DRAFT 12/12/24

Digital Outcomes and Biomarkers in Neuropsychiatry and Neurology – the Path Forward

Gahan Pandina, PhD

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Abstract: The field of neuropsychiatry and neurology are continually searching for tools to help better understand disease neurobiology that can be leveraged to enable more efficient clinical trials. This is particularly important in orphan diseases, where less is known about the natural history and clinical course. Digital outcomes and other biomarkers are becoming more available, and increasing computer power is enabling complex analytic techniques and use of large, disparate datasets. This talk will highlight some of the issues in use of digital outcomes and biomarkers in neuropsychiatry and neurology and provide an example from a clinical trial of Autism Spectrum Disorder.

Disclosure

- Dr. Pandina is a full-time employee of Janssen Research & Development, LLC, and a Johnson & Johnson stockholder

What are biomarkers and digital outcomes, and why are they important?

A biomarker is "… a substance that indicates the presence of a biological material, organism, or physiological condition." (Oxford Dictionary)

A digital outcome is an objective measures of behavior or digital signals that (hopefully) relate to disease(s) and/or symptom(s) of interest.

Both:

- … can serve as proxy measures of important aspects of disease / symptoms.
- … might enhance or replace commonly used subjective outcome measures as endpoints in clinical trials and improve research efficiency and quality

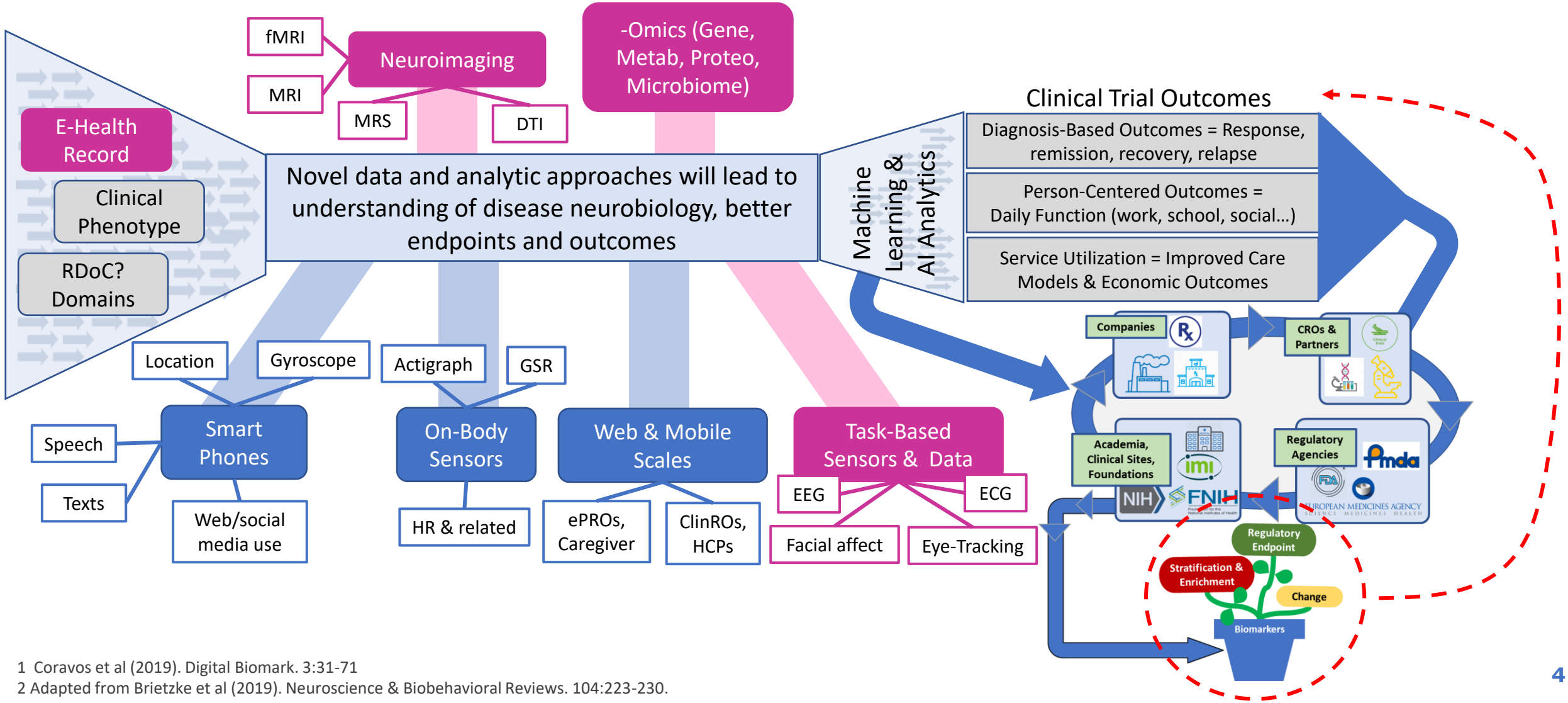
But how can they enhance clinical trial outcomes?

