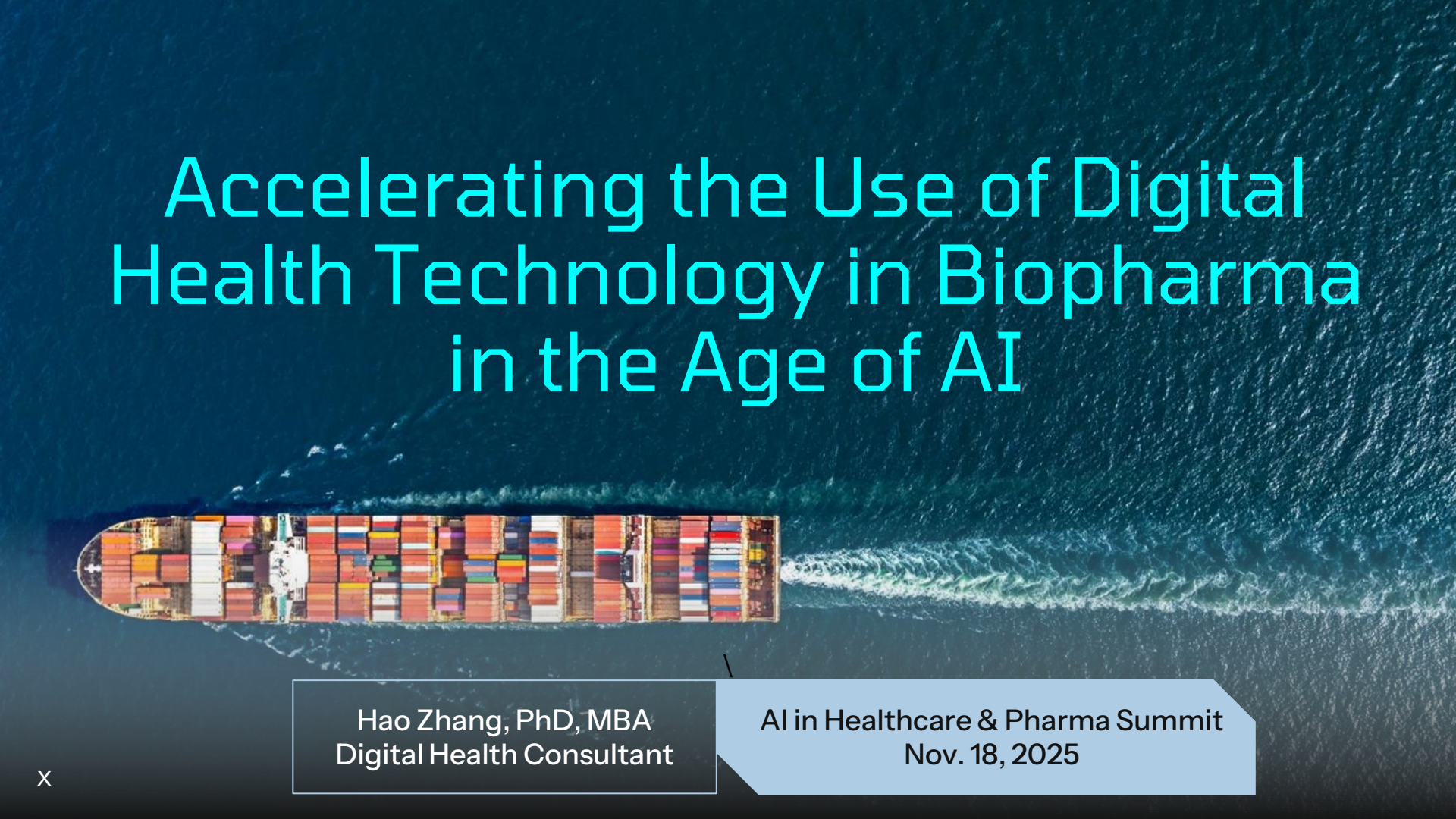
Accelerating the Use of Digital Health Technology in Biopharma in the Age of AI



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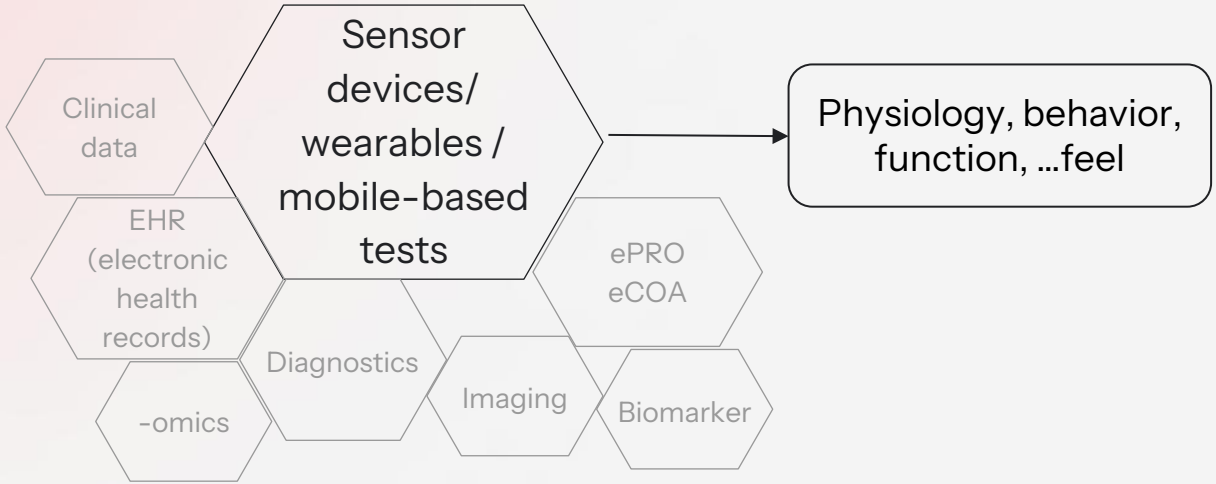
Disclaimer

- Views and perspectives are my own, not representing any organization
- Most cases and examples are from my past work projects, or products and services evaluated for them
- All info from published sources
- Examples do not represent endorsement for any specific product or service

- Acknowledgement: many of the illustrations created with Napkin.ai

Digital Health Technologies (DHTs)

and their digital measures, propelled by AI,
are finding ever broader applications across biopharma,
with accelerating progress in methodology and regulatory pathways.



