The rise of digital biomarkers in neuroscience drug development

Will an expansion in the use of effective digital biomarkers help improve the productivity of drug development in neuroscience? Ask **Dr J. Mark Treherne**, **Dr Jenny Barnett** and **Dr Paula Moran**.

Increasingly, digital biomarkers are becoming more effectively used in the discovery and development of drugs that act in the central nervous system. However, unlike many other areas of drug discovery, the majority of psychiatric and many neurological diseases do not yet have universally accepted biological markers. As a result, many apparently attractive new drug candidates in neuroscience subsequently fail to meet their primary endpoints in clinical trials. In oncology, by contrast, stratified medicine approaches that target the right patient with the right drug at the right time are becoming the conventional way forward for successful new drug registrations. Psychiatric and neurological drug development is entering a new realm where stratified approaches are finally being applied successfully. This article reviews the challenges and solutions required to expand the use of digital biomarkers to meet the growing demand for more effective drugs that act on the central nervous system.

According to the World Health Organization (WHO), one in every eight people in the world live with a mental disorder. Hundreds of millions of people worldwide are affected by neurological

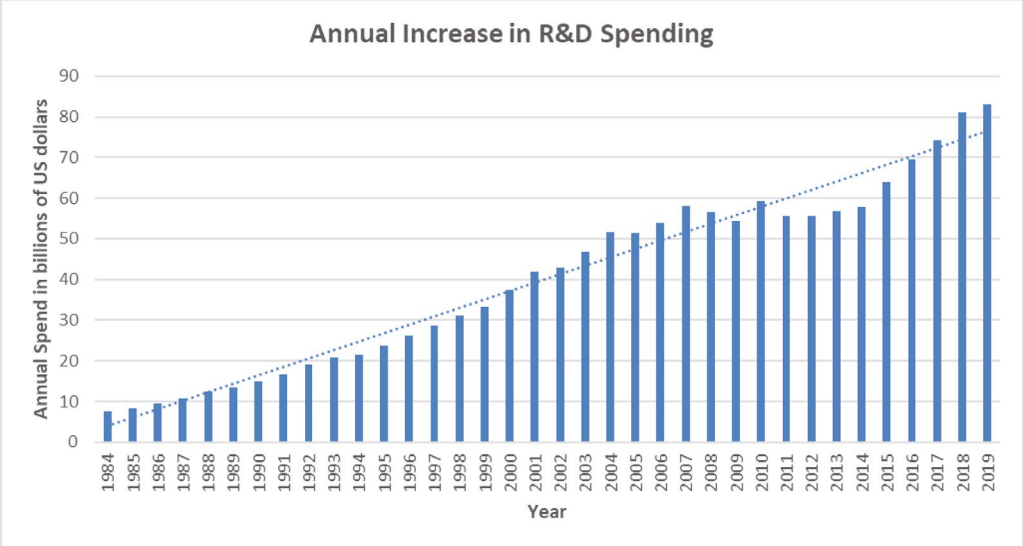

Figure 1: *Increasing annual research and development spending from 1984 to 2019. Adjusted to the value of billions of 2019 US dollars. The raw data are extracted from the CBO's April 2021 report Research and Development in the Pharmaceutical Industry: https://www.cbo.gov/publication/57025*

Figure 2: *Abbreviated patient reported outcomes, delivered on consumer grade wearables such as the Apple Watch, provide a convenient means of capturing day-to-day variation in patient reported symptoms with high accuracy and low patient burden. Copyright of image: Cambridge Cognition with permission.*

disorders. More than 6 million people die because of stroke each year. It is estimated that there are 47.5 million people globally with dementia with 7.7 million new cases every year. Alzheimer's disease is the most common cause of dementia and may contribute to 60 to 70% of cases. Despite the increasing unmet medical need, standard pharmacotherapy has not changed for decades. Consequently, there is an urgent and unmet need for the discovery of novel improved treatments.