- Biomarkers are excellent… if a 'true proxy' (disease biology or outcome), but they often aren't
- Digital measures may be more important in orphan disease, which LACK disease-related data
- Should enable, rather than slow down or increase complexity of, drug development

Digital Medicine, Phenotyping, and Biomarkers in Clinical Trials

Digital Medicine: use of technologies as tools for measurement and intervention in service of human health[1]

Digital Phenotyping: momentary quantification of individual phenotype via mobile apps, web, or other personal devices[2]



1 Coravos et al (2019). Digital Biomark. 3:31-71

2 Adapted from Brietzke et al (2019). Neuroscience & Biobehavioral Reviews. 104:223-230.

But, the math for developing orphan disease endpoints doesn't work well…

- Orphan diseases are (by definition) rare
  - Micro-community cannot accommodate large validation and development programs…
  - … however, endpoints still require (sufficient) validation
- Limited knowledge requires flexibility… and fortitude
  - May need to rely on limited datasets, and take the best possible route
- Lack of data can't be solved by AI / ML
  - Bad data in a small dataset has an even bigger impact than in a large dataset

- However… we can leverage the broader ecosystem, across neuropsychiatry and neurology

First… a simple question… what is the problem?

Example 1: Diophantine equation

- "Summing of three cubes"
- Formula: $x^3+y^3+z^3=k$
  - k = all numbers from 1 to 100
  - Which x, y, z values sum to k, for each number?
- Last remaining number (in 2019) was 42 (for Douglas Adams fans)…
  - Took >1M hours of computing time (Charity Engine)
  - Answer:
    - X = -80538738812075974
    - Y = 80435758145817515
    - Z = 12602123297335631

Example 2: Standard Model Lagrangian formula - string theory

- Describes fundamental forces in the universe and all the known the elementary particles (first 1/3 of formula shown below…)

