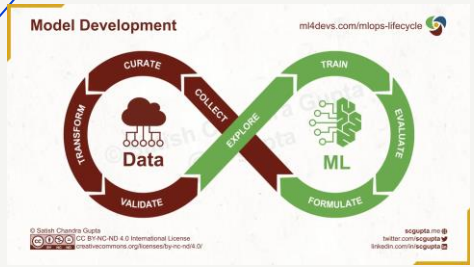
Building successful learning loops with Data & ML/AI

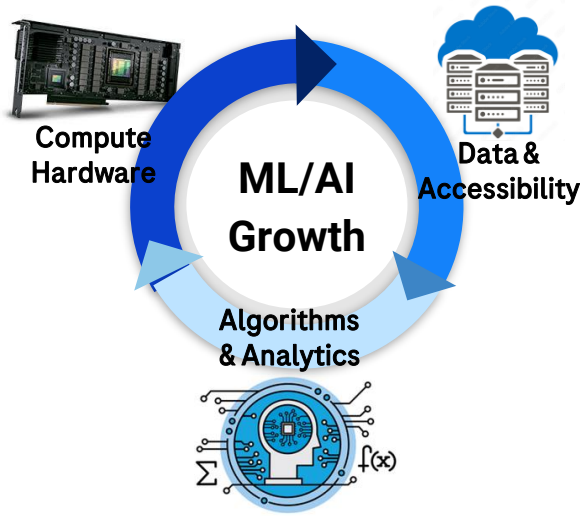
Intelligent Health 2024

Scott Oloff



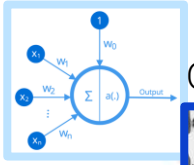
- Patterns in what’s advanced the ML/AI field
- The necessary people for iterative ML/AI growth
- Practical examples
- What’s coming in the future

ML/AI - Examples of what's gotten us here



1943

Artificial "Neuron"

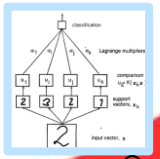


Colossus

kNN

$$d(x,y) = \sqrt{\sum_{i=1}^{n}(x_i - y_i)^2}$$

SVM

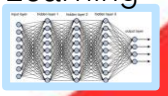


GPU

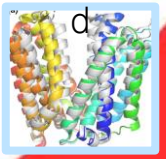
Cloud

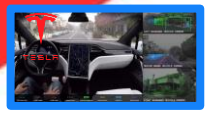
GenBank

Deep Learning

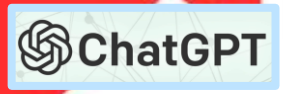


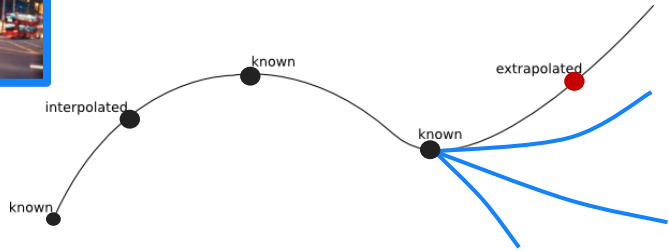
AlphaFold





LLMs





Sustainable growth of ML/AI requires at least 3 key roles:

Domain/Process Expert:

Defining the problem we want to solve

ML/AI Expert:

Build or Apply model(s) to the problem

Data/Tech Expert:

Bringing data together for the model(s) to use

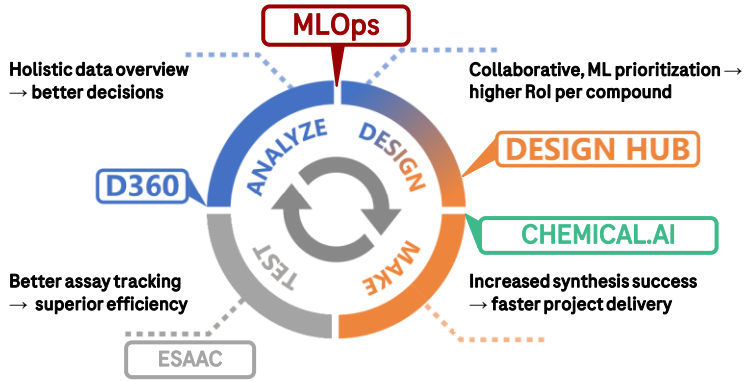
Using ML/AI to increase efficiency of small molecule early R&D