Overview and agenda

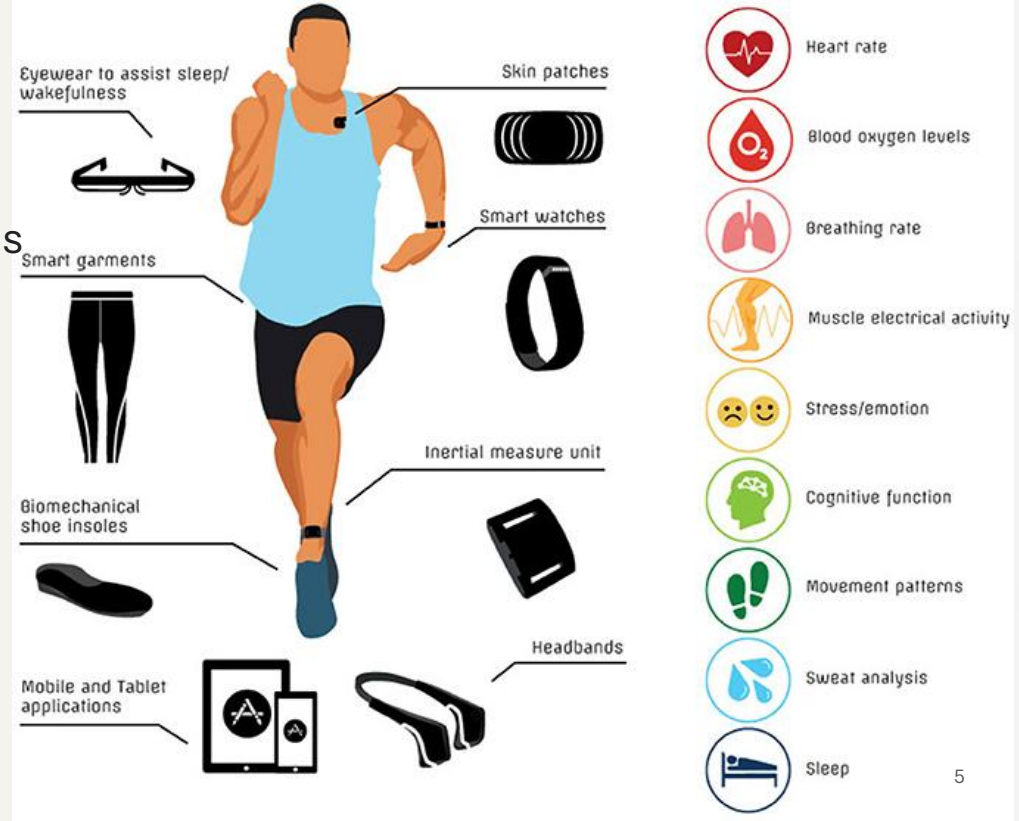
DHT's roles along biopharma pipeline:

1. Efficacy endpoints
2. Screening and recruiting
3. Safety monitoring
4. Building digital twin
5. RWE & payer reimbursement
6. "Around-the-pill" digital health products
7. Building foundational AI systems that understand health and diseases

1. DHT-Derived Digital Endpoints: Efficacy Measures for Decision Making and Pivotal Trials

Promises:

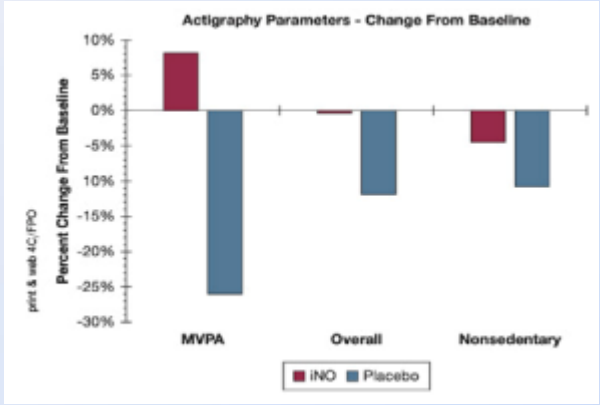
- Higher frequency, continuous
- Ecologically valid / Remotely collected
- Objective, real-time collection so avoids recall bias
- Potentially higher sensitivity
  - Earlier go/no-go decisions (often internal ESoE)
  - Reduced sample size
  - Reduced trial time



ESoE: early sign of efficacy
DiMe Society (link)
Peake et al 2018 (link),

Case Examples

Bellerophon used primary endpoint moderate-to-vigorous physical activity (MVPA) in trials for pulmonary hypertension.



FDA Agreement

Reduce Phase 3 sample size

Wearable Data

300 -> 140

MVPA as Secondary Endpoint

showed efficacy in Phase 2 Trial

Slow Clinical Trial

High costs, slow completion

Recruitment challenge

Accelerated Trial

Reduced costs, faster completion

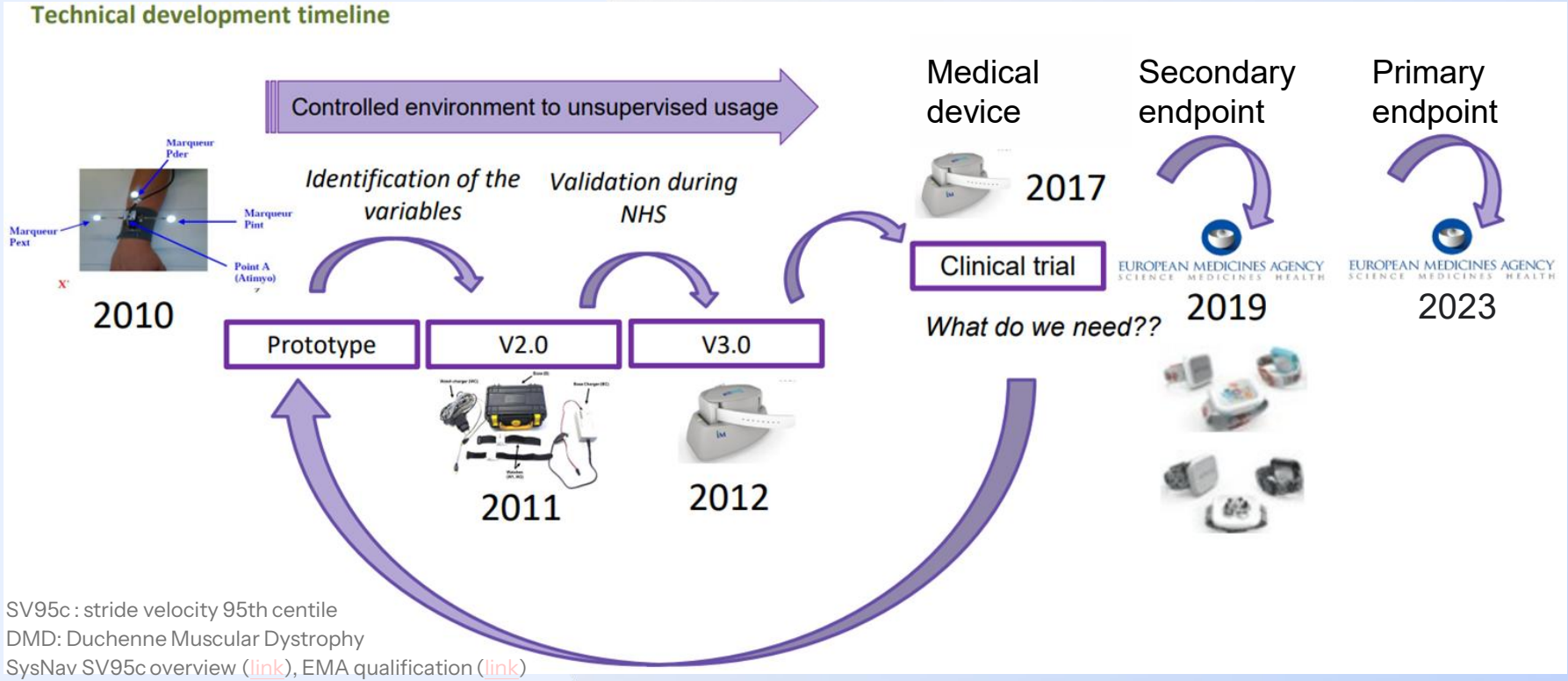
18 months sooner

MVPA: a level of activity quantified by actigraphy device

Amtris (Formerly ActiGraph) Bellerophon case study (link)