$$
\begin{aligned}
\mathcal{L}_{\mathrm{SM}} = {} & -\frac{1}{2}\partial^{\nu} g^{a\mu}\partial_{\nu} g_{a\mu} - g_s f^{abc}\partial^{\mu} g^{a\nu} g^{b}_{\mu} g^{c}_{\nu} - \frac{1}{4} g_s^2 f^{abc} f^{ade} g^{b\mu} g^{c\nu} g^{d}_{\mu} g^{e}_{\nu} \\
& -\partial^{\nu} W^{+\mu}\partial_{\nu} W^{-}_{\mu} + m_W^2 W^{+\mu} W^{-}_{\mu} - \frac{1}{2}\partial^{\nu} Z^{0\mu}\partial_{\nu} Z^{0}_{\mu} + \frac{m_W^2}{2c_w^2} Z^{0\mu} Z^{0}_{\mu} - \frac{1}{2}\partial^{\nu} A^{\mu}\partial_{\nu} A_{\mu} + \frac{1}{2}\partial^{\mu} H\partial_{\mu} H - \frac{1}{2} m_H^2 H^2 \\
& +\partial^{\nu}\phi^{+}\partial_{\nu}\phi^{-} - m_W^2\phi^{+}\phi^{-} + \frac{1}{2}\partial^{\nu}\phi^{0}\partial_{\nu}\phi^{0} - \frac{m_W^2}{2c_w^2}\left(\phi^{0}\right)^2 - \beta_H\left[\frac{2m_W^2}{g^2} + \frac{2m_W}{g} H + \frac{1}{2}\left(H^2 + \left(\phi^{0}\right)^2 + 2\phi^{+}\phi^{-}\right)\right] + \frac{2m_W^4}{g^2}\alpha_H \\
& -i g c_w\left[\partial^{\nu} Z^{0\mu}\left(W^{+}_{\mu} W^{-}_{\nu} - W^{+}_{\nu} W^{-}_{\mu}\right) - Z^{0\nu}\left(W^{+\mu}\partial_{\nu} W^{-}_{\mu} - W^{-\mu}\partial_{\nu} W^{+}_{\mu}\right) + Z^{0\mu}\left(W^{+\nu}\partial_{\nu} W^{-}_{\mu} - W^{-\nu}\partial_{\nu} W^{+}_{\mu}\right)\right] \\
& -i g s_w\left[\partial^{\nu} A^{\mu}\left(W^{+}_{\mu} W^{-}_{\nu} - W^{+}_{\nu} W^{-}_{\mu}\right) - A^{\nu}\left(W^{+\mu}\partial_{\nu} W^{-}_{\mu} - W^{-\mu}\partial_{\nu} W^{+}_{\mu}\right) + A^{\mu}\left(W^{+\nu}\partial_{\nu} W^{-}_{\mu} - W^{-\nu}\partial_{\nu} W^{+}_{\mu}\right)\right] \\
& -\frac{1}{2} g^2 W^{+\mu} W^{-}_{\mu} W^{+\nu} W^{-}_{\nu} + \frac{1}{2} g^2 W^{+\mu} W^{-\nu} W^{+}_{\mu} W^{-}_{\nu} + g^2 c_w^2\left(Z^{0\mu} W^{+}_{\mu} Z^{0\nu} W^{-}_{\nu} - Z^{0\mu} Z^{0}_{\mu} W^{+\nu} W^{-}_{\nu}\right) \\
& +g^2 s_w^2\left(A^{\mu} W^{+}_{\mu} A^{\nu} W^{-}_{\nu} - A^{\mu} A_{\mu} W^{+\nu} W^{-}_{\nu}\right) + g^2 s_w c_w\left[A^{\mu} Z^{0\nu}\left(W^{+}_{\mu} W^{-}_{\nu} + W^{+}_{\nu} W^{-}_{\mu}\right) - 2A^{\mu} Z^{0}_{\mu} W^{+\nu} W^{-}_{\nu}\right] \\
& -g\alpha_H m_W\left[H^3 + H\left(\phi^{0}\right)^2 + 2H\phi^{+}\phi^{-}\right] - \frac{1}{8} g^2\alpha_H\left[H^4 + \left(\phi^{0}\right)^4 + 4\left(\phi^{+}\phi^{-}\right)^2 + 4\left(\phi^{0}\right)^2\phi^{+}\phi^{-} + 2H^2\left(\phi^{0}\right)^2 + 4H^2\phi^{+}\phi^{-}\right] \\
& +g m_W W^{+\mu} W^{-}_{\mu} H + \frac{1}{2} g\frac{m_W}{c_w^2} Z^{0\mu} Z^{0}_{\mu} H + \frac{1}{2} i g\left[W^{+\mu}\left(\phi^{0}\partial_{\mu}\phi^{-} - \phi^{-}\partial_{\mu}\phi^{0}\right) - W^{-\mu}\left(\phi^{0}\partial_{\mu}\phi^{+} - \phi^{+}\partial_{\mu}\phi^{0}\right)\right] \\
& -\frac{1}{2} g\left[W^{+\mu}\left(H\partial_{\mu}\phi^{-} - \phi^{-}\partial_{\mu} H\right) + W^{-\mu}\left(H\partial_{\mu}\phi^{+} - \phi^{+}\partial_{\mu} H\right)\right] - \frac{1}{2}\frac{g}{c_w} Z^{0\mu}\left(H\partial_{\mu}\phi^{0} - \phi^{0}\partial_{\mu} H\right) \\
& +i g\frac{s_w^2}{c_w} m_W Z^{0\mu}\left(W^{+}_{\mu}\phi^{-} - W^{-}_{\mu}\phi^{+}\right) - i g s_w m_W A^{\mu}\left(W^{+}_{\mu}\phi^{-} - W^{-}_{\mu}\phi^{+}\right)
\end{aligned}
$$

Biomarker/Endpoint Selection Process: Qualification Path or “Part of IND”?

