What Does “Digital” Mean for Biopharma R&D?

Improving Drug Discovery and Development - and Our Drugs Portfolio

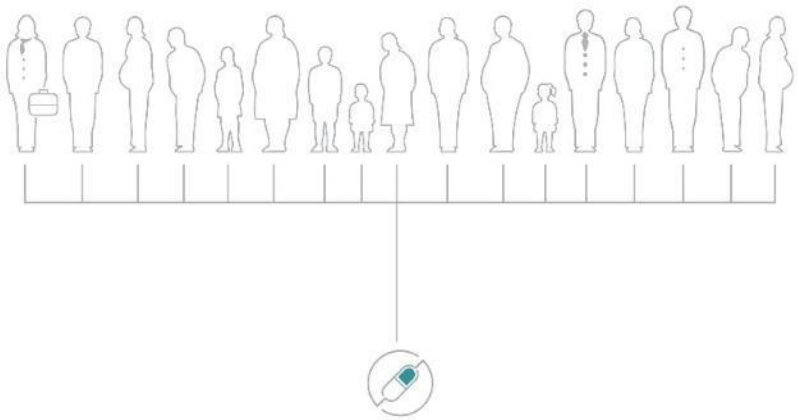
Dr Bryn Roberts, *Global Head of Operations & Informatics*
Roche Pharma Research & Early Development

PRISME Forum Technical Meeting – May 23rd 2019

Roche *pRED*

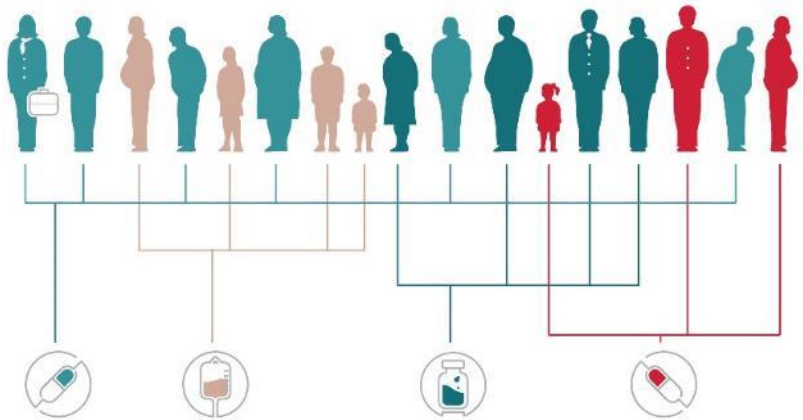
Personalised Healthcare (PHC)

The application of "Precision Medicine"



Medical practice and treatment

Traditionally



Medical practice and treatment

Today and Tomorrow

"Focus on digital innovation to enable pRED to make breakthrough medicines of the future and stay at the forefront of drug discovery"

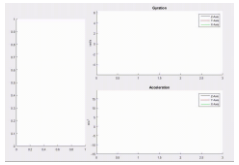
pRED Digital Strategy – enhancing data-driven R&D

Leveraging transformation in big data, technology & computational paradigms

Data

FLATIRON

Genomics england

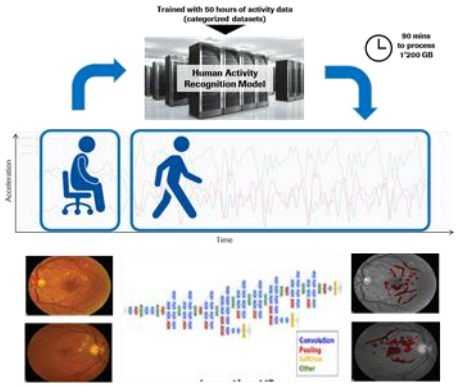


- Scale, variety, complexity
- Real world (RWD), real time
- FAIR-ification

Technology

- Sensors, wearables, mobile
- Connected app ecosystem
- IOT, blockchain, cloud

Compute



- High performance compute
- Machine learning (ML)
- Deep learning (DL)

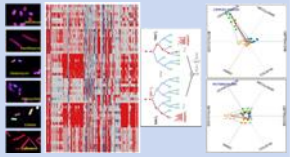
Digital priority areas for pRED

Enabling innovation and driving efficiency, effectiveness & productivity in research

1. Augmented discovery

Computer-aided drug design & optimisation

Advanced analytics & AI for research



Smart infrastructure & resource optimisation

RICB *in vivo* building

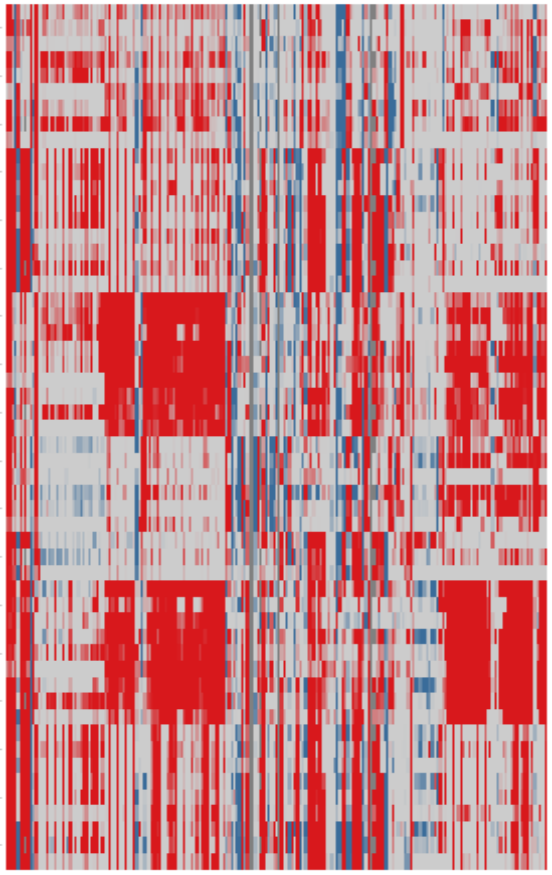
Research laboratory automation 4.0

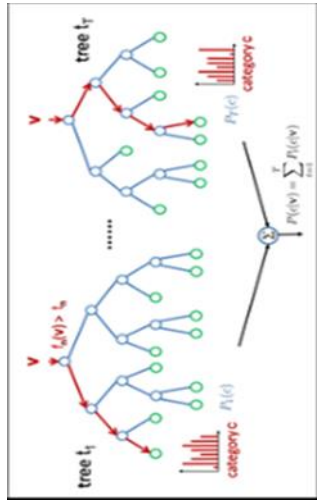
Bacterial Phenotypic Profiling

Predicting mechanism of novel antibiotic candidate molecules

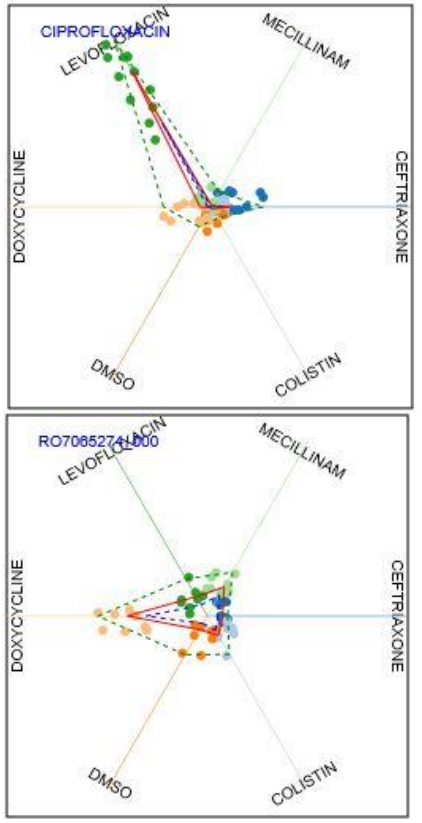
High Content Screening assay with sub-lethal compound concentrations