Case Examples

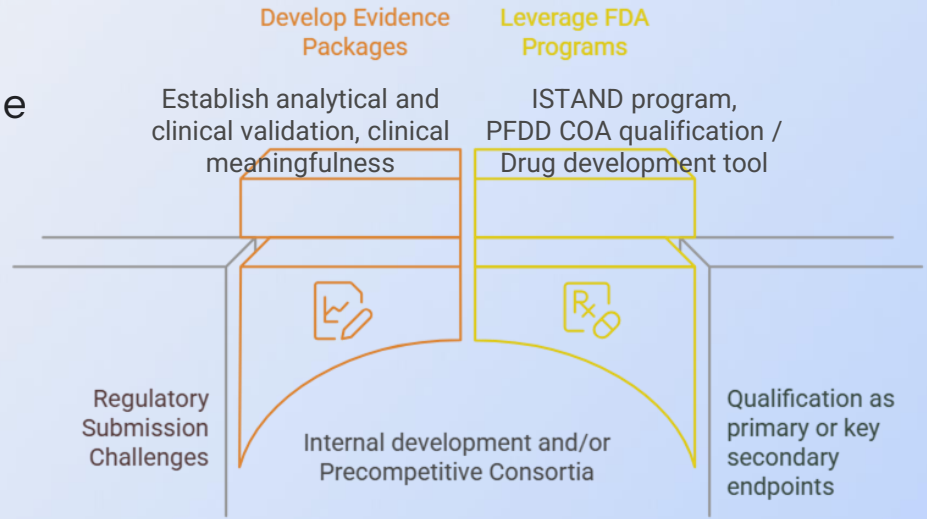
The decade+ winding road to the first digital efficacy endpoint qualified by EMA – SV95c for DMD.



SV95c : stride velocity 95th centile
DMD: Duchenne Muscular Dystrophy
SysNav SV95c overview (link), EMA qualification (link)

Critical hurdles, AI's role and path forward

- **No FDA-approved drug has used a DHT-derived primary endpoint yet**
  - Regulatory qualification very few cases so far, evidentiary package bar
  - Long development cycle
- **AI's role**
  - AI/ML algorithms often as cornerstone
  - Harmonize diverse device data into standards
- **Regulatory framework and pathways**



PFDD: patient focused drug development (link)
COA: clinical outcome assessment
ISTAND : Innovative Science and Technology Approaches for New Drugs (link)

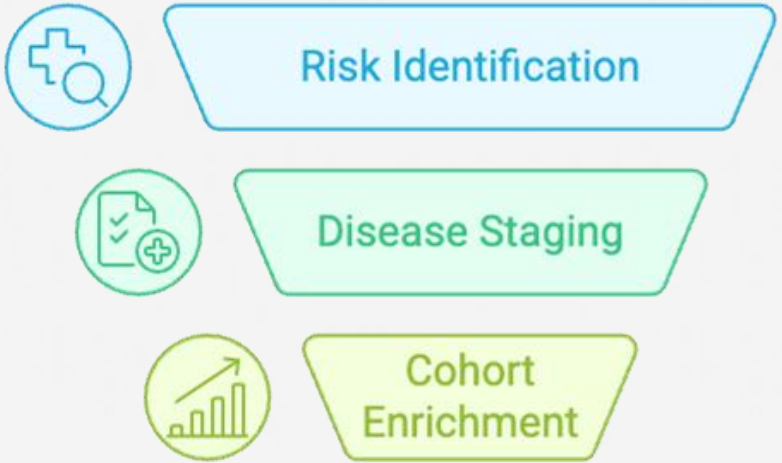
2. Screening Acceleration, Precision Patient Stratification and Enrichment with DHT

Find the right patient faster by:

- Mobile health apps and tests
- Real-world data / EHR
- Digital diagnostics
- Wearable digital measures

⇕

IC / EC

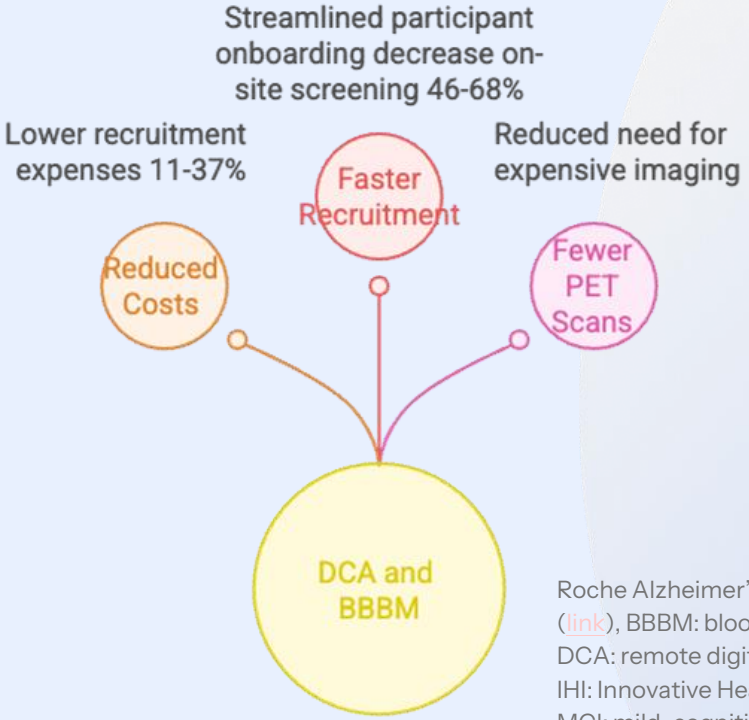


faster trial, reduced cost,
higher chance of success

IC: inclusion criteria;
EC: exclusion criteria

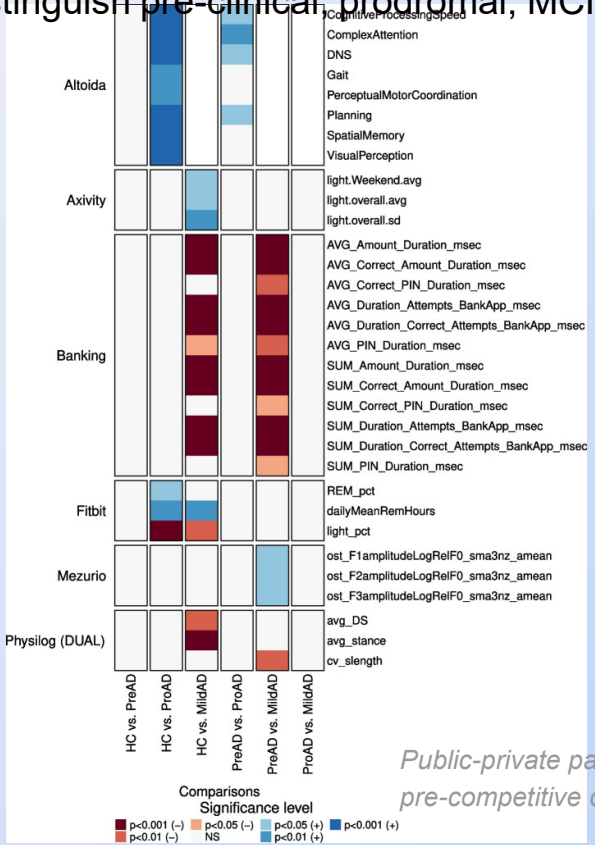
Case Examples: Alzheimer's Trials

Roche modeling for Alzheimer's trials suggests faster trial completion and reduced overall trial cost with -