Research productivity is the problem, especially in neuroscience

The pharmaceutical industry is highly dependent on the productivity of its research and development expenditure to source innovative solutions for the discovery of the next generation of new drugs. However, current drug pipelines do not always meet the growth expectations of their shareholders for discovering cost-effective and efficacious new therapies. This increasing pressure to improve research productivity is largely due to high levels of pipeline attrition, a particular issue for drugs acting in the central nervous system (CNS), frequently due to not meeting their primary endpoints in clinical trials. In particular, the ever-increasing research and development costs required[1]. This long-term trend is illustrated in Figure 1, taken from data archived by the Congressional Budget Office (CBO) 2021 Report[2]. Research tools for effective decision making in drug discovery and development, are more effective when they select therapeutic candidates in a way that correlates with clinical utility in humans[3]. Otherwise, they probably lead to drugs that do not work. Analysis of this problem has revealed that the ability to detect good therapeutic candidates is extremely sensitive to the predictive validity of the decision-making tools that are used[3]. In this context, predictive validity refers to how well an assay or test can predict a meaningful clinical outcome. Consequently, tests based on digital biomarkers are poised to have a major impact on neuroscience research.

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The opportunity for digital biomarkers in drug development

Digital biomarkers can be defined as objective, quantifiable, physiological or behavioural measures collected by electronic devices and used to explain or predict health-related function. Unlike many areas of medical research, such as oncology or cardiovascular disorders, the majority of psychiatric and many neurological diseases do not have universally accepted biological markers. Psychiatry relies for diagnosis on subjective clinical assessment using consensually derived guidelines such as those given in the WHO's International Classification of Disease or the American Psychiatric Association's Diagnostic and Statistical Manual. Approximately every decade these guidelines in turn are revised by agreement among psychiatrists about what currently best represents what they are seeing in the clinic and the latest research evidence. In contrast, the pace of advancement in basic and clinical neuroscience research is much more rapid, thanks to new technical advances particularly in the ability to image the brain and synthesise new compounds. Consequently, the pace of new biological discoveries far outstrips the pace at which clinical diagnostic criteria can be revised, meaning that in many cases these do not map onto each other accurately. This disconnect and time-lag

create an inevitable translational problem at almost every stage of the drug development process. Compounding these problems, the very existence of conventional disease categories in psychiatry has been called into question. Frequent comorbidity means that a patient can meet the criteria for several disorders simultaneously, such as anxiety and depression. This can increase variability for clinical trials that strictly recruit patients with a 'single' disorder, making it harder to achieve clinical endpoints. Focus on single disorders has also skewed research away from investigation of common underlying biological pathways that exist. Drugs that treat these disorders largely interact with brain circuitries and receptors that network across multiple brain systems and are almost never biologically specific to a single disorder.

In an attempt to direct research efforts away from these constraints and towards more meaningful biological frameworks, the National Institute of Mental Health initiated work on the Research Domain Criteria (RDoC) in 2009. This framework proposed to guide research through focus on a series of psychological dimensions seen in many psychiatric and neurological disorders such as cognition, positive and negative valence (reward and punishment), arousal and social processes; and to integrate research findings from multiple levels of enquiry such as molecular, cellular, circuitry, physiology, behaviour and self-report. While this approach has been criticised for not emphasising psychological factors sufficiently, it may help to guide drug development strategy more precisely directed towards specific symptoms and brain circuits irrespective of clinical diagnoses. This requires a 'reframing' of psychiatric diagnoses into functionally relevant but transdiagnostic indications. For example, rather than developing a drug specifically for cognitive impairment in schizophrenia, it may be possible to target reduced cognitive flexibility consequent to reduced dopamine in the prefrontal cortex. Such a drug could then potentially be used in many disorders including Parkinson's and Alzheimer's diseases, as well as schizophrenia, thus better reflecting the transdiagnostic nature of impaired cognitive flexibility.