Allowing scientists to focus on what really matters

Integration of ML/AI and computational design in small molecule research

Status quo: Design expertise localized to SMEs; limited exchange across teams/organizations

Leveraging ML/AI, Automation, Design Hub and Chemical.AI as part of 'Lab in a loop'



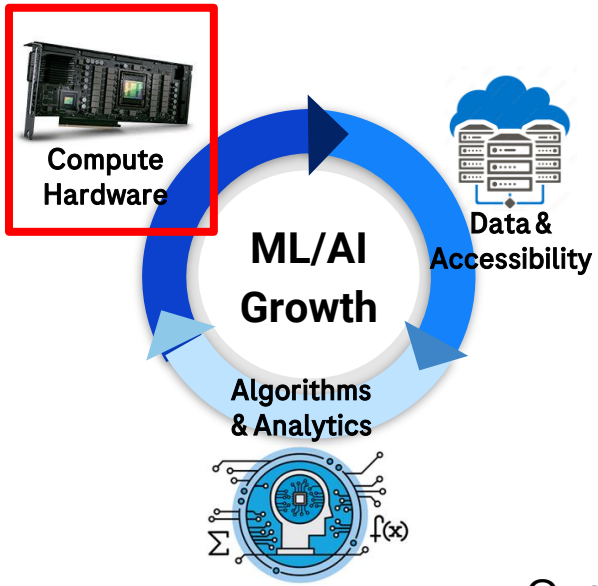
Key benefits

- Enhanced collaboration
- More efficient learning cycles
- Streamlined decision making
- Increased research efficiency

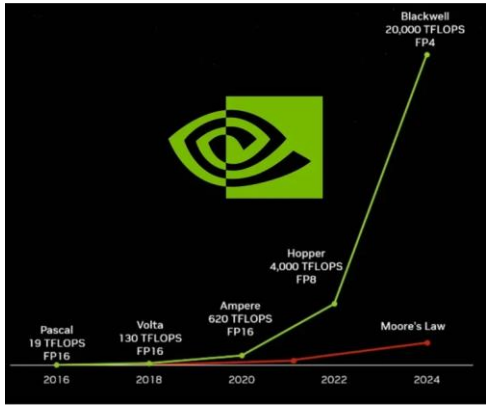
- ML/AI and computational design tools aid experts in early R&D drug discovery for integrated, synergistic approaches between machine and human
- We aim to enable the entire drug discovery engine with ML/AI from idea generation to synthesis & activity predictions.
- R&D efficiency has been enhanced by streamlining collaboration and knowledge management, allowing scientists to focus on decision making

AI=artificial intelligence; ML=machine learning; ESAAC=enabling smart assay-activity cascade

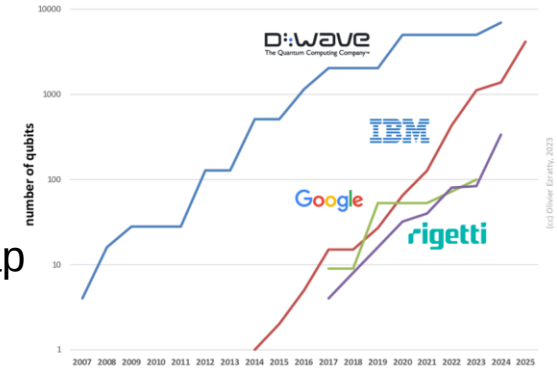
ML/AI - Compute hardware accelerating growth



GPU Performance Growth



Quantum Computing the next leap

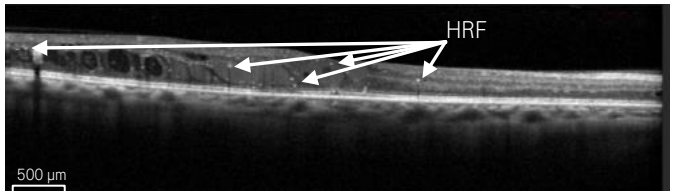


Will completely change the types of problems we can solve

Applying a deep learning algorithm in ophthalmology

HRF may be a potential biomarker for disease severity and progression in DME

Hyperreflective foci (HRF)