Roche Alzheimer's trial screening modeling (link), BBBM: blood-based biomarkers , DCA: remote digital cognitive assessments
IHI: Innovative Health Initiative
MCI: mild-cognitive impairment
RADAR-AD paper (link)

IHI RADAR-AD project explores digital measures to distinguish pre-clinical, prodromal, MCI patients



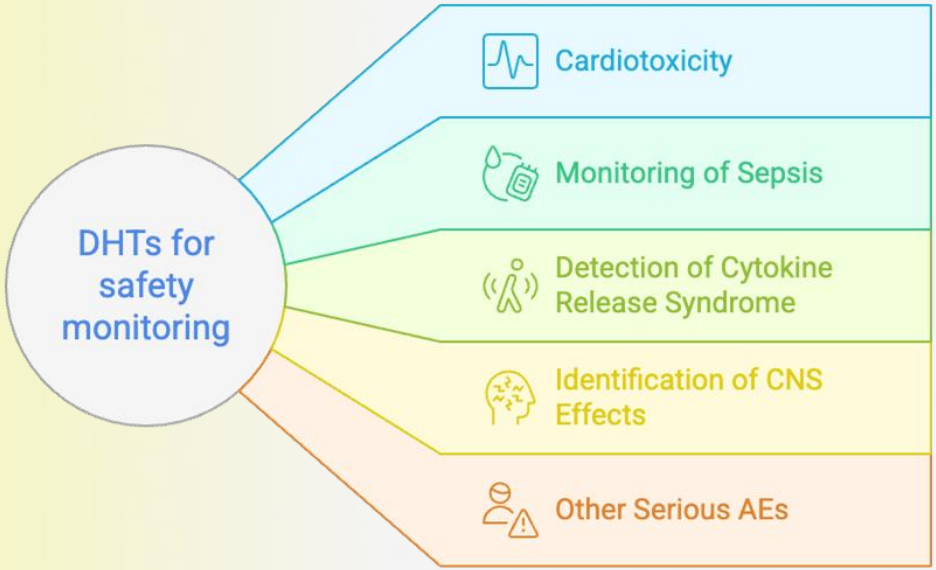
Public-private partnership, pre-competitive consortium

Critical hurdles, AI’s role and path forward

- **Adoption to pick up**
  - Method validity / regulatory uncertainty
  - Operation barrier (sponsor, site)
  - Data privacy
- **AI’s role**
  - AI/ML algorithms as cornerstone, incorporating wide data sources
  - New digital diagnostics
  - Predictive modeling: treatment response, adverse event risk
- **The frontier**
  - Neuroscience, rare disease areas
  - EHR integration
  - Federated learning

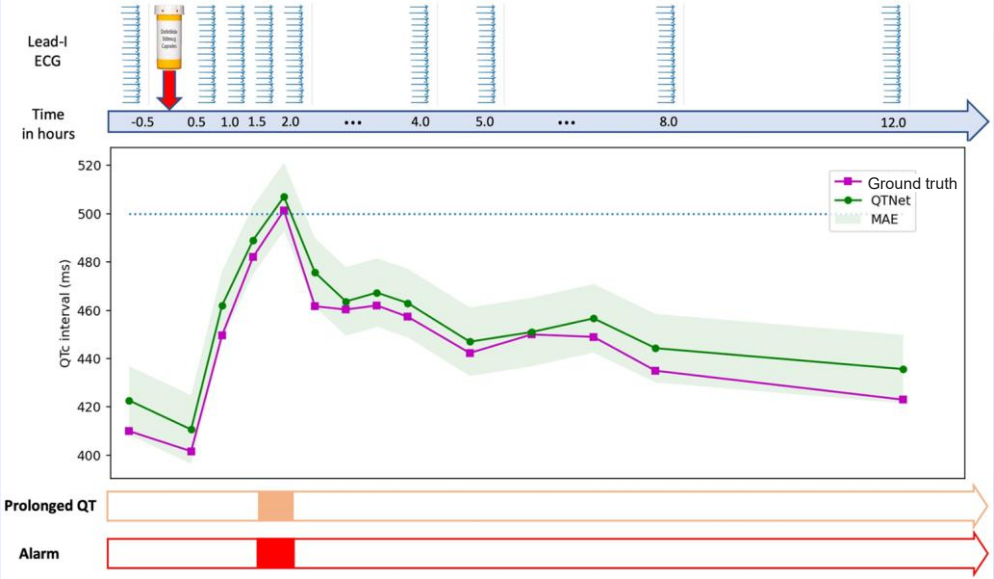
3. Enhancing Patient Safety and Monitoring with DHT

Continuous, passive monitoring to catch adverse events (AEs) earlier



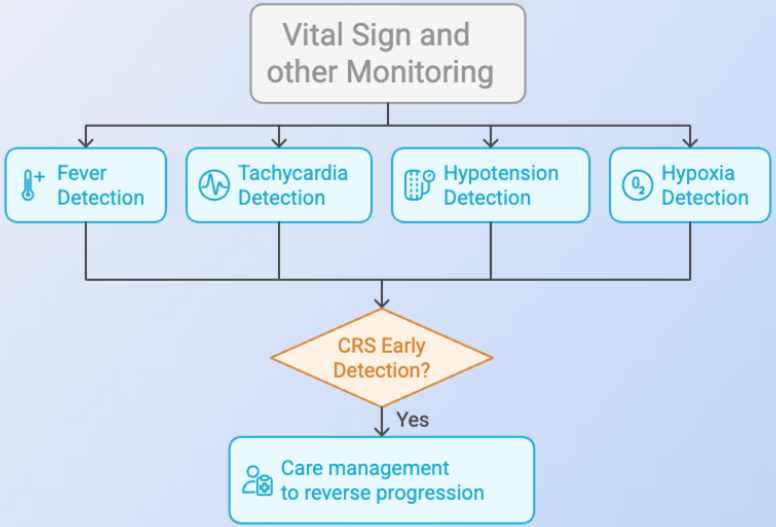
Case Examples

Measuring QT prolongation with single-lead ECG



FDA allowing ambulatory ECG for QT as supplement to 12-lead ECG method (link to latest guidance)
Alam et al 2024, QT prolongation with single lead ECG (link)
DiMe Society De-risking CRS project (link)

