Foveal Thickness (CFT) above threshold (250μm and 400μm)

Example performance: prediction of CFT ≥400μm: AUC of 0.97 (95% CI = 0.88–1.00; sensitivity = 90.0%; specificity = 94.0%; N=45 CFPs)

Transfer of “knowledge” using CFPs from the Kaggle Diabetic Retinopathy challenge - binary classifier for severity

Prediction of optical coherence tomography measures of diabetic macular thickening from color fundus photographs

To gain insight into the inner workings of the DL models, attribution maps were created using guided back-propagation.

These maps display the image locations that the DL model focused on to make its decision about the presence of MT.

Example of map created by the DL model to detect MT with CFT > 250 μm

Example of map created by the DL model to detect MT with CFT > 400 μm


Machine learning: Prediction of response to anti-VEGF treatment in Patients with nAMD using SD-OCT

A Machine Learning Approach to Predict Response to Anti-VEGF Treatment in Patients With Neovascular Age-Related Macular Degeneration Using SD-OCT

Objectives
- The purpose of this study was to develop a machine learning model to predict the response to anti-VEGF therapy in patients with neovascular age-related macular degeneration (nAMD) using spectral-domain optical coherence tomography images.

Methods
- A machine learning algorithm was trained on a dataset of SD-OCT images from patients with nAMD who received anti-VEGF treatment. The model was validated using a separate dataset of images from a different group of patients.

Results
- The model achieved an accuracy of 85% in predicting the response to treatment, with a sensitivity of 80% and a specificity of 90%.

Conclusions
- Machine learning can be a useful tool in predicting the response to anti-VEGF treatment in patients with nAMD.

nAMD = neovascular age-related macular degeneration; SD-OCT = spectral-domain optical coherence tomography; ARVO, April 2019
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Digital biomarkers
Providing enhanced patient insights and novel endpoints

- Clinical trials utilizing **mobiles, wearables** and **gaming** devices
- More **sensitive, precise** and **objective**
- **Continuous** and **longitudinal** measurement captures episodic and rare events
- Reduced **assessment burden** and greater **real-world relevance**

Multiple Sclerosis
Parkinson’s Disease
Huntington’s Disease
Spinal Muscular Atrophy
Autistic Spectrum Disorders
Angelman’s Syndrome...
Active tests

Designed for specific symptom domains and patient populations

Acceleration left/right

Acceleration forward/backwards

Continuous passive monitoring
AI (deep learning) classification of activity & performance in daily tasks
Roche HD digital monitoring platform has been developed to assess disease progression in clinical trials

**Patients with HD in the RG6042 global development program receive a smartphone and smartwatch**

### ACTIVE TESTS

<table>
<thead>
<tr>
<th>Patient-reported outcomes</th>
<th>Cognitive tests</th>
<th>Upper body motor tests</th>
<th>Stability and gait</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily GU</strong></td>
<td>EQ-5D-5L</td>
<td>SDMT</td>
<td>Speeded tapping</td>
</tr>
<tr>
<td><strong>Weekly</strong></td>
<td></td>
<td><strong>Draw a shape</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Weekly</strong></td>
<td></td>
<td><strong>Chorea</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Daily</strong></td>
<td><strong>Balance</strong></td>
<td><strong>U-turn</strong></td>
<td><strong>2-minute walk</strong></td>
</tr>
</tbody>
</table>

### PASSIVE MONITORING

**Activities of daily living**

- **Gait**
- **Chorea**
- **Activity levels**

With smartphone and smartwatch

- **Gait**
- **Chorea**
- **Activity levels**

**Equipped with the smartphone and smartwatch, actively and passively monitored**

- Patients first complete active tests using these tools in a teaching session in the clinic. The active tests are then done remotely at home and at follow-up clinical visits.
- For passive monitoring, patients are asked to carry the devices with them as they go about their daily activities.
- The sensor data are securely transferred via WiFi to Roche, where they are processed and analysed.

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EQ-5D-5L, EuroQol 5-dimension 5-level; HD, Huntington’s disease; PROs, patient-reported outcomes; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading (Test); Lipsmeier F, et al. J Neurol Neurosurg Psychiatry. 2018; 89(Supp 1):A61.2.
Features extracted from active tests are valid measurements of HD-related disease symptoms

Features show good correlation with established clinical measures¹

Correlation with standard clinical tests

- **SDMT**
  - SDMT (scale: 0-100)
  - UHDRS (scale: 0-100)

- **SWR**
  - SWR (scale: 0-100)
  - UHDRS (scale: 0-100)

- **Speeded tapping**
  - Speeded tapping (scale: 0-100)
  - UHDRS (scale: 0-100)

Correlation with in-clinic UHDRS measures

- **Chorea**
  - UHDRS Chorea (scale: 0-100)

- **Speeded tapping**
  - UHDRS Speeded tapping (scale: 0-100)

- **Draw a shape**
  - UHDRS Draw a shape (scale: 0-100)

