The Digital Race for Early Detection and a Cure

The urgent need for disease-modifying therapies will require further adoption of data-driven digital solutions for acceleration of development timelines with powerful, more efficient clinical trial designs

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Neurodegenerative diseases are defined by the progressive dysfunction, degeneration, and death of nerve cells in the brain and peripheral nervous system resulting in cognitive or motor deficits. Examples include: Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, among others. Alzheimer's disease (AD) is the prototypical and the most common neurodegenerative disease in the world. In the US, it is the most expensive disease to treat and the sixth-leading cause of death; an ageing population means these trends will worsen (1). While deaths in the US from other leading causes have decreased, the number of deaths from AD has more than doubled in the last decade. AD and related dementias will cost Medicare and Medicaid $206 billion in 2020 and, if unaddressed, the costs are projected to reach an unsustainable $1 trillion by 2050 (1).

Despite the costs, there are no disease modifying therapies available to treat major neurodegenerative diseases, revealing a significant opportunity for industry (2). The pace of innovation of therapeutics for these diseases has been significantly hampered by unique barriers to efficient clinical trials for neurodegenerative diseases. The very nature of these diseases makes efficient diagnostics and measurement of outcomes difficult, therefore prolonging clinical trials and slowing innovation of therapeutics. On the other hand, lack of existing effective therapies has prevented adequate investment in development of effective diagnostics or symptom monitors. "It's a bit of a chicken and egg problem," Bill Gates has summarised, referring to AD (3). Recent advances in digital medicine and other technologies, however, can be deployed creatively to help address these clinical trial barriers through more effective disease screening, diagnosis, outcomes measurement, and ultimately improved management of patients.

Growing Challenges to Clinical Trials

Clinical trials represent the most expensive phase of the drug development process. An increasingly complex clinical development environment has led to ever-higher costs related to challenges around patient recruitment, retention, and protocol adherence. *Forbes* recently summarised some of these daunting difficulties: 80% of trials do not meet enrolment deadlines; 37% of research sites fail to meet their enrolment targets; and 10% of sites fail to recruit even a single patient. Once recruited, difficulties continue as 35% of patients may drop out and another 35% may not adhere trial protocols. The delays in recruitment and enrolment are hugely consequential with reported losses averaging up to $1.3 million per day for a given drug candidate. Deviations from trial protocols can cost $1 million per trial in lost productivity alone (4).

Challenges to Neurodegenerative Disease Biomarkers

Effective biomarkers within a therapeutic area can greatly enable clinical trial designs. Neurodegenerative diseases present unique challenges to biomarker development compared to other therapeutic areas:

1. Anatomy: The central nervous system (CNS) is a 'privileged' area of the body encased in the bone of the skull and vertebrae and separated from the remainder of the body by the blood-brain barrier and other protective barriers. Direct access to the CNS for biopsy to measure pathology is, therefore, limited (5)
2. Slow decline: Neurodegeneration often occurs slowly with progression of pathology and symptoms occurring over many years to

decades. Measurements of potential treatment effects either need very sensitive outcomes measures to detect small differences, or long timelines to allow significant disease progression to take place

3. Pre-symptomatic phase: Growing bodies of evidence support that in most neurodegenerative diseases, slowly progressing brain pathology and subtle cognitive, sensory, motor, or behavioural changes are likely present some 10-15 years before patients develop noticeable symptoms (known as phenoconversion) or have an established clinical diagnosis (6-7). Screening patients and detecting treatment effects in a disease phase without clear symptoms presents an obvious challenge

Limitations of Current Neurodegenerative Disease Clinical Trials

Ineffective clinical trials are a major driver of the exorbitant cost of neurodegenerative disease drug development. On average, the pharmaceutical industry incurs an estimated cost to bring each new compound to approval of $2.8 billion (including cost of capital, cost of failures). For AD drug development, costs substantially exceed other therapeutic areas with total costs of AD drug development estimated at $5.6 billion, often taking over 13 years from preclinical studies to approval by the FDA (8). In comparison, estimated cost of a cancer treatment development is $794 million (8). Phase III clinical trials represent the most expensive phase of the drug development process. In neurodegenerative disease, trials have faced unique limitations:

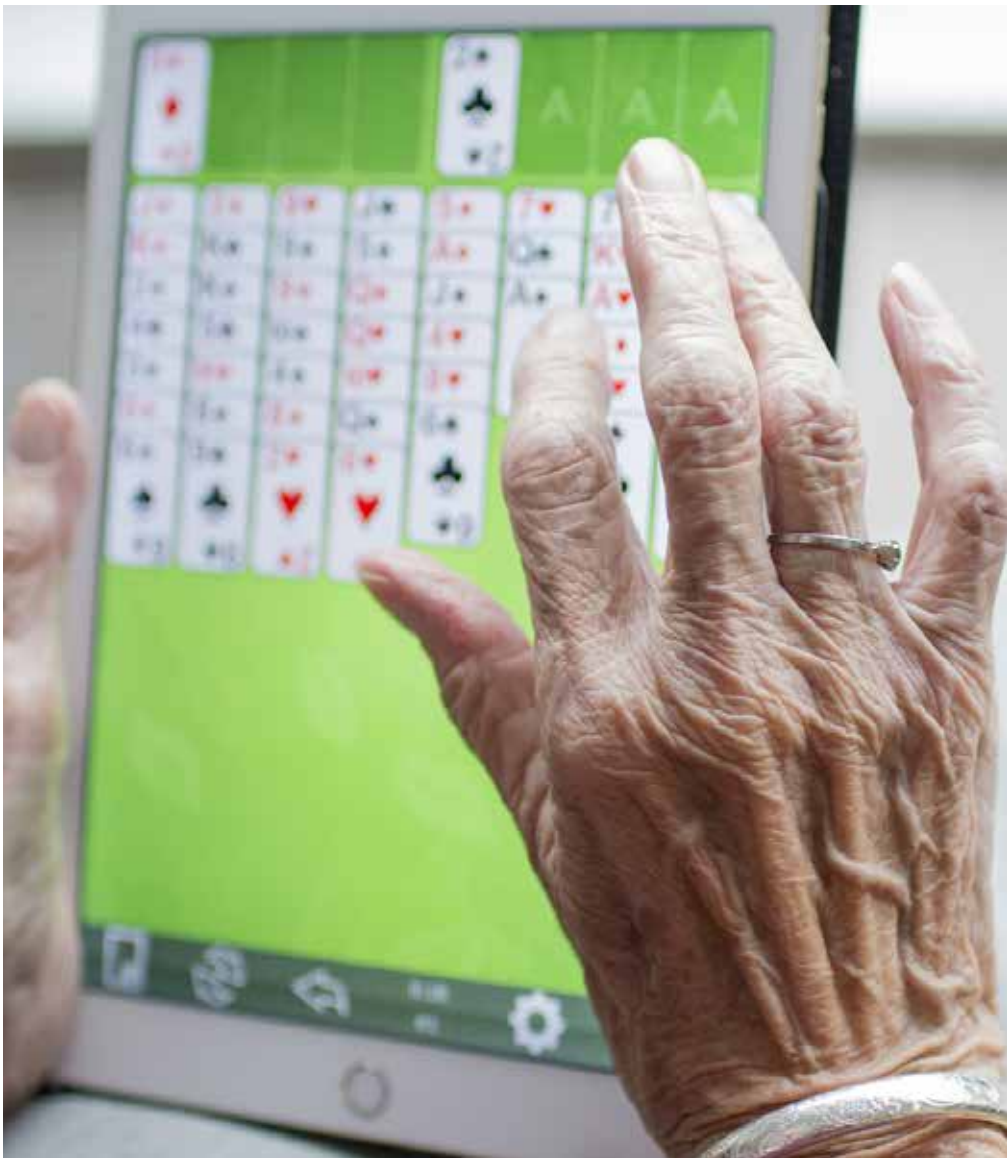
Inefficient Screening, Diagnosis, and Segmentation

Most diagnosed neurodegenerative diseases are still usually established based on patient symptoms and clinician-administered rating scales (5). Unfortunately, results of clinical assessments can be highly variable and subjective; for example, diagnosis of AD by clinical assessment alone is only around 70-80% accurate (9). This means 20-30% of patients in a whole generation of prior AD therapeutic trials likely did not even have AD. Reliance on assessment of symptoms for screening/diagnosis also means, by definition, that patients early in their disease process, before phenoconversion, with only subtle symptoms or no symptoms are not being identified for clinical trials.