Early detection of CRS in immuno-oncology therapy

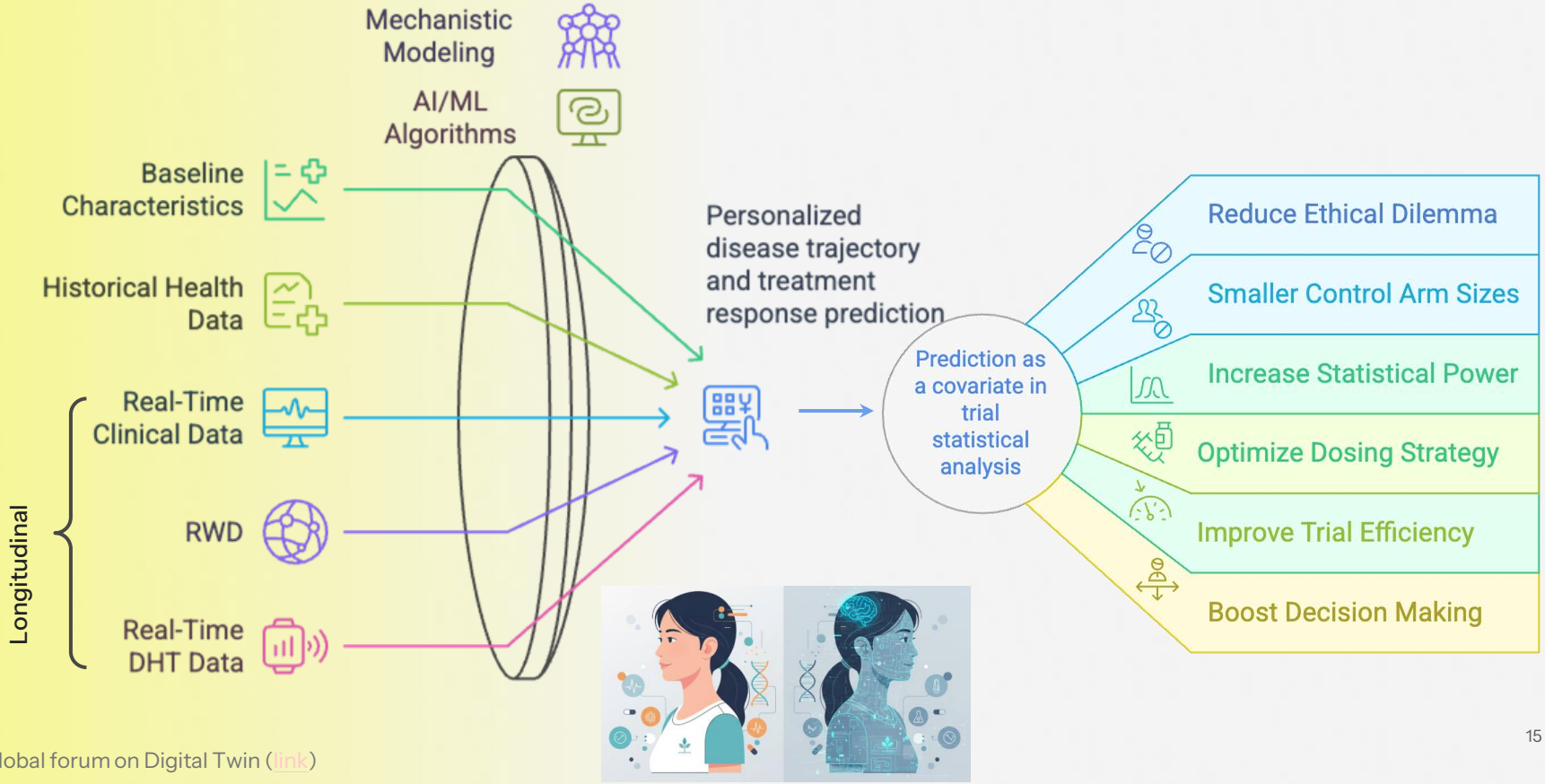


(Sepsis early detection can follow a similar method, may needs differential diagnosis)

Critical hurdles, AI’s role and path forward

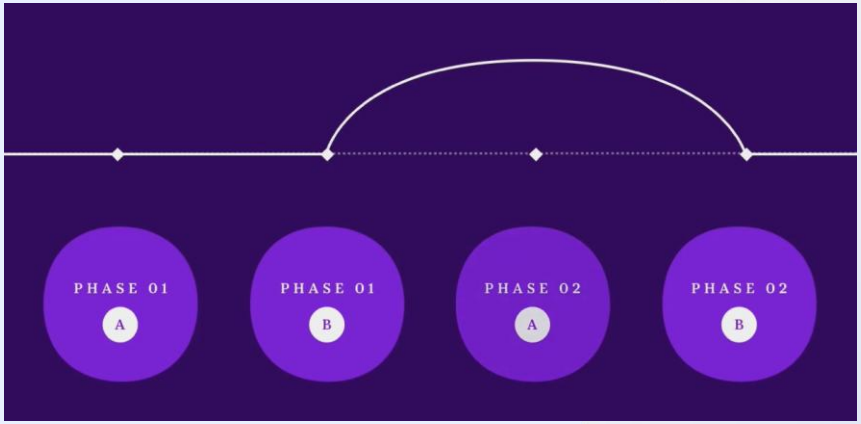
- **Methods still under development**
  - Scarcity of existing data
  - False alarm burden vs. false negative liability
  - Regulatory path
- **AI’s role**
  - AI/ML algorithms on multi-modal data superior than conventional thresholding
  - Personalized alarm
- **Efforts moving forward**
  - Collect data; algorithm > SoC
  - CRS Care product (as in next section)

4. DHT Feeding Continuous Data for Digital Twin in Trials



Case examples, AI's role and path forward

Sanofi Used Digital Twin to Skip a Phase2a Lunsekimig Asthma Trial

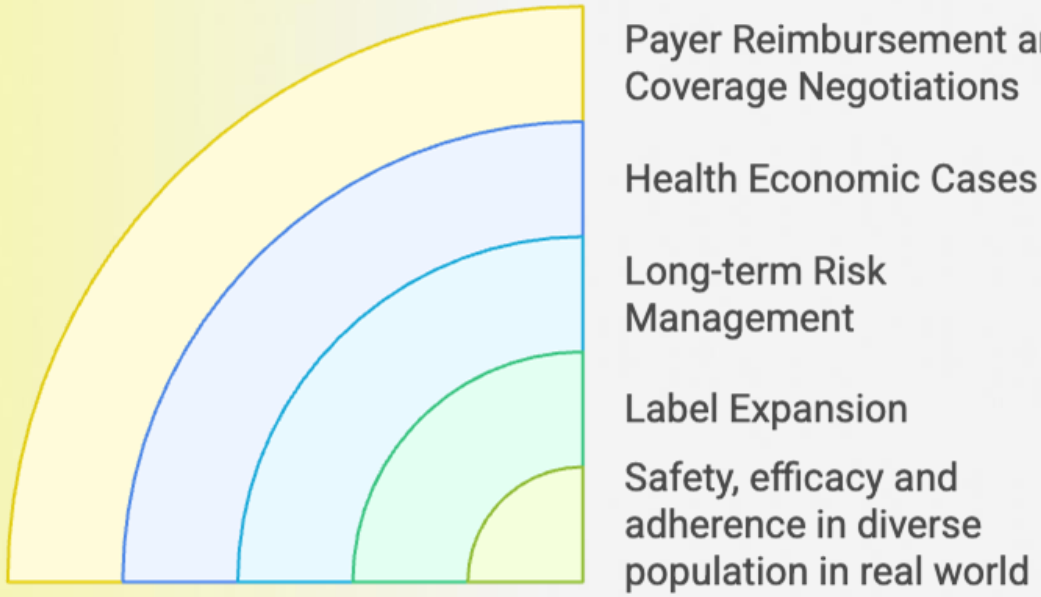


*(*In this example, DHT use not mentioned)*

- **Approach still under exploration**
  - AI model validation
  - Regulatory uncertainty
- **AI's role**
  - Multi-modal fit-for-purpose modeling
  - Personalized, longitudinal outcome prediction
- **Efforts moving forward**
  - Multi-sponsor consortia to pool historical trial data
  - FDA ISTAND qualification path?
  - Explainable AI

Sanofi presentation (link) and intro to digital twin for trials (link)
ISTAND : Innovative Science and Technology Approaches for New Drugs (link)