multi-parametric fingerprints





multi-class probabilistic predictions

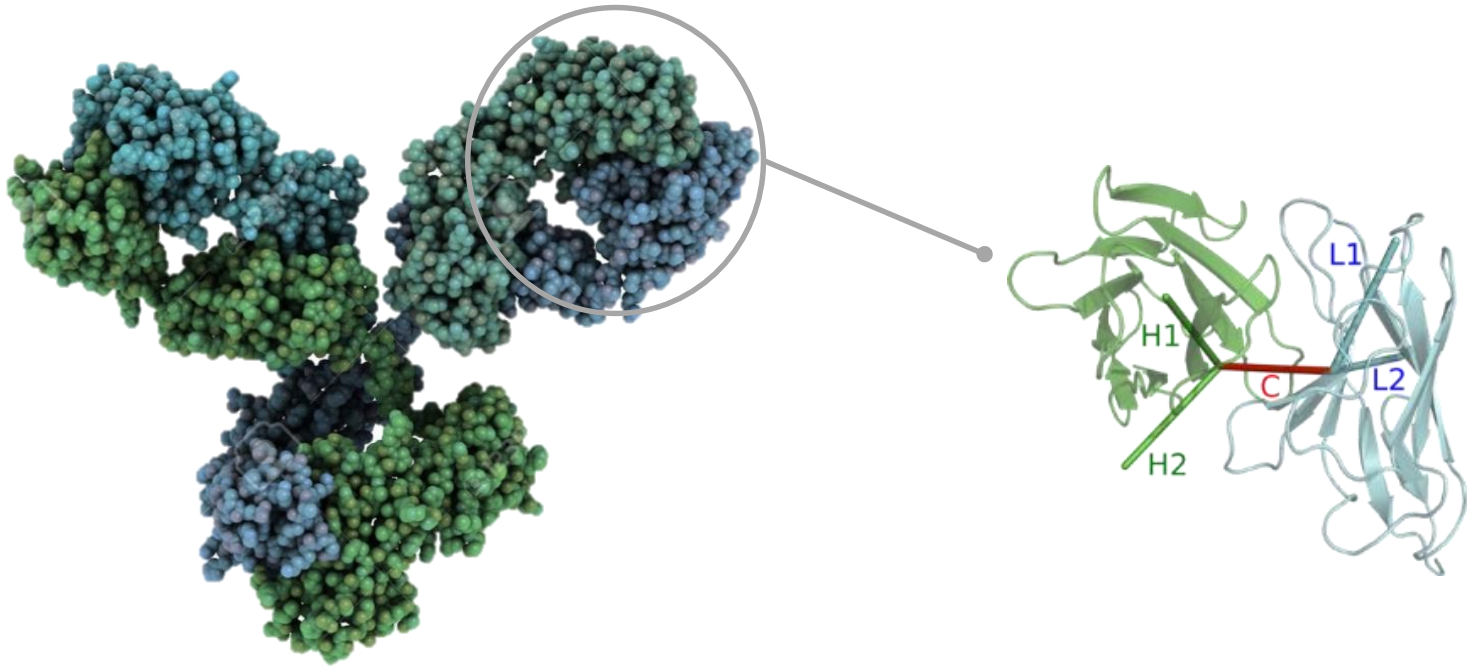


The Random Forest algorithm provides robust, fast and interpretable classification of reference compounds and similarity probabilistic predictions of test compounds

Machine learning-powered antibiotics phenotypic drug discovery *Zoffmann S, Vercruysse M, Benmansour F, Maunz A, et al. 2019, Scientific Reports* ***9****, Article: 5013*

Predicting VH–VL Domain Orientation for Antibodies

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



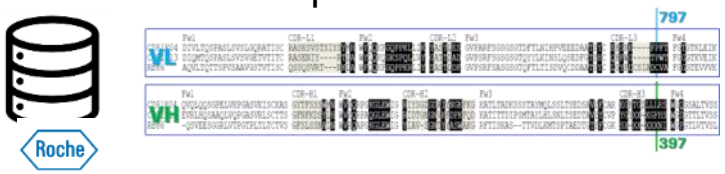
Relative orientation of the VH and VL domains codetermines the topology of the antigen-binding site

Prediction of VH–VL domain orientation for antibody variable domain modeling Bujotzek A, et al. 2015, Proteins **83**, 681-695

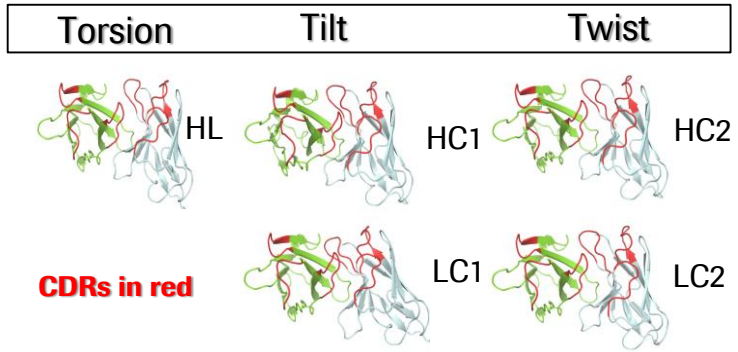
Predicting VH–VL Domain Orientation for Antibodies

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

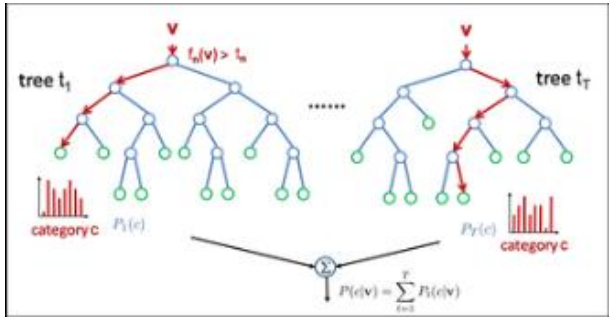
Extract mAB sequences and crystal structures from public and internal data sets



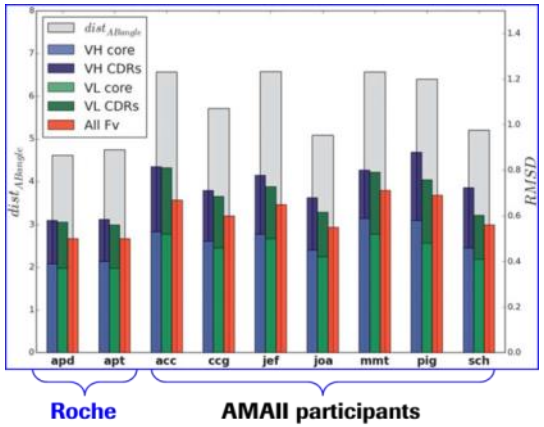
Describe orientation by 5 angles & C length