Figure 3: *A cardinal test of episodic memory, the CANTAB Paired Associates learning, is typically used to assess memory function in older adults. Unlike traditional cognitive tests, these digital assessments require no special knowledge or training on the part of the patient or clinician, and can be used in worldwide clinical trials without requiring cultural or language adapation. Copyright of image: Cambridge Cognition with permission.*

As the majority of psychiatric and neurological illnesses involve some aspect of brain pathology, it makes sense that brain imaging measures, both structural (cortical thickness) and functional (strength of connections between brain regions), are widely investigated as potential predictors of individual differences to psychopathological symptoms. If reliably found, measures derived from imaging the brain in these disorders should provide the clearest exploitable biomarker. However, while structural and functional changes of various kinds have been found in almost every CNS disorder, it is becoming increasingly clear that such approaches have a replication issue. The latest meta-analyses[4] suggest that many thousands of individuals would be required to achieve statistical validity and that brain-wide associations between brain imaging measures and psychopathology are weak. This inevitably means that a high number of the prior small studies were underpowered, showed inflated effect sizes and failed to replicate. In larger sample sizes, replication rates improve and effect size inflation decreases. Interestingly, more robust effects are detected for functional imaging than for structural changes, and for cognitive tests versus mental health questionnaires. The robustness of cognitive tests, alongside their ability to be used reliably and at scale, suggest that these might provide grounds for more stable biomarkers.

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The solution provided by digital biomarkers

The ongoing absence of objective assessments in psychiatry and neurology is one reason why digital biomarkers are uniquely placed to improve drug development in neuroscience. In essence, diagnosis and treatment decisions in psychiatry are based on a clinician's interpretation of the patient's report of internal experiences such as mood, anxiety and cognition. In neurology, while neuroimaging can provide diagnostic insight, most clinical

decisions are nonetheless based on a combination of self-report and clinician observation of symptoms such as tremor or gait. Both neurology and psychiatry therefore require the patient or clinician to objectively recall how the symptoms have developed and change over time – particularly tricky in the many disorders in which memory problems are present, or where objective judgement may be influenced by low mood.

One simple way in which digital biomarkers can therefore help improve accuracy is by recording a new or changing symptom in the moment. Ideally this would occur 'passively', in other words without requiring any input from the patient. For example, changes in step count, walking speed, sleep duration or heart rate variability – all available from consumer grade wearables such as smartphones, the Apple Watch or Oura ring – can provide an objective picture of short- and long-term changes in symptoms. For mood, anxiety or pain, states which cannot be automatically read by wearables, studies have shown that asking for very brief inputs from the user (responding to one or two questions per day, for example, illustrated in Figure 2) is highly acceptable to patients and can provide accurate longitudinal data to enable better collaborative decision-making between clinicians and patients.

New artificial-intelligence-derived biomarkers show great promise, including those that can use voice, facial expression or changes in social contact derived from personal devices as early signals of diagnosis or relapse[5]. However, accelerated by Covid, reliable at-home assessments on patients' own or study-provided devices are already relatively widespread in neuroscience clinical trials. Both simple 'active' assessments (such as abbreviated cognitive tests or patient reported outcomes) as well as passive digital biomarkers can be used to help fill in the picture as to the efficacy and safety of new drugs in between scheduled clinic visits. In addition, these devices can collect multivariate data that provides new insights into the complex interactions between mental state, physical health, and day to day function. This is important because for many CNS conditions, the massive unmet medical need is not just in better control of the cardinal symptoms, but equally in providing a better quality of life through reduced side effects and increased functional independence.

The ability to link to functional relevance, as well as biological basis, is one reason why cognitive biomarkers have become increasingly valued in psychiatry and neurology. While older forms of cognitive assessment such as the Mini Mental Status Exam suffered many methodological disadvantages, fully automated assessments are useful in providing objective, non-invasive and hence highly scalable assessments of brain function. In early-stage clinical development, cognition offers a means to translate target engagement from preclinical to human studies, look for early signs of brain safety and/or efficacy, and hence support decision-making. In later stages, digital cognitive assessments are widely used as endpoints in CNS trials, as well as in childhood or late-life diseases where measuring long-term brain safety is key to regulatory approval (illustrated in Figure 3).