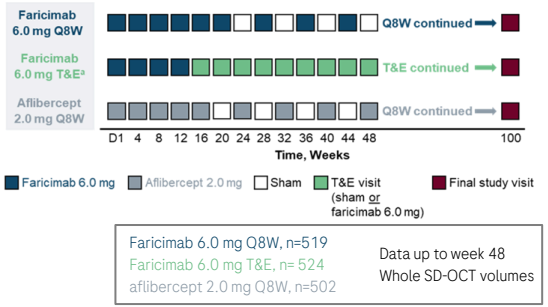


- HRF are small, highly reflective objects found in the retina of DME and nAMD patients[2-4]
- Potential to be used as imaging biomarkers in DME, as presence at baseline may predict poor vision outcomes[5,8-10]
- Vabysmo dual Ang-2/VEGF-A pathway inhibition suspected to add to known effect of VEGF-A of reducing HRF[5-7]

Post-hoc analysis of Vabysmo (YOSEMITE/RHINE) using a deep learning-based algorithm[1]

ARVO 2023

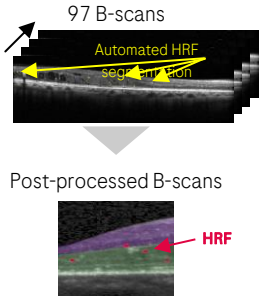
Trial design



Faricimab 6.0 mg Q8W, n=519
Faricimab 6.0 mg T&E, n= 524
aflibercept 2.0 mg Q8W, n=502