Train Random Forest classifier to predict angles from sequence



Test on independent dataset



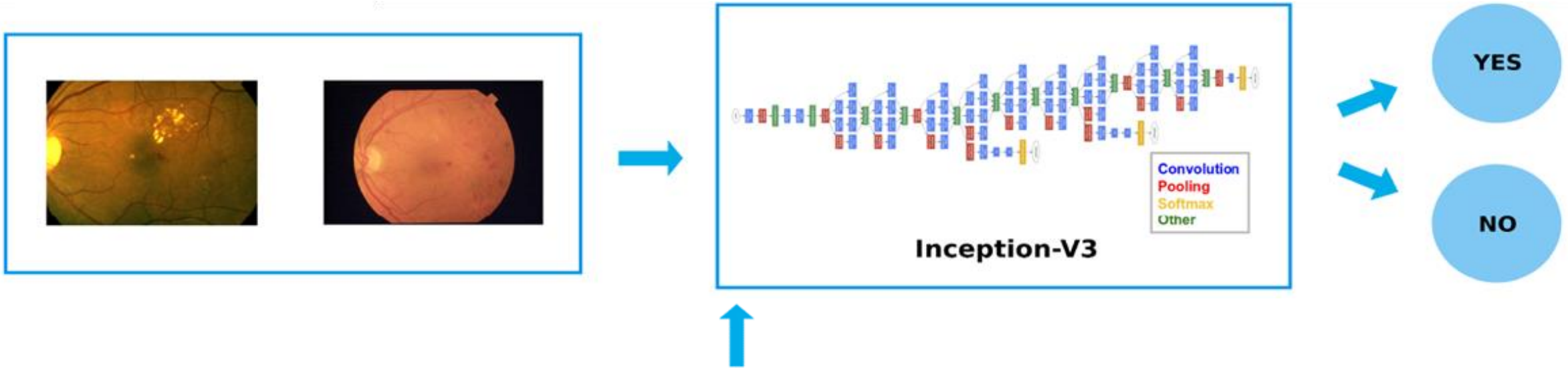
- ✓ *Roche classifier outperforms other methods*
- ✓ *Now part of the mAB engineering workflow in LMR*

Prediction of VH–VL domain orientation for antibody variable domain modeling Bujotzek A, et al. 2015, Proteins **83**, 681-695

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)



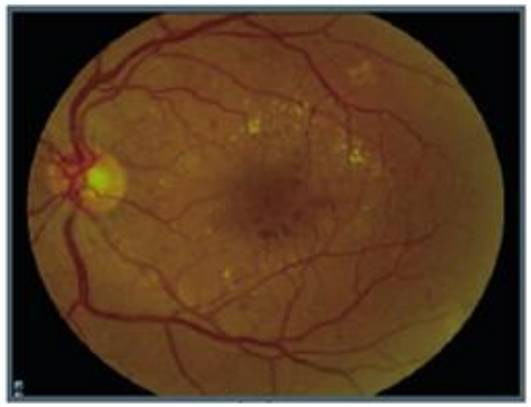
Transfer of "knowledge" using CFPs from the Kaggle Diabetic Retinopathy challenge - binary classifier for severity

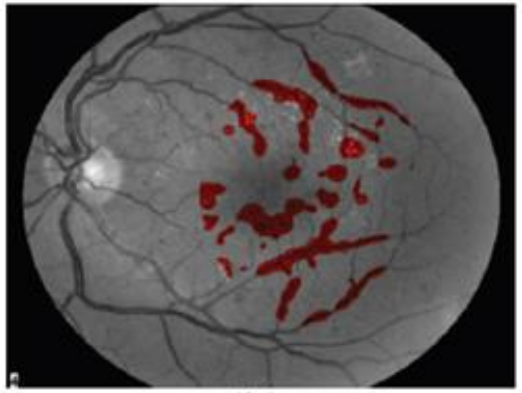
Example performance: *prediction of CFT≥400µm: AUC of 0.97 (95% CI= 0.88–1.00; sensitivity= 90.0%; specificity= 94.0%; N=45 CFPs)*

Deep learning predicts OCT measures of diabetic macular thickening from color fundus photographs *Arcadu F, Benmansour F, Maunz A, et al. 2019, Invest Ophthalmol Vis Sci.* ***60****, 852–857*

Prediction of Optical Coherence Tomography Measures of Diabetic Macular Thickening from Color Fundus Photographs

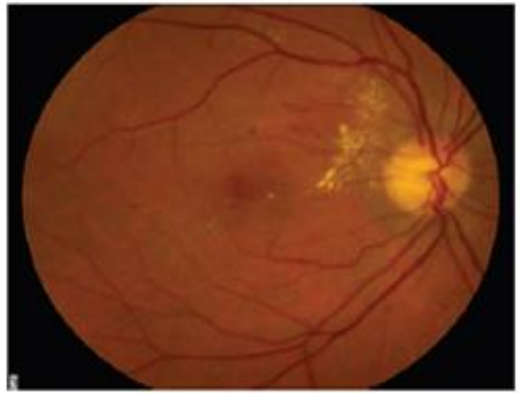
To gain insight into the inner workings of the DL models, attribution maps were created using guided back-propagation.

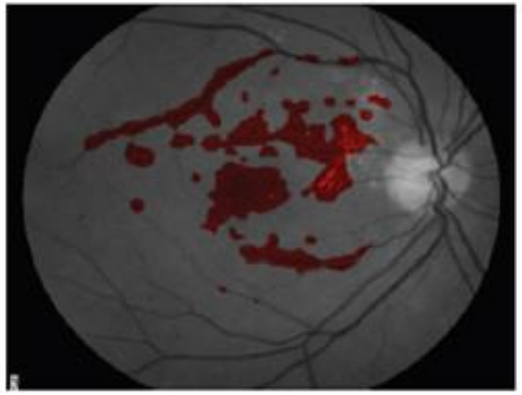




Example of map created by the DL model to detect MT with CFT > 250 µm

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 > 400 µm

Insights and predictions based on clinical data enable biomarker development, reverse translation, patient cohort selection, etc.

Deep learning predicts OCT measures of diabetic macular thickening from color fundus photographs *Arcadu F, Benmansour F, Maunz A, et al. 2019, Invest Ophthalmol Vis Sci.* ***60****, 852–857*

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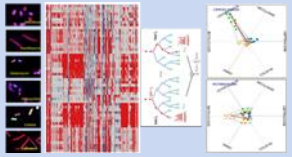


Smart infrastructure & resource optimisation

RICB *in vivo* building

Research laboratory automation 4.0

In Vivo Research (IVR) Building Drivers

Applying Digital and Automation technologies to create a reference IVR facility

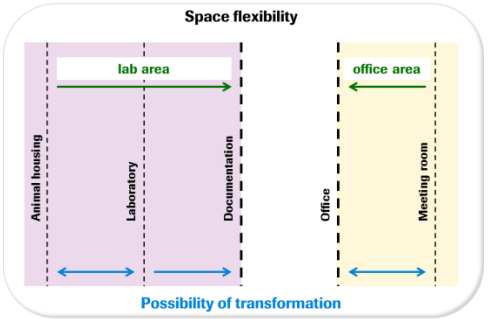
Innovation → Scientific Quality and Productivity

Ergonomics → Great place to work

RIBIS

Roche In Vivo Building IT System

Flexibility → From ‘me’ to ‘us’