5. DHT Data for Post-Market Real-World Evidence (RWE) & Payer Reimbursement

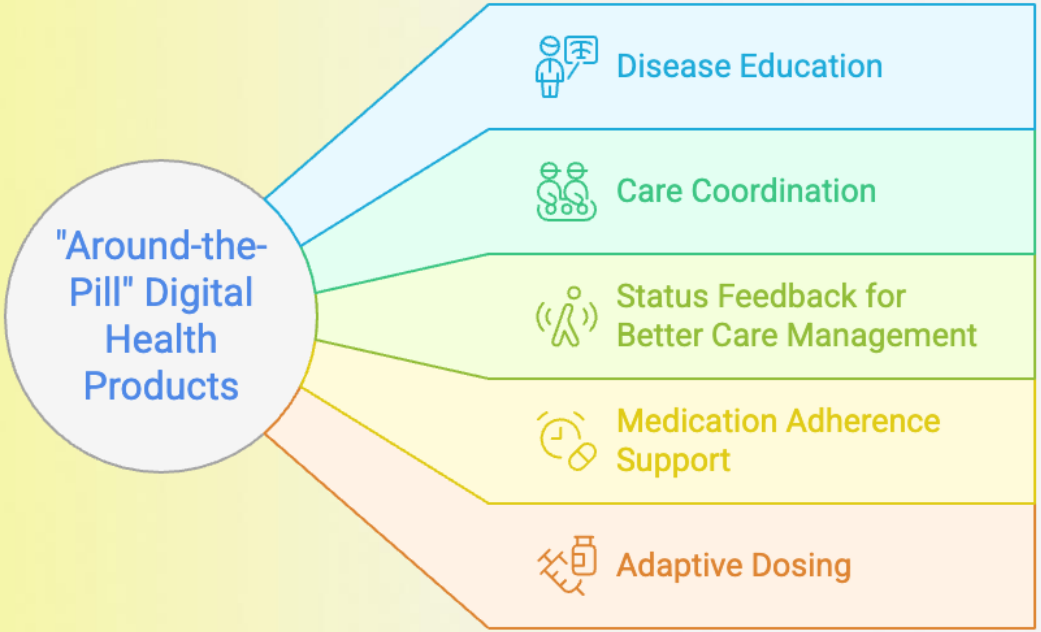


Critical hurdles, AI's role and path forward

- **Integrating into general RWE approach**
  - Extension from use for efficacy and safety in RCT
  - Case examples scarce so far
  - DHT as an upcoming component of RWD
  - RWD integration fragmented; data privacy
  - Payer criteria for DHT/RWE-based evidence still explored
- **AI's role**
  - Predictive Risk Stratification
  - Real-Time Safety Signal Detection
  - Adherence Prediction & Intervention
  - Modeling health economics and outcomes
- **Efforts moving forward**
  - Engage payers early in trial design to align on RWE evidentiary standards
  - Use distributed and federated data networks

RCT: randomized control trials
RWD: real-world data
RWE: real-world evidence

6. Turn DHT into Care Products: DTx, SaMD, PDURS etc

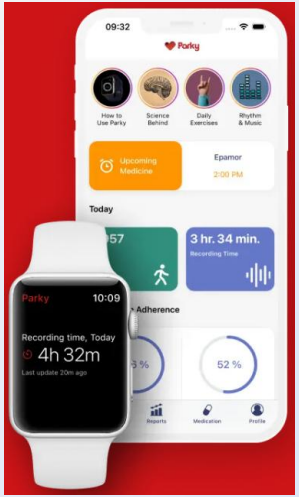


DTx: digital therapeutics
SaMD: software-as-medical-device
PDURS: Prescription Drug Use-Related Software

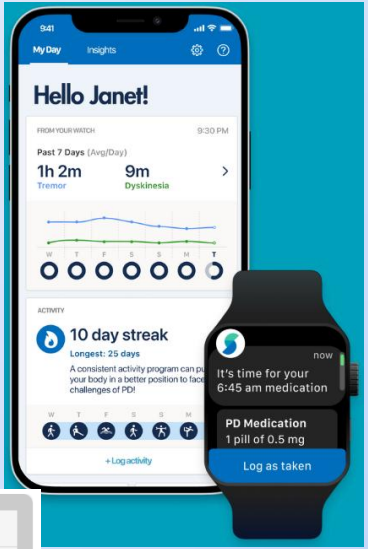
Case Examples: Crowded Market for Parkinson's Management

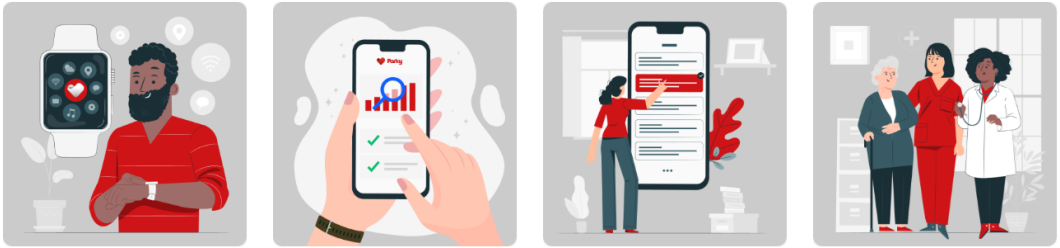
NeuroRPM – Rx

H2O Therapeutics Parky app



Rune Labs StrivePD

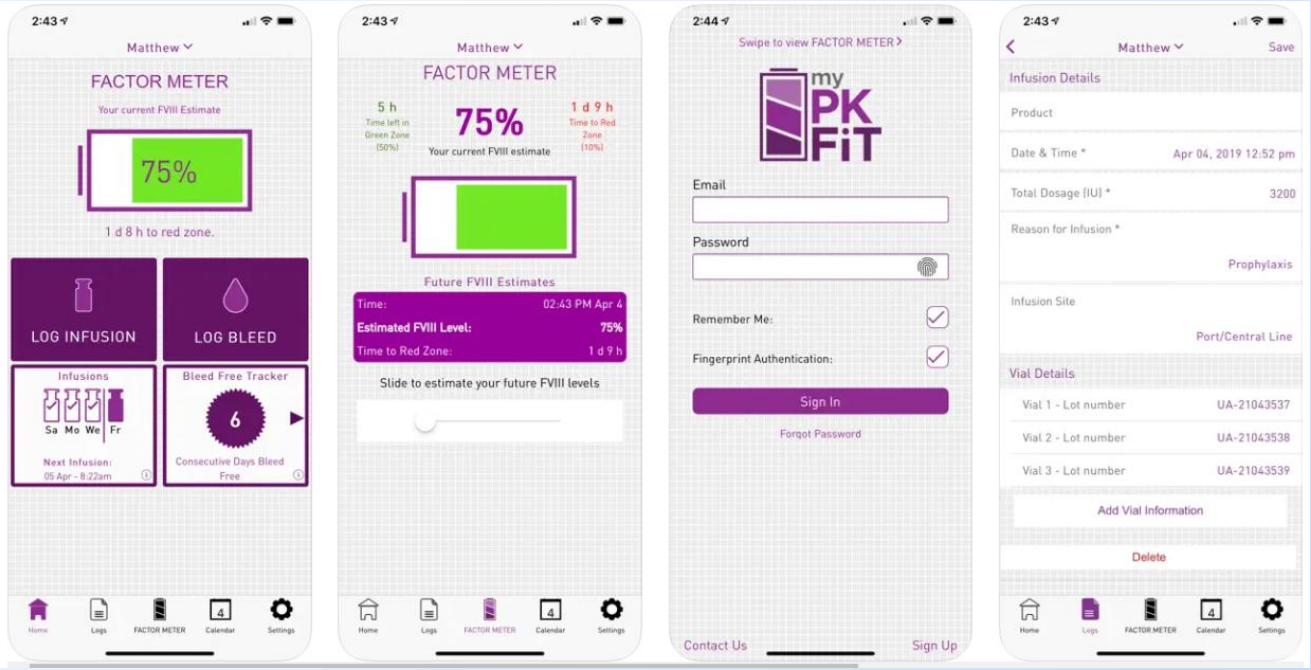




NeuroRPM (link)
H2O (link)
Rune Labs (link)