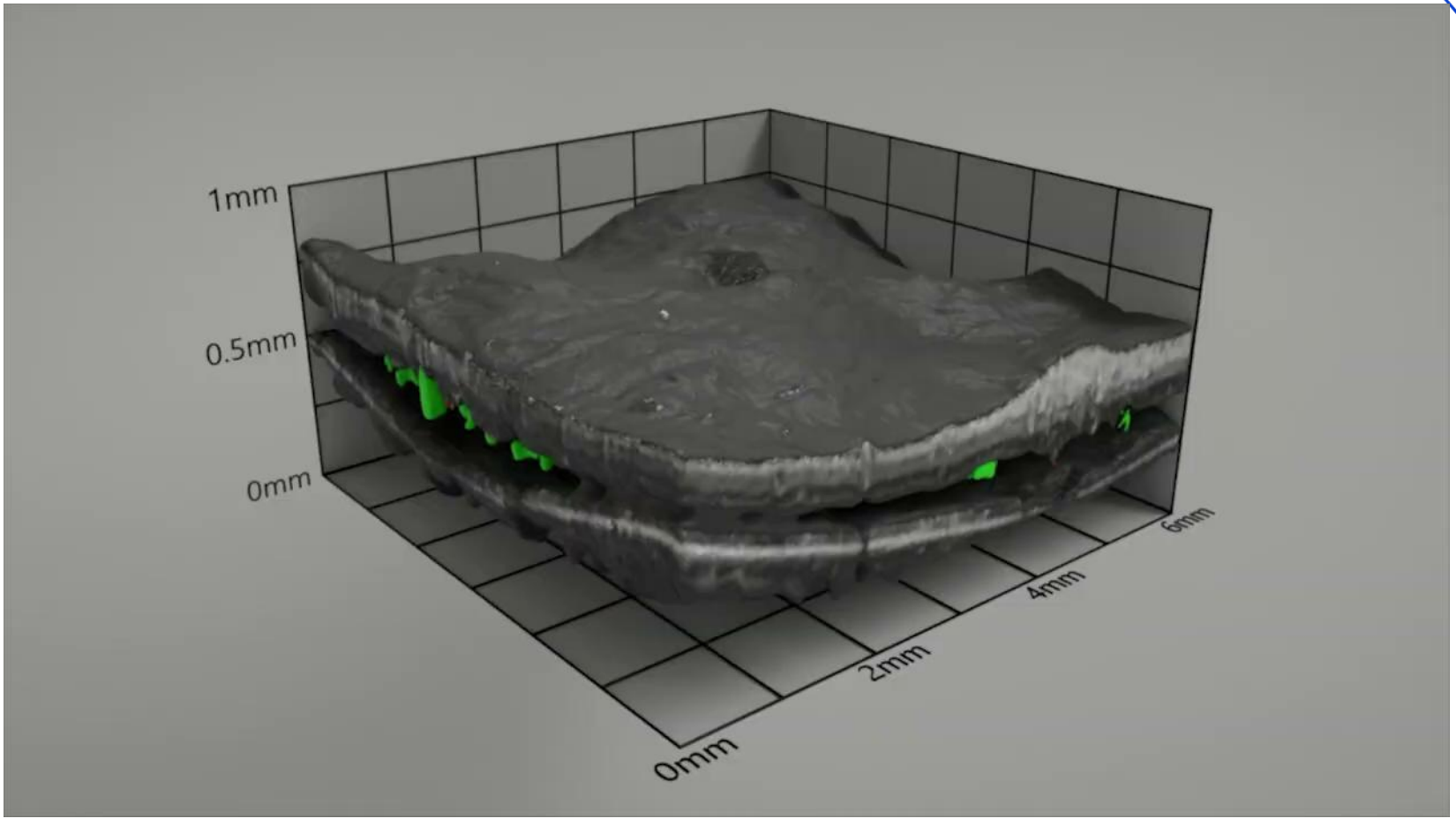
Data up to week 48
Whole SD-OCT volumes

HRF detection



- Pooled YOSEMITE/RHINE data up to week 48 was used for post-hoc analysis to compare the effect of Vabysmo vs aflibercept on resolution of retinal HRF in eyes with DME
- All ~50,000 OCT volume scans were analyzed using a deep-learning based algorithm for automated HRF segmentation
- HRF analysis using human graders would be infeasible, and was only made practical via the deep-learning algorithm

[1]Maunz et al., ARVO 2023; [2]Bolz M et al. Ophthalmology. 2009;116(5):914-920; [3]Zhu R et al. BMC Ophthalmol. 2022;22(1):382; [4]Coscas G et al. Ophthalmologica. 2013;229(1):32-37; [5]Vujosevic S et al. Acta Ophthalmol. 2017;95(5):464-471; [6]Rübsam A et al. J Diabetes Res. 2021;2021:8820216; [7]Ceravolo I et al. Diagnostics (Basel). 2020;10(6):413; [8]Zur D et al. Ophthalmology. 2018;125(2):267-275; [9]Chatziralli I et al. Diabetes Ther. 2017;8(6):1393-1404; [10]Kang JW. Retina. 2016;36(9):1630-1639; Ang-2=angiopoietin-2; DME=diabetic macular edema; HRF= hyperreflective foci; SD-OCT=spectral-domain optical coherence tomography;VEGF-A=vascular endothelial growth factor-A


1mm
0.5mm
0mm
0mm
2mm
4mm
6mm

Vabysmo treatment leads to fast and durable HRF reduction

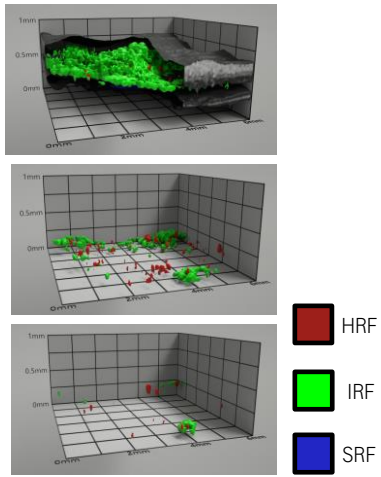
DL algorithm approach suitable for post-hoc analysis across therapeutic areas

3D SD-OCT imaging analysis of representative Vabysmo patient[1]

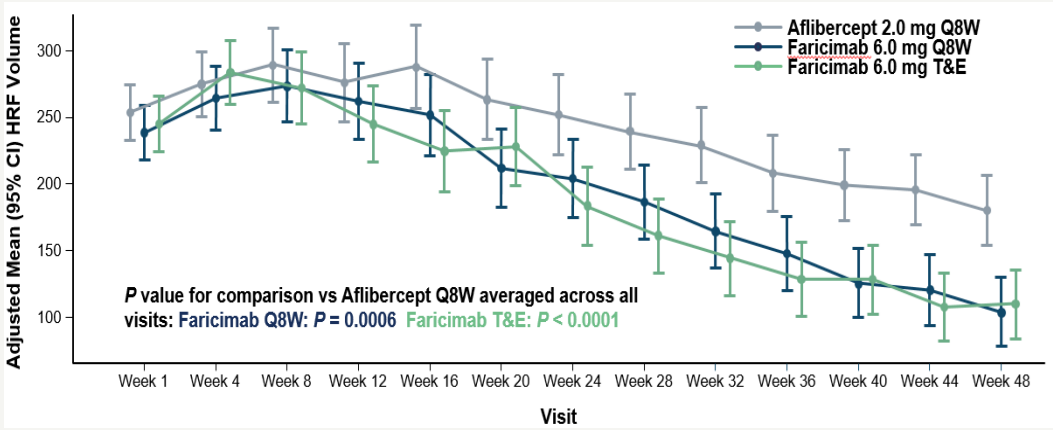
Baseline
BCVA: 57 letters
CST: 553 µm
HRF count:[a] 78