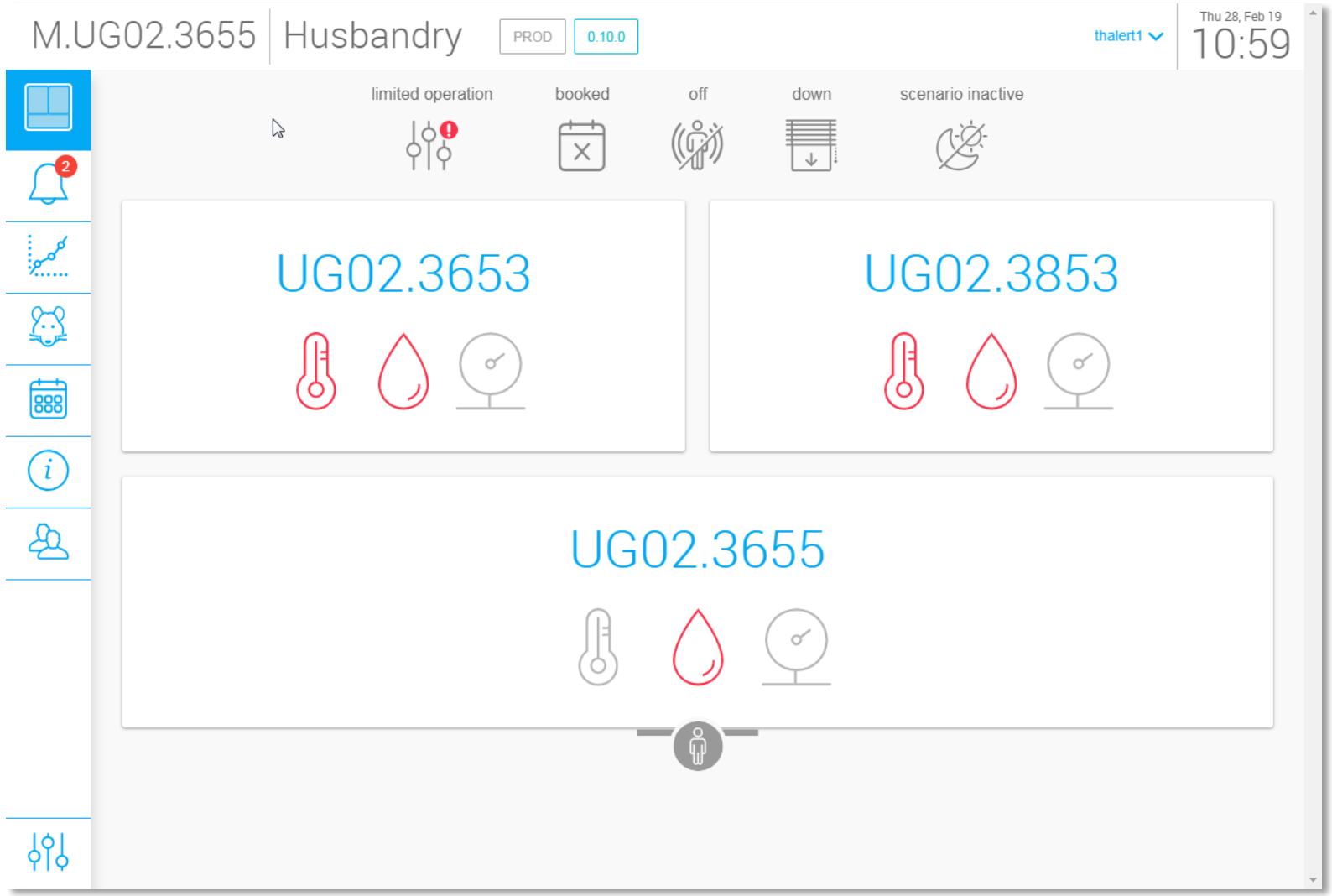


Environmental Monitoring and Controls

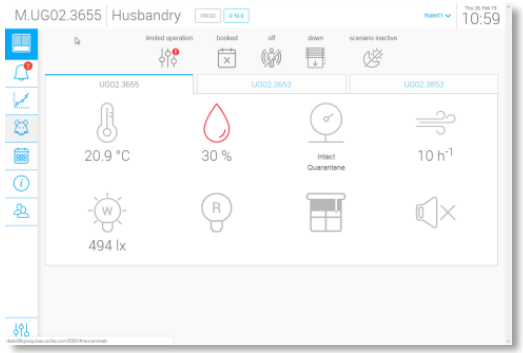
First in industry in-house development - Room Panel interface

Room Panel Interface Examples

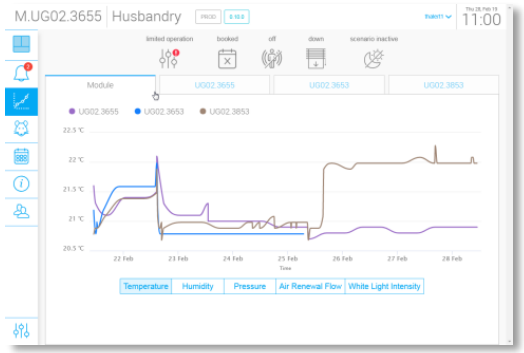
Also available anywhere, anytime via desktop and mobile devices