As specific, repeatable and reliable measures of brain networks or functions, cognitive assessments can provide powerful biomarkers that help sharpen the target for neuroscience drug development. That cognition is one of the six domains of RDoC and reflects the fact that cognitive dysfunction

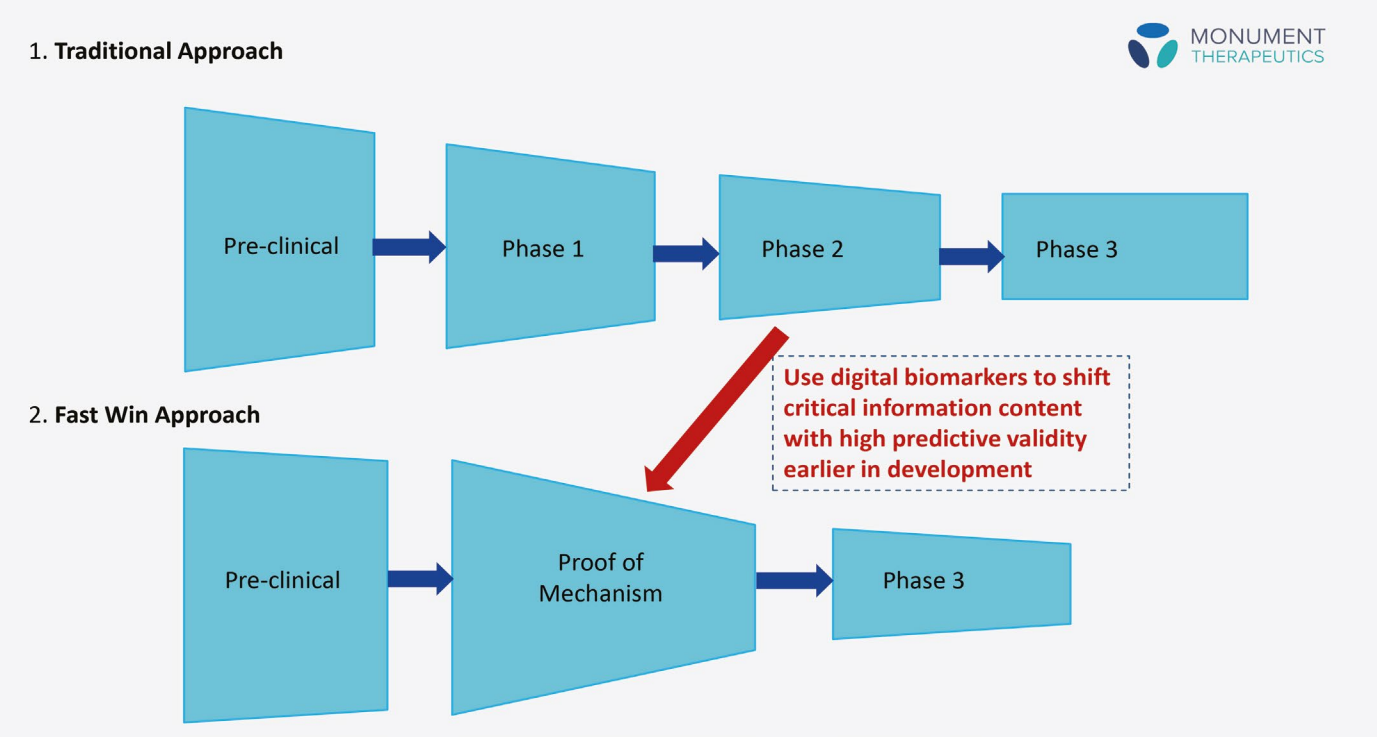

Figure 4: *The traditional paradigm of drug development compared with an a digital biomarker development paradigm referred to as quick-win alternative, whereby technical uncertainty is decreased before the expensive later development stages (Phase III). It is proposed that digital biomarkers would enable proof-of-mechanism studies without compromising patient saftey. This figure has been re-drawn and simplified based on the referenced publication by Paul et al.[9]*

is widespread not only in dementia-causes diseases, but also those of development (such as autism, attention-deficit hyperactivity disorder) and mid-life (mood disorders, schizophrenia, addictions). At Monument Therapeutics we are using cognitive biomarkers to overcome some of the limitations of heterogeneity in selecting patients for clinical trials based on categorical diagnoses. Our hypothesis is that, whatever other pathologies may be present, using specific cognitive biomarkers to detect presence of a given brain abnormality increases the likelihood that any single, targeted therapeutic is likely to positively affect the entire sample. This stratified approach is gaining traction not only among the research community, but now also among major pharmaceutical companies, with several CNS-focussed companies recently describing their own strategies based around precision medicine.