Question / Issue	Orphan-Specific Challenge
What drug development phase?	• Almost always Ph1B… though we call it Phase 2
Do you have access to biomarker technology?	• Maybe in adjacent populations?
Do you have a large clinical population?	• No
Are biomarker data available in population?	• (see clinical population)
Is there a single objective outcome of interest?	• Not usually…
Do we have a validated subjective measure?	• Probably not…
Is there significant clinical heterogeneity?	• Almost always…

Evaluate potential pathway regulatory, timing, cost, and probability of success…

Select IND Pathway

- Precision neuroscience approach requires more targeted strategies, more complex in orphan disease
- Starting to utilize qualification path as a complementary approach, with availability of large precompetitive datasets (AMP-SCH / AD / PD, AIMS2Trials, ABC-CT, etc.)

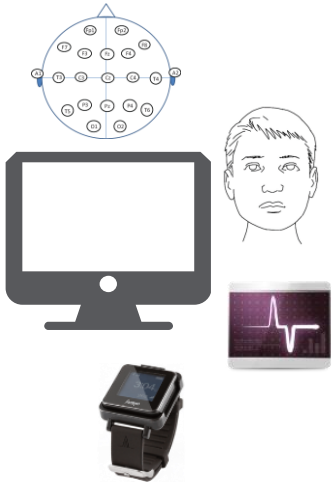
Lab-based biosensor platform and experiments

Jake
Janssen Autism Knowledge Engine

JAKE Sense

Biosensors in home and lab create sensitive objective endpoints for clinical research

- Continuous biosensors at home (actigraphy)
- Biosensors (eye-tracking, EEG, ECG, facial expression/affect) and computer-based tasks in the research lab with computer tasks to evoke ASD symptom markers



Identify ASD biomarkers for stratification/ enrichment and change, and assess clinical trial outcomes

Site-based task battery includes:

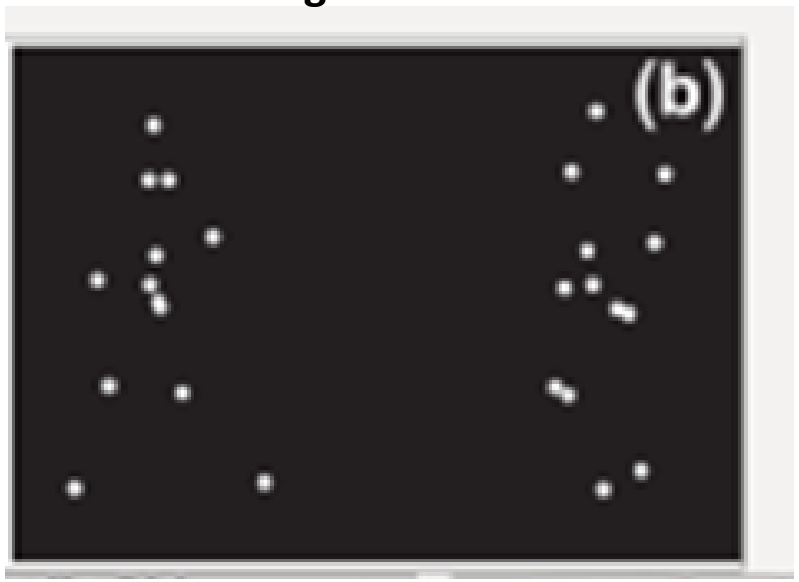
- Computer-presented tasks completed at study center periodically during the study
- 11 brief, hypothesis-driven sensor experiments
  - Videos and static images
  - Each experiment is designed to
    - … elicit biomarker-specific responses
    - … link to ASD behavior / biology
- Four continuously measured biosensors
  - Eye tracking: visual scan
  - EEG: electrical brain activity
  - ECG: cardiovascular
  - Facial affect: facial features

Ness et al (2019). Frontiers Neurosci: 13:111

Is eye tracking a biomarker for social perception and/or function in ASD?