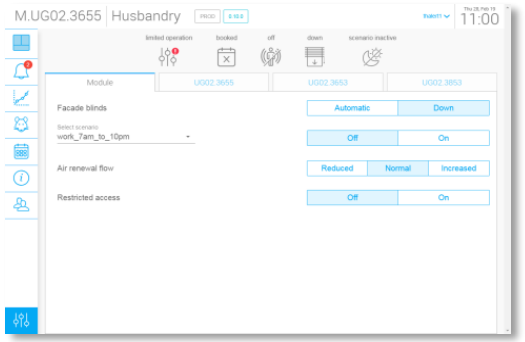
Module



Room



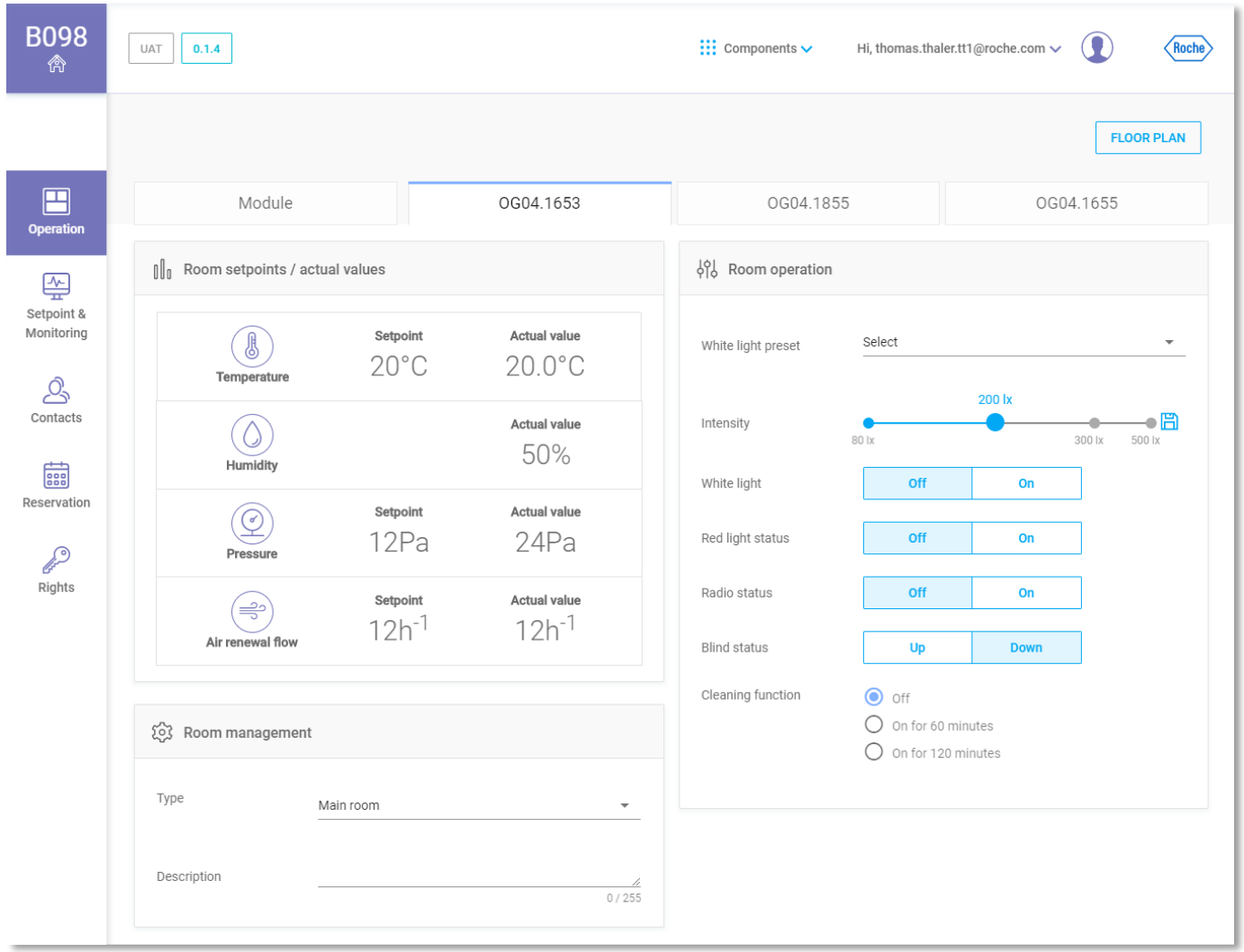
History



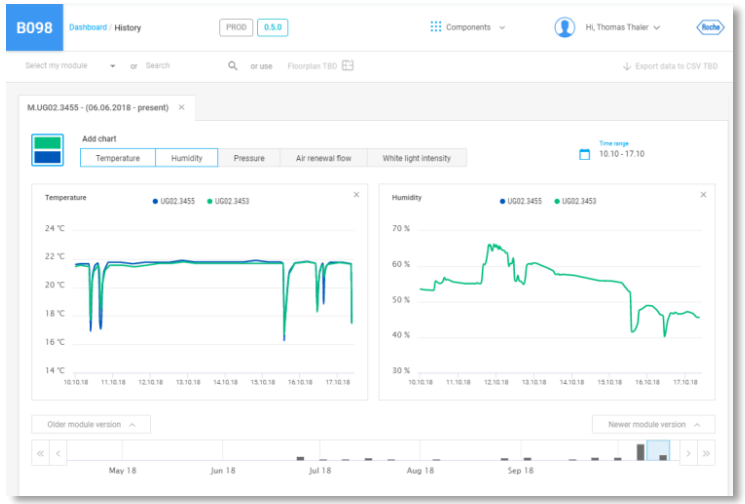
Operation

Overall Building Management

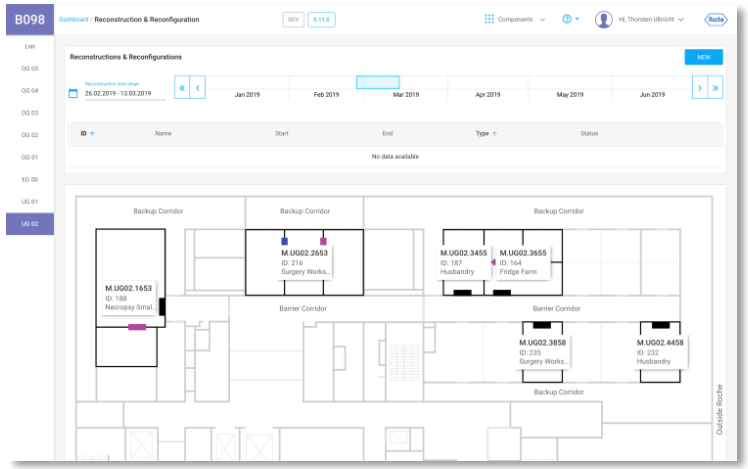
Additional functionality available in the desktop application



Building Management – Module Operation



Alarms



Reconstruction

Augmented Reality and Voice Interfaces in the Laboratory

Video examples of pilots

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Enabling our clinical programmes, and engaging patients & investigators

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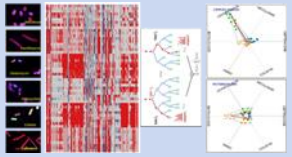


Smart infrastructure & resource optimisation

RICB *in vivo* building

Research laboratory automation 4.0

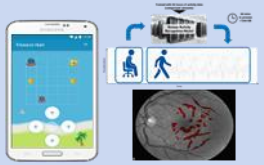
2. Connected healthcare for early development

Patient centricity - engaging on their journey

Interacting with & supporting patients and investigators

Data-enabled workflows & decision support

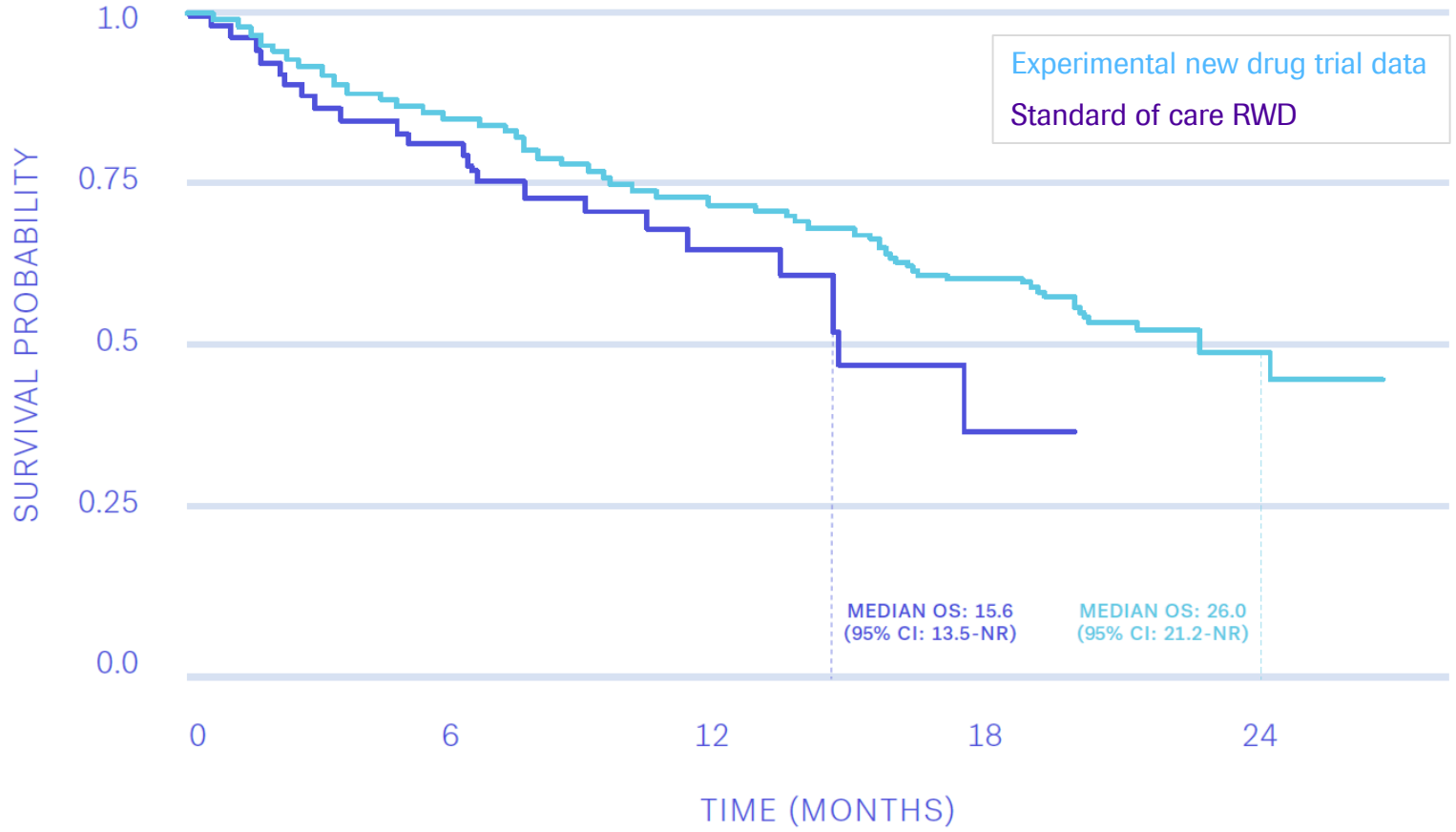
Digital clinical readouts & AI interpretation



Developing an External Control with RWD

A 'better' comparator, reduced cost and patient benefit

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



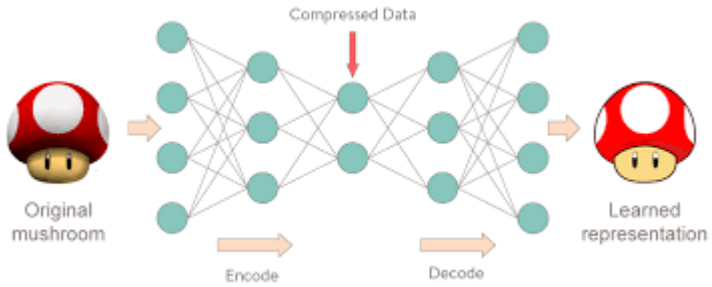
Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib Davies J, Martinec M, Delmar P, Coudert, et al. 2018, Journal of Comparative Effectiveness Research, Jun 26(0).