Week 16
BCVA: 77 letters
CST: 190 µm
HRF count:[a] 25

Week 48
BCVA: 78 letters
CST: 191 µm
HRF count:[a] 4



Comparison of Vabysmo and aflibercept treatment effect on HRF reduction[1]



- A post hoc analysis of YOSEMITE and RHINE demonstrated greater retinal HRF volume reductions in Vabysmo- vs. aflibercept-treated eyes at week 48
- Volume reductions indicate suppression of pathways that mediate inflammation
- Better resolution of the pathological manifestations of DME with Vabysmo support the therapeutic potential of dual Ang-2/VEGF-A inhibition in retinal disease

[1]Singh et al., 2023 AAO Congress; [a]Total retina, 3 mm; [b]ILM to OPL-HFL; [c]OPL-HFL to RPE; [d]Based on the median ([e]or Q3 if median zero) at week 48 relative to baseline; [e]The upper quartile is presented for this parameter as the median values are zero in the faricimab arms. Each bar represents the ratio of the median (or Q3) HRF volume at week 48 to baseline for the relevant treatment group and location; HRF=hyperreflective foci; Q3=quartile 3; Q8W=every 8 weeks; T&E=treat-and-extend; 3D-OSCT=3-dimensional spectral-domain optical coherence tomography; IRF=intraretinal fluid; SRF=subretinal fluid; BVCA=best-corrected visual acuity; CST=central subfield thickness

Exploring the potential of Quantum Computing

Pushing the boundary of Scientific Excellence

- **Simulation**: Quantum Chemistry
  - *In the area of chemistry simulation we want to explore the potential of quantum computing to get deeper insights in the binding of an inhibitor to a catalytic site of a protein.*
- **Optimization**: Protein Folding - Energy Minimization
  - *We want to use classical chemical force fields to build and evaluate the most challenging (both to model and experimentally determine) part of antibody 3D structure. We will research the optimization problem of finding the minimum energy conformation using Quantum Computing.*
- **Machine Learning**: Chemistry property prediction
  - *Machine learning, including supervised and unsupervised learning is applied throughout pRED value chain. An example is the prediction of chemical properties given the molecular structure. There are different approaches proposed in the research community to design ML algorithms for quantum hardware.*

Chemistry Simulation: https://onlinelibrary.wiley.com/doi/10.1002/qua.26975

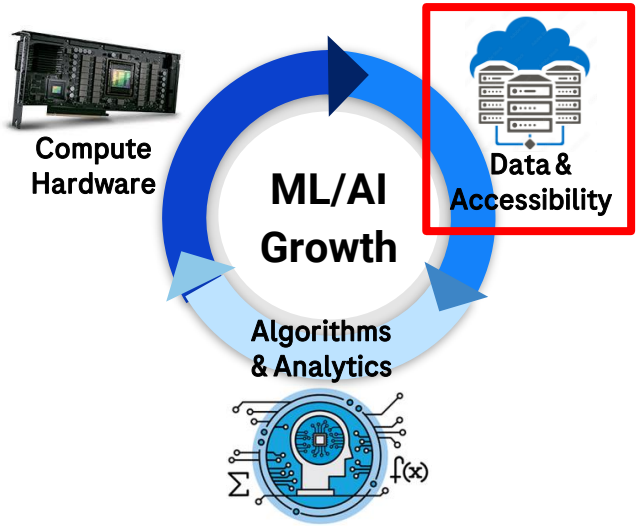
Optimization/ Protein Folding: https://www.frontiersin.org/articles/10.3389/fddsv.2022.908870/full