Activity Monitoring

Biological Motion



Visual Exploration Task

Visual Social Attention

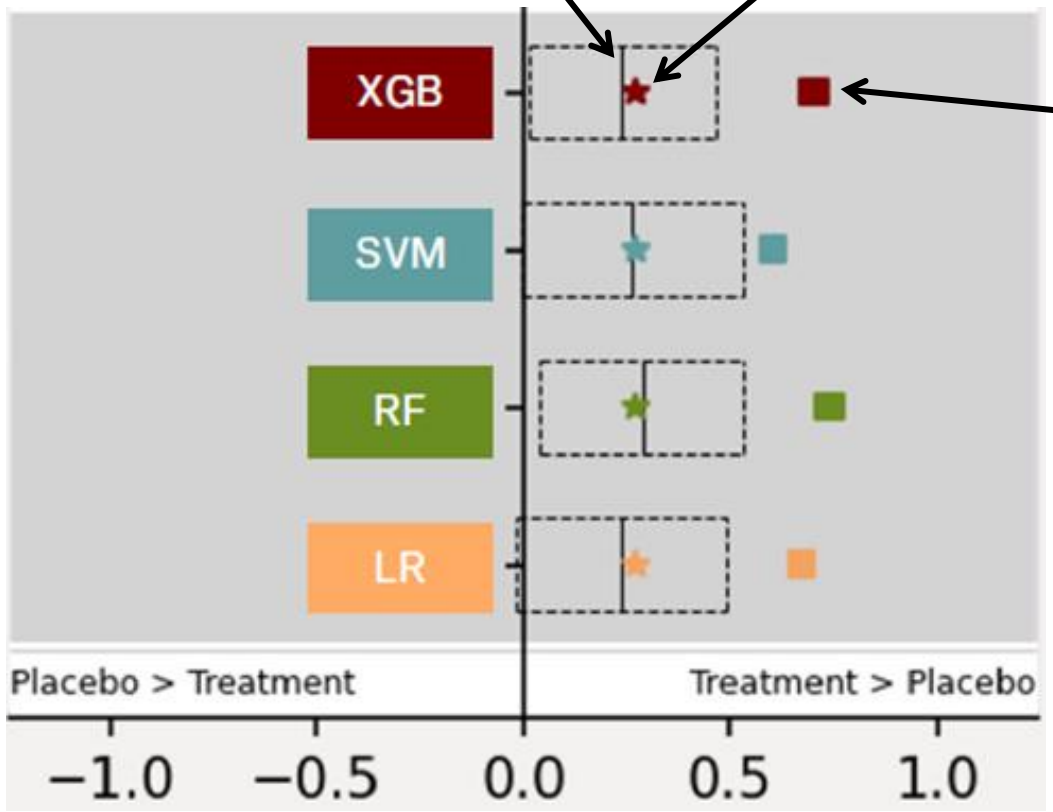
Machine learning approach with eye tracking data enhances detection of clinical trial outcome in ASD placebo-clinical trial

Compared ADOS score enrichment alone with combination of ADOS scores and ET features to enhance pt.

Dotted box: Mean (SD) Cohen's d distribution corresponding to randomly removed patients in tx and PBO groups to match the same N as selected in ML + clinical criteria approach 100 times

Stars: Cohen's d for **ADOS-2 score driven patient selection**

Squares: Cohen's d for **ML eye tracking + ADOS-2 score driven patient selection**



- Four machine learning models used to predict treatment effect
- Utilized SRS Total Score as outcome

Conclusions

- Addition of ET features to clinical diagnostic scores, using model-driven machine, enhanced efficacy outcome in PoC clinical trial
- Biomarkers can be used to identify common clinical characteristics to use for *future* enrichment approaches in subsequent studies

Caveats & Conclusions - Digital Outcomes

- Orphan diseases are rare – normal drug development approach is harder
  - What is “minimum threshold” for validation of endpoints, biomarkers, and digital outcomes?
- Borrow tools across the ecosystem to advance scientific understanding
- Digital outcomes are easily accessible and available… true biomarkers are few…
  - May help accelerate biomarker and novel endpoint development
- AI / ML can be helpful, but will not solve the problem of small datasets
  - Solve the right problem: remember Diophantine / Lagrangian
  - Fancy analysis cannot correct for bad / too little data
- Endpoint and biomarker development requires persistence, iteration, and flexibility
- Clinical meaningfulness is important: disease outcomes of interest, functioning