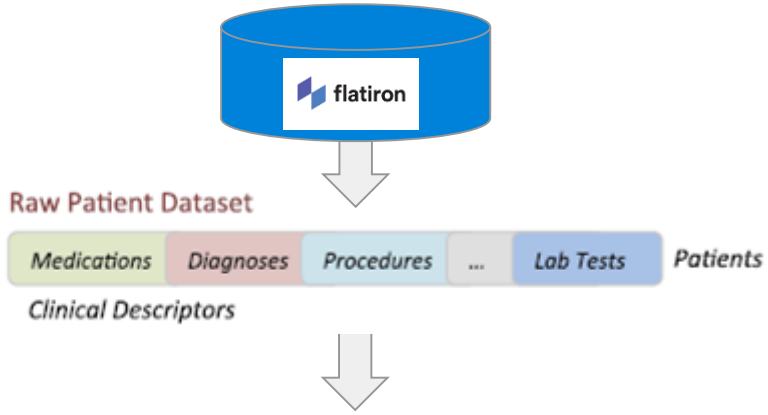
Cohort Matching with Propensity Scores

Autoencoder for improved Propensity Score Matching

Autoencoder

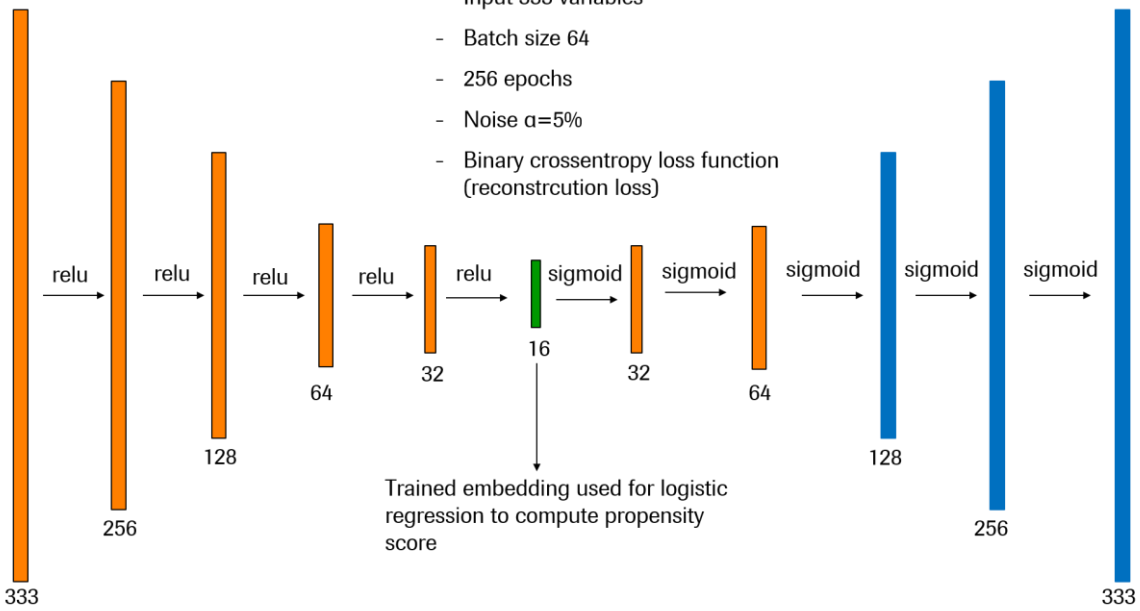
- Artificial neural network
- Unsupervised learning of efficient codings
- Purpose: dimensionality reduction
- ~ Non-linear extension of PCA





Autoencoder Details

- Input 333 variables
- Batch size 64
- 256 epochs
- Noise α=5%
- Binary crossentropy loss function (reconstrcution loss)



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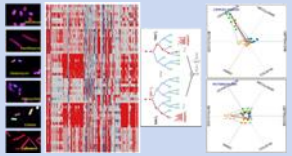

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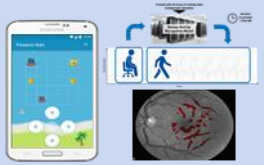
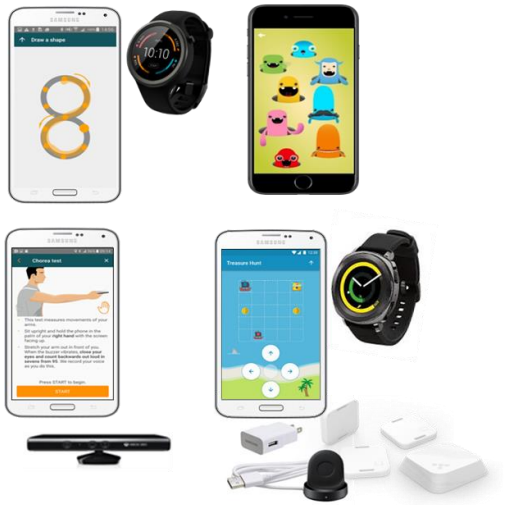
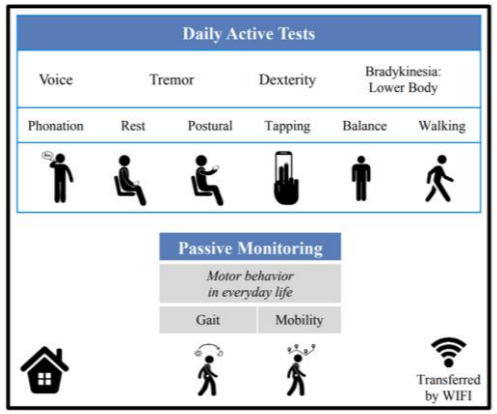


Digital Biomarkers

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**

Progress in digital biomarkers

Comprehensive & innovative portfolio of differentiated tools in multiple symptom domains