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With a new generation of digital biomarkers now available for deployment, are we reaching new consensus for neuroscience research? The authors of this article believe that it is and widespread adoption by pharmaceutical companies seems imminent. Ultimately, the utility of biomarkers in CNS should be not only in facilitating more targeted and effective drug development, but as a means of correctly identifying whether a specific patient is more or less likely to benefit from any given medication. What all areas of neuroscience need most of all is better drugs for clinicians to choose from. But after decades of stagnation, there is now new hope for patients with the recent approval of a ketamine-based treatment for depression[6], and a muscarinic treatment for schizophrenia likely to be approved next year[7]. With these new mechanisms, and others such as psychedelic-based therapeutics also now entering late-stage trials[8], we may now be entering a new era of options for treating both severe and common CNS conditions. At this point, digital biomarkers could move from providing value in developing drugs to demonstrating value, efficacy and safety at a health system and individual level. With better options for treatment and a huge unmet medical need, digital biomarkers may have an important role to play in getting the right patient on the right drug at the right time for treating their underlying neuropathology.

By increasing the overall probability of achieving successful outcomes in Phase III studies by focusing on biologically relevant proof-of mechanism studies earlier in development could be transformational for the pharmaceutical industry[9]. For example, this approach could reduce the need to run multiple traditional Phase II studies that can be constrained by the recruitment of conventional cohorts of patients. This concept is illustrated in Figure 4. Consequently, the improved design of clinical trials and the interpretation of clinical data based on tests with higher predictive validity have the potential to reduce the ever-increasing research and development costs of new drugs.

REFERENCES:

1 Schlander et al. (2021). PharmacoEconomics 39:1243–1269
2 Congressional Budget Office Report (2021): https://www.cbo.gov/publication/57126
3 Scannell et al. (2022). Nature Reviews Drug Discovery (in press)
4 Marek et al. (2022). Nature, 603, 654-660.
5 Sverdlow et al. (2021). Frontiers in Psychiatry, 12:640741. doi: 10.3389/fpsyt.2021.640741
6 Singh et al. (2020). Lancet Psychiatry, 7, 3, 232-235
7 https://investors.karunatx.com/news-releases/news-release-details/karuna-therapeutics-announces-positive-results-phase-3-emergent
8 https://psychedelicalpha.com/data/psychedelic-drug-development-tracker
9 Paul et al. (2010). Nature Reviews Drug Discovery, 9, 203-214

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Dr Mark Treherne has been involved in the biopharmaceutical industry for over 25 years and previously led the neurodegeneration research group at Pfizer's research facility in Sandwich. He has helped to raise over £300 million for early-stage biotechnology companies and out-licensed therapeutic assets for upfront payments, milestones and royalties exceeding £1.5 billion. Dr Treherne is currently Chairperson of Monument Therapeutics. He has a PhD in Pharmacology from the University of Cambridge.

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Dr Jenny Barnett has an MA in Experimental Psychology from Oxford University and a PhD from the University of Cambridge. At Cambridge Cognition, she worked on over 100 clinical trials utilising cognitive assessments before spinning out Monument Therapeutics, a novel drug development company which uses digital biomarkers to apply a stratified medicine approach to CNS disorders. She is an honorary member of the University of Cambridge Department of Psychiatry.

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Dr Paula Moran is a pioneering research scientist and an honorary Associate Professor at the University of Nottingham. Following a PhD from the National University of Ireland, she has had academic roles at the Institute of Psychiatry, Kings College London and University of Nottingham, where she led collaborations with several pharmaceutical industry partners. She is best known for her translational research on abnormal information processing in both animal and human models.