Optimization/ Molecular Sampling: https://arxiv.org/abs/2204.01821

Machine Learning: https://quantum-journal.org/papers/q-2022-12-22-881/

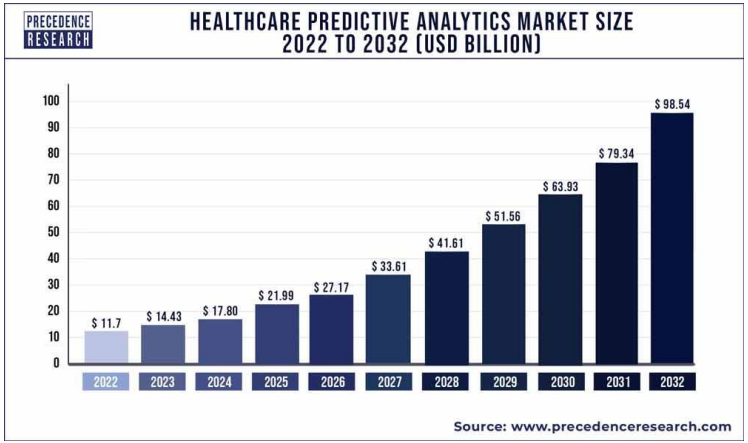
Machine Learning: https://arxiv.org/abs/2209.08167

Data feeds the ML/AI growth engine - Example: New patient healthcare analysis markets are being created



- Exponential growth in healthcare data
- Unmet patient needs and treatment comparisons can now be more quantifiably measured
- Helps us learn more to create even better therapies for our patients

Data availability provides benefits to patients by better understanding disease progression and patient-treatment responses



Leveraging RWD to optimize patient eligibility criteria

Significantly increased patient recruitment rate for an early stage Oncology asset

Background

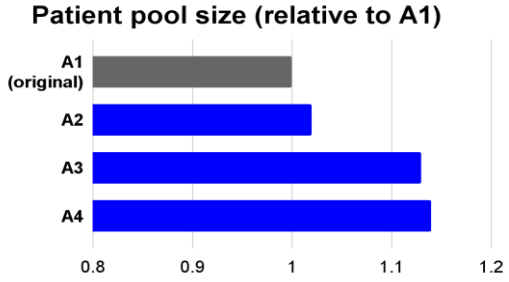
- Ongoing trial in Oncology of a CIT was experiencing **slow enrollment**
- **Stringent eligibility criteria** identified as key bottleneck

Solution

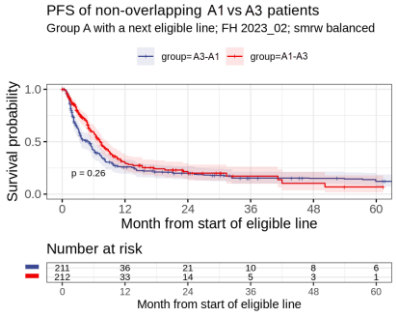
- **Flatiron Health RWD** was used to build virtual study cohorts with different eligibility patient criteria and test for effect on **increasing patient pool** and **rwPFS prognosis**

Result

~15% increase in patient pool possible by updating eligibility criteria



No significant difference in rwPFS between original and A3 scenario



New eligibility criteria implemented into Ph I

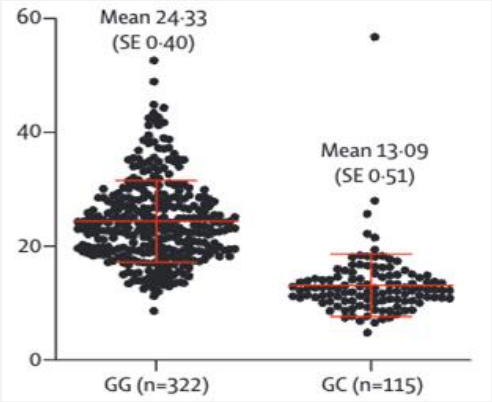
Recruitment rate significantly increased

Improved patient inclusion

RWD=real-world data; CIT=cancer immunotherapy; rwPFS=real-world progression free survival