Multiple Sclerosis

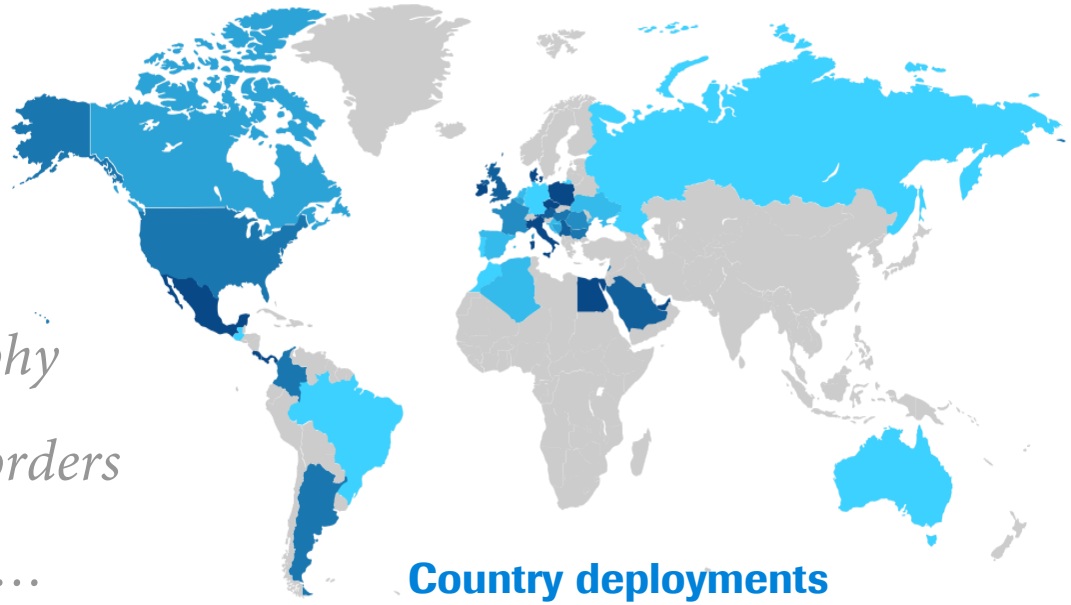
Parkinson's Disease

Huntington's Disease

Spinal Muscular Atrophy

Autistic Spectrum Disorders

Angelman's Syndrome…



Country deployments

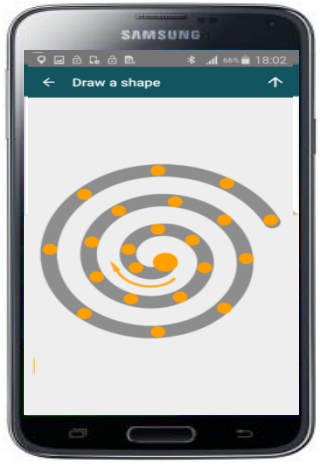
40 countries	**>150 clinical sites**	**4k installed devices**	**2.5k smartphones**	**1.5k smartwatches**

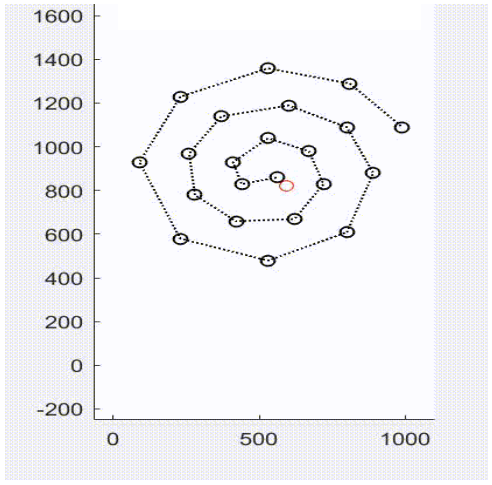
Roche scientists inventing new dBM assessments

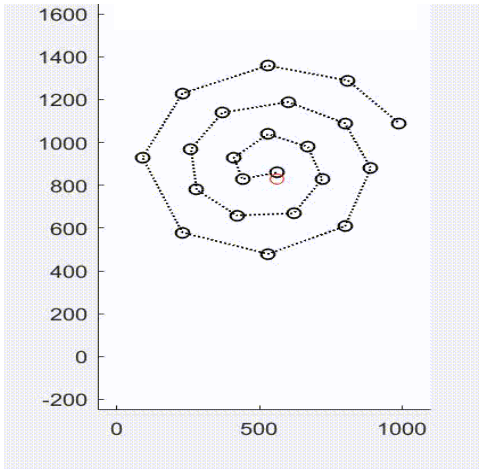
"eDraw a Shape" remote assessments offers rich clinical data

	Subject A	Subject B
Classical 9-Hole Peg Test	**17** seconds	**37** seconds
	8 seconds	**15** seconds

Floodlight: Draw a Shape

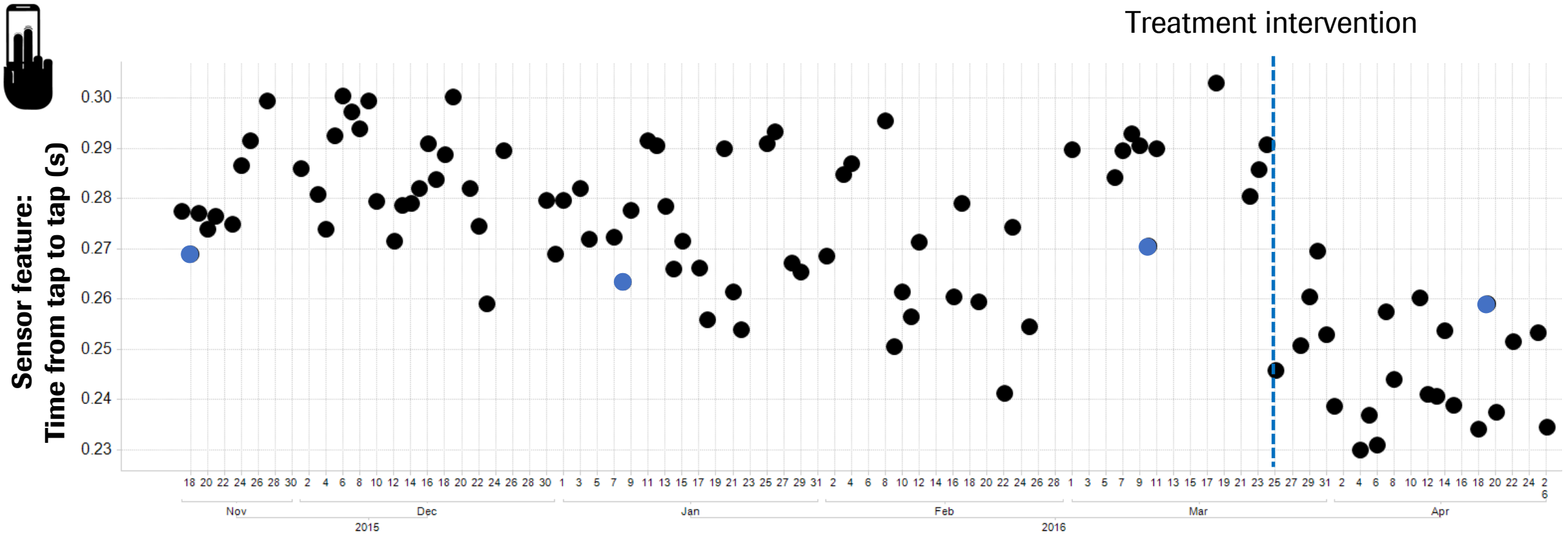






Continuous monitoring versus regular in-clinic measurements

Potential to pick up treatment effects faster and more accurately

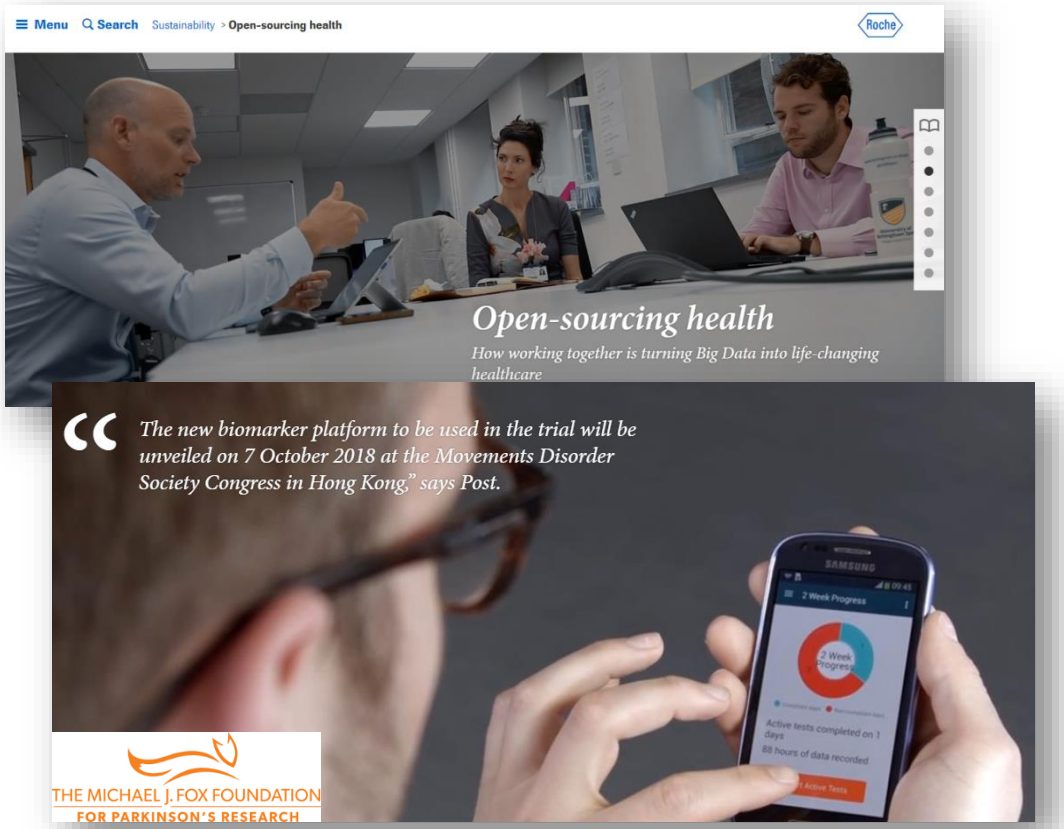


- datapoint at day of clinical visit
- data from continuous measurement using sensors