Case Examples

Shire/Takeda built classic SaMD guiding prophylactic dosing for Hemophilia drug based on PK measure:



SaMD: software-as-medical-device, PK: pharmacokinetics

Intro do MyPKFit and Hemophilia apps (link)

Critical hurdles, AI's role and path forward

- **Reimbursement**
  - Payers' criteria still evolving
  - Clinical evidence bars (tiered?)
  - Healthcare adoption
- **AI's role**
  - Powers components of product
  - Personalization & Adaptive Interventions
- **Efforts moving forward**
  - More HEOR evidence for payers
  - Carve out separate pathways
  - Partner with EHR & embed in clinical workflows
  - Policy traction with DTA/ATA efforts in Capitol Hill

DTA: Digital Therapeutics Alliance
ATA: American Telemedicine Association

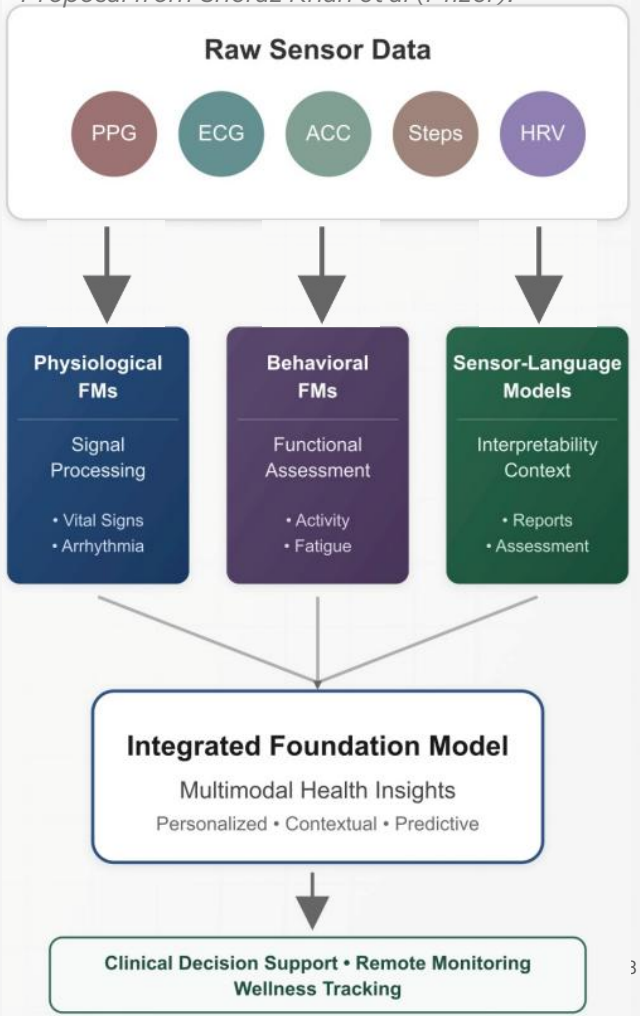
7. Building AI Systems that Understand Human Health and Diseases with DHT

Ultimately, all health-related industries building insights and action on:

Comprehensive Health State

Outputs:
- Disease risk scores
- Wellness indices
- Alert generation
- Trend analysis
- Anomaly detection
- Recommendations
- Clinical insights

Proposal from Sheraz Khan et al (Pfizer):



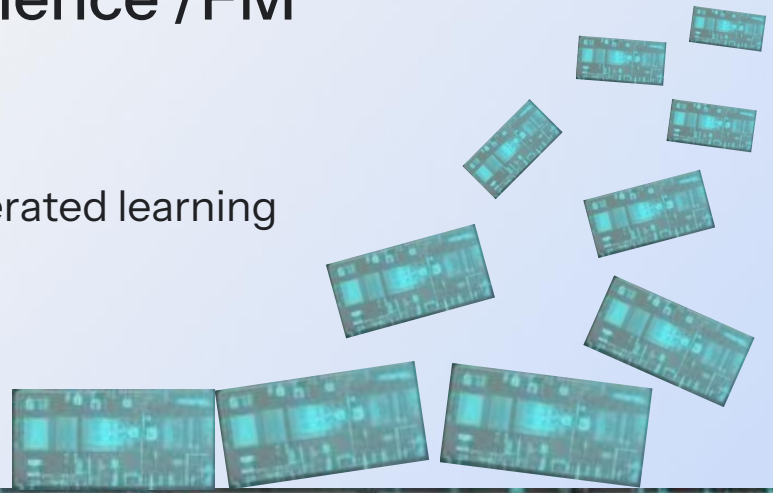
Samsung health sleep and sleep apnea (link)
Pfizer's Sheraz Khan et al advocate at CTTI (link), FM: foundation model
Sensor-language model from Google Research (link)

Outlook for Building DHT Based Science /FM

Potential approaches forward

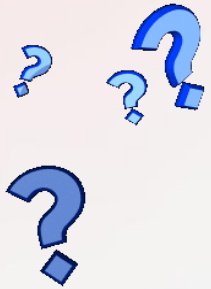
- One-at-a-time & grand foundation models
- Multiple sponsor/source data consortia & federated learning
- Hybrid consumer-medical-grade ecosystem

FM: foundation model



Concluding considerations

- Wide range of DHT use cases, varied maturity => build infrastructure beyond pilots
- Validations are fundamental requirements
- Regulatory paths clarity emerges => strengthen regulatory science
- AI as the critical enabler and facilitator
- Prioritize AI governance and transparency, reduce bias
- Anticipating digital health science's AlphaFold moment



Look forward to further discussions: HaoZhangNeuro@gmail.com

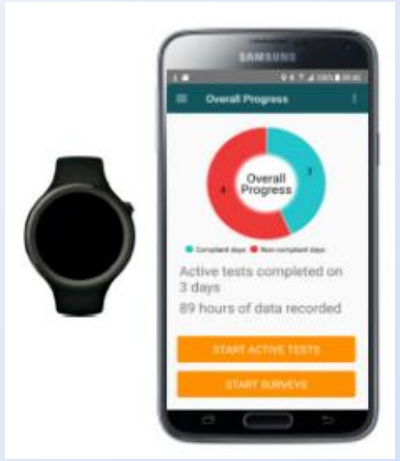
Appendix

Case Examples: internal decision making

Roche PD mobile application used in Roche's Phase2 trial

- ➔ "detected potential disease modifying effect of prasinezumab"
- ➔ trial now moved to Phase3

App V3 licensed by Neuron23 Inc. as the primary endpoint in the global Phase 2 NEULARK clinical trial of NEU-411



PASSIVE MONITORING		
Bradykinesia and Activities of Daily Living		
Gait	Armswing & Gesture	Mobility
Daily	Daily	Daily