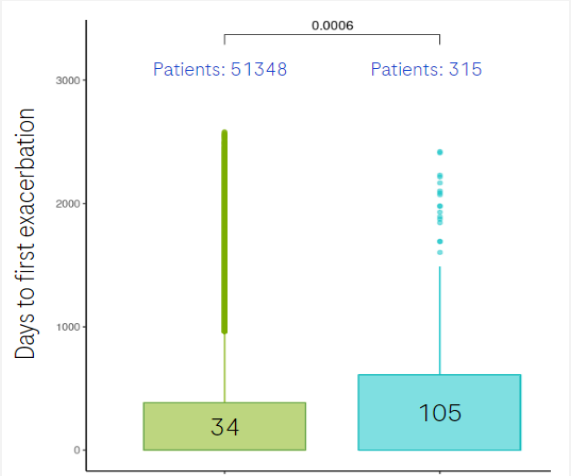
Genetic and real world data support the creation of new therapies

Genetic Data



A genetic variant that decreases Target X levels is associated with a lower risk of a particular disease.

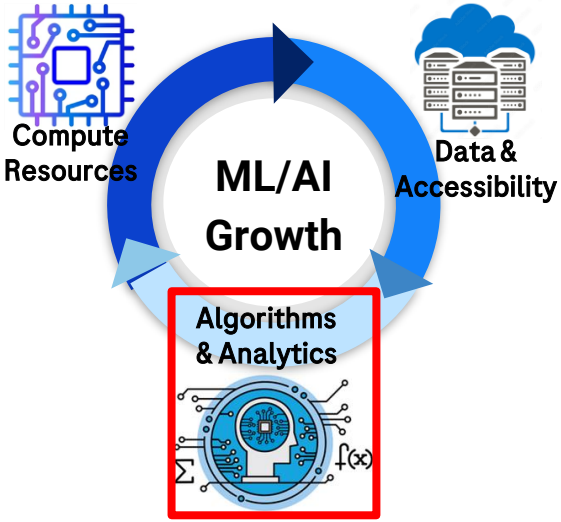
Real World Data

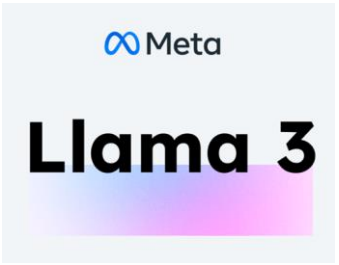


Patients taking a drug for Target Y have reduced disease exacerbations

Growing amounts of Genetic data & RWE supports the selection of future drug targets

ML/AI Growth - New algorithms have propelled data analysis





Possible next leap additions in AI

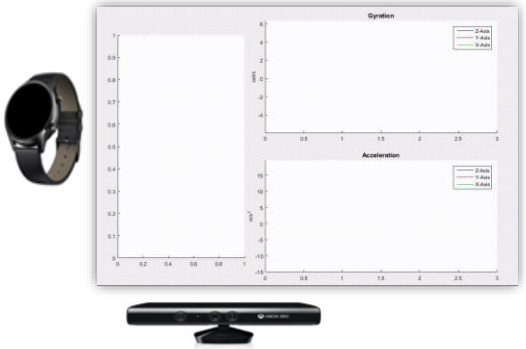
- Reinforcement Learning
- Node & Parameter Pruning/Addition
- Confidence metrics
- Abduction