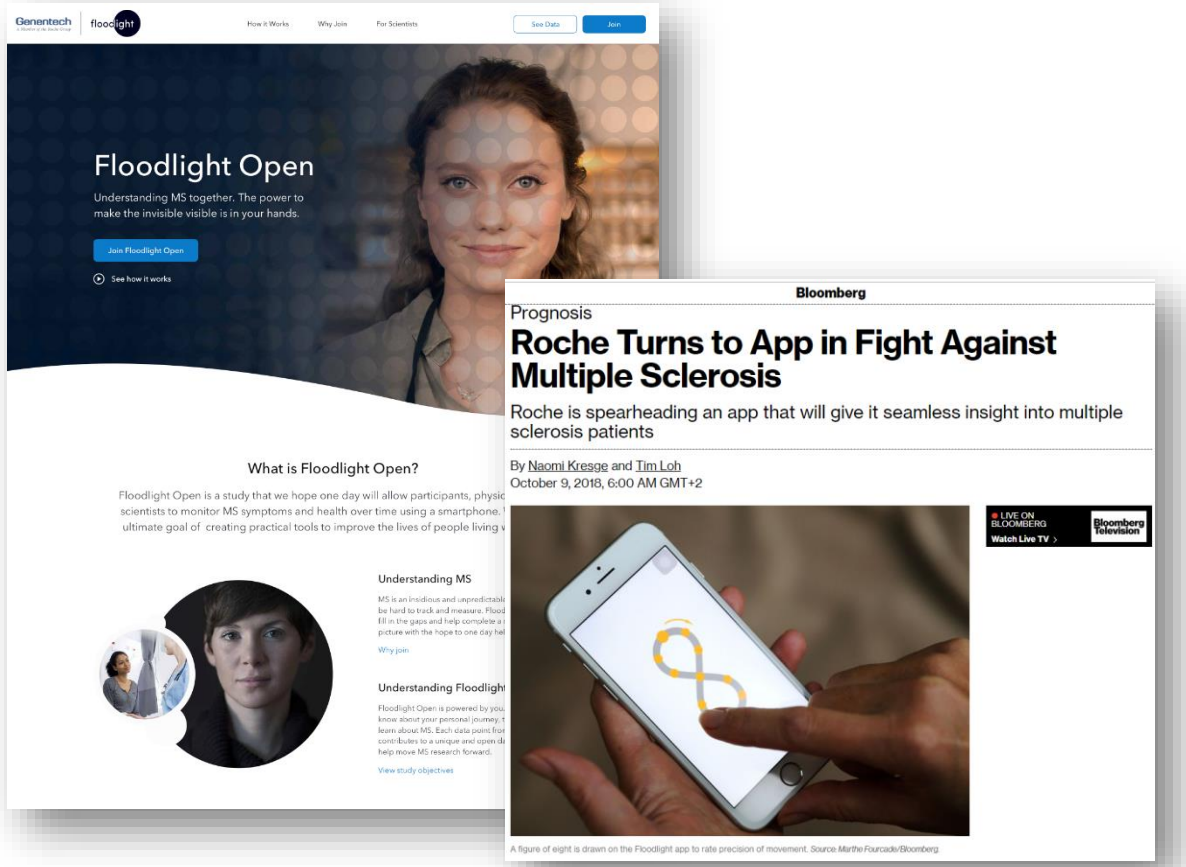
Working with the external scientific community

Establishing robust digital outcome measures tailored to our development programmes

Parkinson's disease



Multiple Sclerosis



Digital priority areas for pRED – detailed investment areas

Pivoting from digital biomarkers to digital therapeutics

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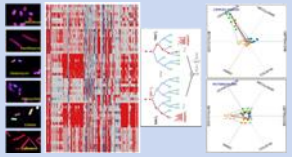
Computer-aided drug design & optimisation

Advanced analytics & AI for research



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3. Digital therapeutics

Optimising the Medicine

Augmenting the Medicine

AI=artificial/augmented intelligence

Around & beyond the medicine

Digital solutions offer the opportunity for personalised healthcare solutions beyond the "pill"

Around

Optimising the Medicine

Treatment selection and management, e.g. earlier access, dose optimization

Automation of delivery

Patient empowerment, e.g. monitoring & reporting

Beyond

Augmenting the Medicine

Skills development

Cognitive behavioral therapy

Disease management services

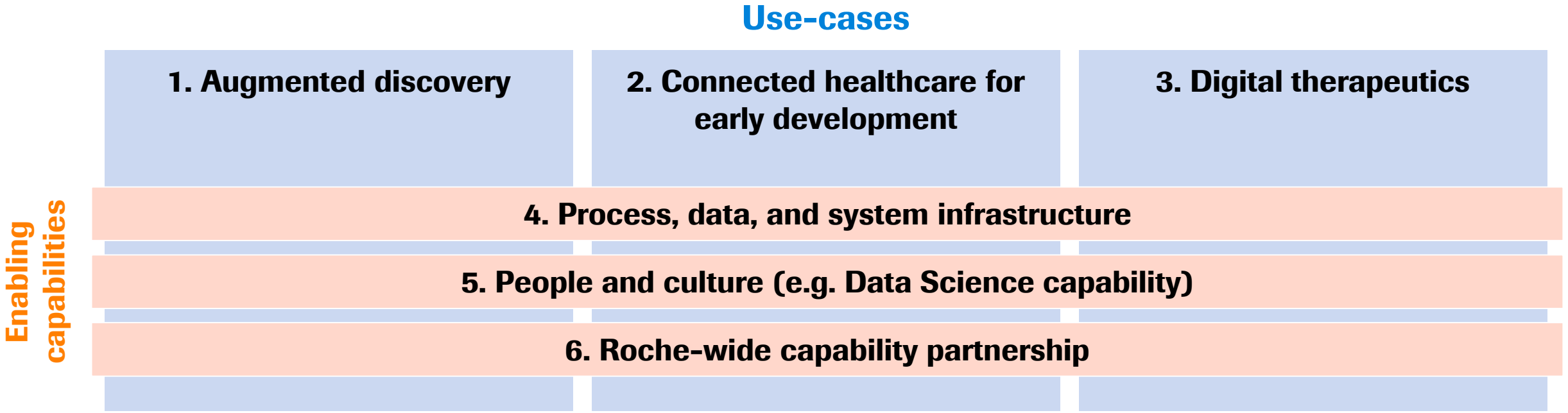
Prognostics & prevention

Human augmentation, e.g. implants, human-computer interfaces (AR, VR), robotic augmentation

Driven by evidence-based, differentiated medical value

Digital priority areas for pRED

To capitalise on digital opportunities, we need to build enabling capabilities & pursue specific use-cases



Enabling pRED & bringing added value across the Roche Group

Doing now what patients need next