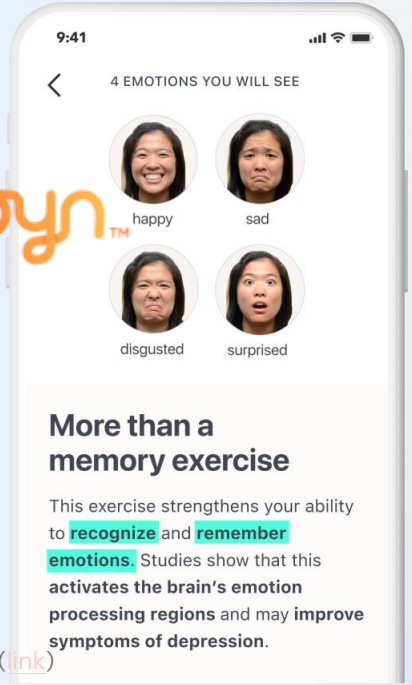
ACTIVE TESTS									
Bradykinesia			*Tremor/Bradykinesia*	*Tremor*			*Rigidity/Postural Instability*		*Cognition*
Draw A Shape	Dexterity	Hand Turning	Speech	Phonation	Postural Tremor	Rest Tremor	Balance	U-Turn	Cognitive Test (SDMT)
Bradykinesia Days (Every 2nd Day)			Alternating		Tremor and Stability Days (Every 2nd Day)				Fortnightly

PD: Parkinson's Disease
App V2 validation publication (link),
Phase2 efficacy evidence with PD app (link)
NEULARK trial (link)

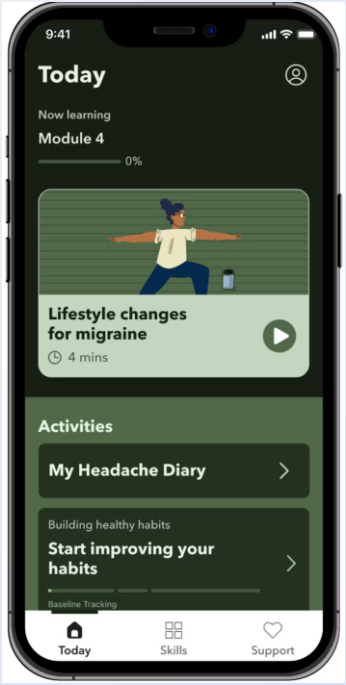
Case Examples

Click Therapeutics spearheading prescription DTx accompanying drugs or stand-alone

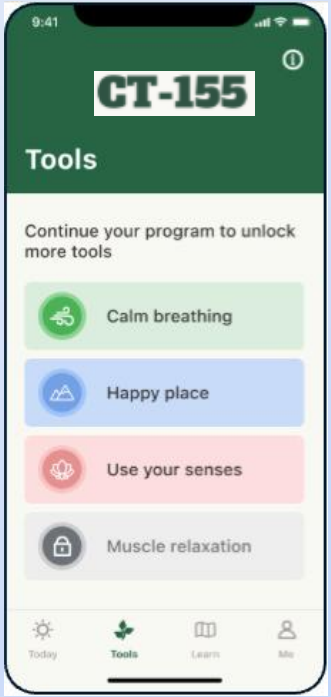
Rejoyn with Otsuka for MDD



CT-132 for Episodic Migraine



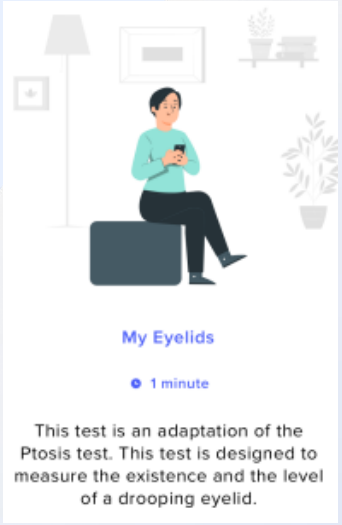
CT-155 with Boehringer for Schizophrenia

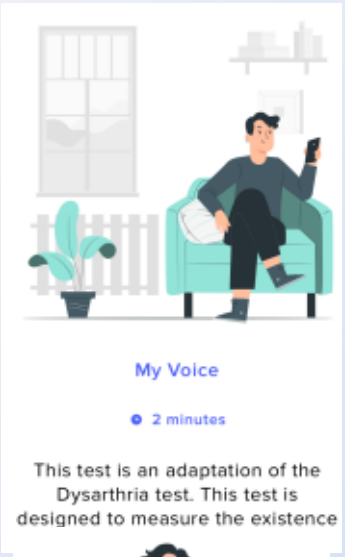


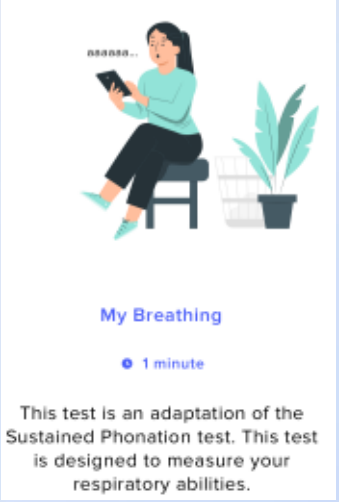
MDD: Major depressive disorder
Otsuka/Click Rejon 2024 (link)
FDA clears Click's CT-132 2025 (link)
Boehringer/Click CT-155 (link)

Case Examples

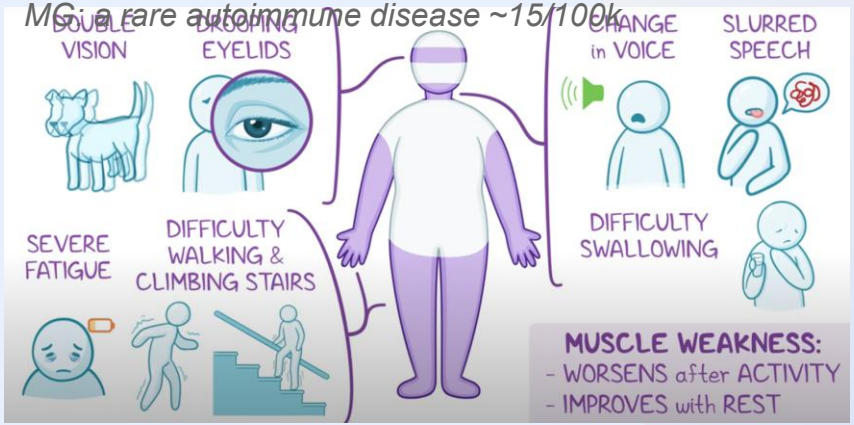
Alexion medical affairs building functional assessments for Myasthenia Gravis (MG) patients to assess disease status and more

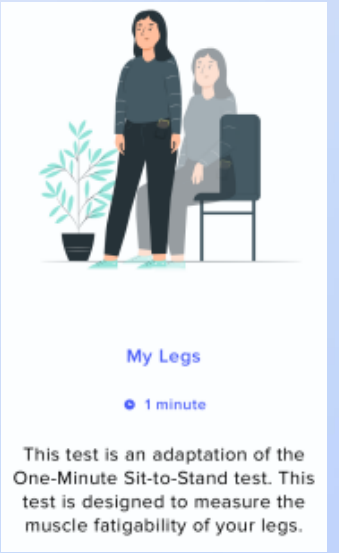






MG: a rare autoimmune disease ~15/100k





MG basics (link), Ad Scientiam ME&MG product instructions in DOMYA study (link)