Algorithm example to generating new insights -

Digital Biomarkers (dBM): Increased precision to measure patient impact

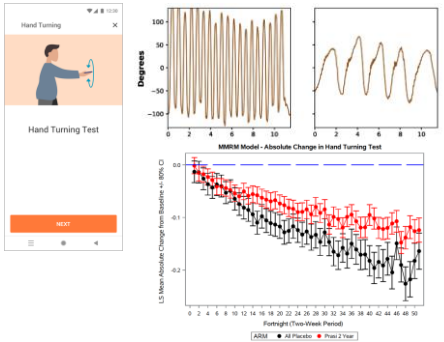
Gait & balance

Measuring walking behaviour and postural stability



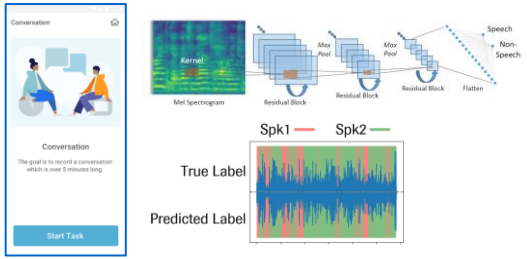
Upper extremity function

Measuring fine motor performance



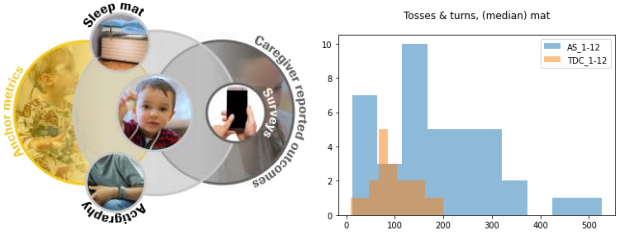
Vocal biomarkers of speech

From basic acoustic to complex semantic features



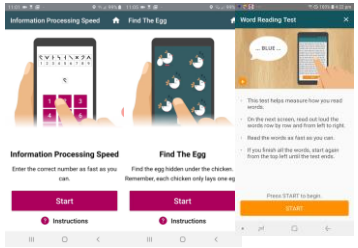
Sleep

Measuring people's sleep



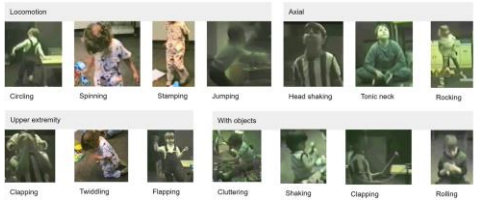
Cognition and social communication

Measuring different cognitive abilities



Passive behaviour monitoring

Measuring social and motor behaviour



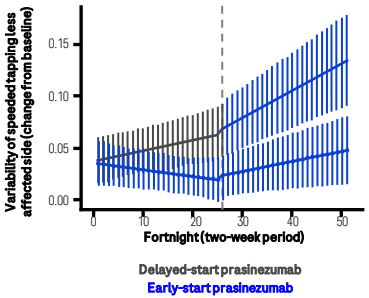
Driving scientific progress and increasing R&D efficiency

Digital biomarkers sensitively measure treatment effects and offer potential efficiency gains

Results

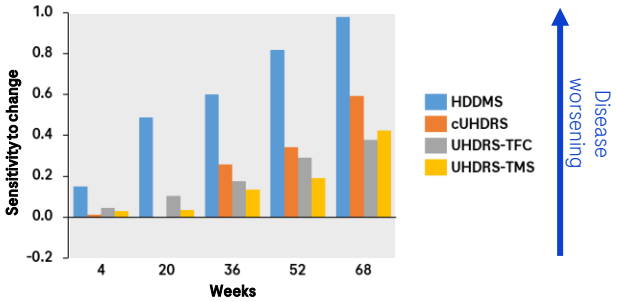
Prasinezumab Ph II (PASADENA) in PD[1]

Speeded tapping test



Tominersen Ph III (GENERATION HD1) in HD[2]

HD digital motor progression score (HDDMS)



HDDMS shows higher sensitivity to change than standard clinical assessments in early HD

Efficiency gains

~40-70% smaller sample size in PD*
vs MD-UPDRS part III at 80% power[1]

Faster trials
due to reduced recruitment duration

~75% smaller sample size in HD
vs cUHDRS at 16M and alpha=0.2[2]

- Data from PD and HD trials show that digital biomarkers can demonstrate treatment effects and have improved measurement sensitivity
- New digital biomarkers are operationally deployable in Ph I & II studies, providing a blueprint for rapid adoption in movement disorder trials
- Faster and leaner trials will increase R&D efficiency and may enable higher asset valuation

*Sample size reduction dependent on trial duration, with ~40% reduction at 12M duration and 70% reduction at 6M duration; [1]Taylor et al., ADPD 2022; [2]Giboin et al., HDTC 2023; PD=Parkinson's disease; HD=Huntington's disease; MDD=minimal detectable difference; MD-UPDRS=Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; HDDMS=Huntington's disease digital motor progression score; cUHDRS=composite unified Huntington's disease rating scale; TFC=total functional capacity; TMS=total motor score; ISS=integrated staging system; DCL=diagnostic confidence level; M=month; MMRM=mixed model for repeated measures; prasinezumab in partnership with Prothena; tominersen in partnership with Ionis

Components of successful ML/AI Learning Loops

- Key people for an ML/AI project
  - ❏ Domain/Process expert
  - ❏ ML/AI expert
  - ❏ Data/Tech expert
- Promote a culture where data is generated with **both analysis and potential future use** in mind
- As more ML/AI impacts are made it **sparks new ideas** where it can be applied

Doing now what patients need next