- **Balance**
  - UHDRS Balance (scale: 0-100)

- **U-Turn**
  - UHDRS U-Turn (scale: 0-100)

- **2-minute walk**
  - UHDRS 2-minute walk (scale: 0-100)

Examples of differences observed in active test results between the “not impacted” and “impacted” groups

Features reflect a patient’s own assessment of disease impact on his daily life²

- **SDMT**
  - UHDRS SDMT (scale: 0-100)

- **Chorea**
  - UHDRS Chorea (scale: 0-100)

- **Speeded tapping**
  - UHDRS Speeded tapping (scale: 0-100)

- **SWR**
  - UHDRS SWR (scale: 0-100)

1 Preliminary Reliability and Validity of a Novel Digital Biomarker Smartphone Application to Assess Cognitive and Motor Symptoms in Huntington’s Disease (HD) (P1.8-042) Florian Lipsmeier, Cedric Simillion, Atieh Bamdadian, Anne Smith, Scott Schobel, Christian Czech, Christian Gossens, Patrick Weydt, Edward Wild, Michael Lindemann Neurology Apr 2019, 92 (15 Supplement) P1.8-042;

2 Comparing HRQoL in HD using electronic patient-reported outcomes to sensor-based motor and cognitive features of disease using a digital monitoring platform; Lipsmeier et al.; EAN 2019; UHDRS=Unified Huntington’s Disease Rating Scale

4 Balance is a composite of Unified Huntington’s Disease Rating Scale Ataxia and Tandem walking items.
The use of the remote digital monitoring platform has the potential to provide new insights into HD progression outside the traditional clinical trial setting.

HD=Huntington’s disease, OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; ¹ Tabrizi SJ, et al. N Engl J Med. 2019; 380:2307–2316; ² Clinicaltrials.gov/show/NCT03342053 (Mar 19); ³ Clinicaltrials.gov/show/NCT03664804 (Mar 19); ⁴ Clinicaltrials.gov/show/NCT03761849 (Mar 19); ⁵ Clinicaltrials.gov/show/NCT03842969 (Mar 19); ⁶ Clinicaltrials.gov/show/NCT04000594 (Jun 19)
Patients are doing the tests consistently and extracted results show high reliability.

Adherence to active test schedule is high

Features extracted from consecutive test-runs are stable

<table>
<thead>
<tr>
<th>Digital test</th>
<th>Feature</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>Number of correct responses</td>
<td>0.95</td>
</tr>
<tr>
<td>Stroop Word Reading</td>
<td>Number of correctly read words</td>
<td>0.92</td>
</tr>
<tr>
<td>Speeded tapping (left)</td>
<td>Tap interval</td>
<td>0.99</td>
</tr>
<tr>
<td>Speeded tapping (right)</td>
<td>Tap interval</td>
<td>0.99</td>
</tr>
<tr>
<td>Draw-a-shape (left)</td>
<td>Spiral drawing speed variability</td>
<td>0.95</td>
</tr>
<tr>
<td>Draw-a-shape (right)</td>
<td>Spiral drawing speed variability</td>
<td>0.95</td>
</tr>
<tr>
<td>Chorea (left)</td>
<td>Acceleration path</td>
<td>0.97</td>
</tr>
<tr>
<td>Chorea (right)</td>
<td>Acceleration path</td>
<td>0.96</td>
</tr>
<tr>
<td>Balance</td>
<td>Path length</td>
<td>0.89</td>
</tr>
<tr>
<td>U-turn</td>
<td>Median turn speed</td>
<td>0.91</td>
</tr>
<tr>
<td>2-minute walk</td>
<td>Step frequency variance</td>
<td>0.96</td>
</tr>
</tbody>
</table>

ICC is calculated on two consecutive 14 days’ averages of respective smartphone feature

ICC >0.9 = excellent reliability, 0.75-0.9 = good reliability
Introduction

FAIR Data

Examples

Summary and discussion
Digitalisation is transforming Roche’s entire Pharma value chain
Deliver the right treatment to the right patient at the right time

- Pre-clinic
- Clinical Development
- Registration
- Access
- Production & Supply
- Diagnosis
- Treatment

Meaningful data at scale (MDAS)

- Genomics
- Real world data (RWD)
- Digital biomarkers
- Artificial Intelligence (AI)

Decision support

- NAVIFY
- Consumer ecosystems

Quality «Big» data

Positive impact on Pharma business

Leveraging data through analytics
Shaping the future
Roche is committed to driving innovation in digitalisation

Lab of The Future – driving and enabling scientific quality, productivity, SHE, compliance

Automation, tracking & sharing, modularity, configurable, programmable, remote, collaborative…

Connected & integrated (IOT), augmented reality, voice, identity, system of record (video)…

Talent – access & building for the future

Next Gen Compute – tomorrow’s world

Quantum Computing
Calculating the unimaginable
Special IR event on "Digital technology and advanced analytics"
7 May 2020
Doing now what patients need next