While direct access to CNS is limited by anatomy, indirect biomarkers of neurodegenerative diseases, such as imaging (including MRI, PET, or SPECT scans with specific radiotracers) or cerebrospinal fluid tests for various disease-associated proteins (such as amyloid or tau for AD) have progressed rapidly in research and can markedly improve diagnostic accuracy. However, for clinical trial deployment as screening tools, these biomarkers face significant challenges due to excessive cost and invasive testing. Even testing blood for risk genes, while useful, only informs a patient's lifetime risk for the disease, but gives little information about timing of disease progression. These markers have not reached integration into routine clinical practice and insurance coverage remains largely absent (5).

Inadequate Outcome Measures

Outcome measures to assess efficacy of neurodegeneration therapeutics are largely based on assessment of



patient symptoms by clinical scales. While their intent is to capture clinically meaningful changes, these assessments face limitations of subjectivity and variability. Unless the trial is many years long, these outcomes have difficulty capturing anything but the largest treatment effects in these slowly progressive diseases. For clinical trials focusing on patients in the early or pre-symptomatic phase of disease, these classic symptom-based outcomes face obvious limitations (5). Furthermore, the difficult problem of clinical trial engagement may be exacerbated in AD by neuropsychological testing, which can last many hours per session, becoming exhausting for patients. Spinal fluid, blood, and imaging biomarkers are being studied as potential outcomes for neurodegenerative diseases, but still face limitations of cost and invasiveness (as already discussed) and remain secondary outcomes in clinical trials as regulatory approval requires demonstrating improvement in clinically relevant measures.

Technological Advancements in Neurodegenerative Diseases

Both research and clinical medicine for neurodegenerative diseases have seen significant advancements driven by technological improvements. Adoption of these measures remains highly variable (10). Some notable technological advancements are:

1. Digital medicine: Wearable sensors, and smartphone-based applications are available with the potential to provide objective, longitudinal, and more granular information about the function of individuals both in clinic and remote environments (5)
2. Electronic medical records and patient management platforms: Nearly complete conversion to electronic medical record systems and patient engagement platforms have allowed for improved efficiencies in health data recording and communication
3. Big Data research: Analysis of large and comprehensive datasets within health systems has improved knowledge of disease mechanisms, diagnostic and therapeutic strategies, drug candidate development, and much more

Digital Biomarkers: Real World Data Becomes Real World Evidence

Digital biomarkers harness the power of sensor technologies to collect objective data reflecting biological, anatomical, or physiological parameters, and then analyse these alternate data streams with algorithms to transform them into clinically interpretable measures. Advanced algorithms using artificial intelligence technology (e.g., machine learning or deep learning), have further increased our ability to recognise fine patterns in these data streams, often beyond detection limits of bedside clinical assessments. Devices including portables (e.g., smartphones), wearables (e.g., watches), implantable devices, and software as a medical device (SaMD) provide data that are largely independent of raters and objective in nature. In the case of SaMD, no additional devices are required of patients, and, when deployed for passive data collection, no structured tasks need to be completed by patients enabling seamless integration with the patient's daily life and more patient-centric trial designs (7). Most importantly, digital technologies promise physiological measurements more sensitive than in-clinic symptom scales, allowing for screening of patients in earlier phases of disease and more sensitive outcome measurements.

Digital biomarkers can be collected with significant cost advantage per patient compared to traditional imaging and invasive biomarkers. They further offer advantages in patient convenience, especially when collected passively and remotely. Remote monitoring also allows for engagement of rural and under-represented populations. These advantages include the possibility of wide deployment of these markers for screening throughout large, representative patient populations or established cohorts. Large populations of patients pre-screened with digital biomarkers can aid in enrichment of screening by traditional methods and the establishment of trial-ready cohorts.

As digital biomarkers include assessments in real world environments, they have the potential to capture more 'ecologically valid' and clinically meaningful data where variations are likely to be reflective of actual patient behaviour. For example, analysis of patient typing dynamics on smartphones can reveal quantitative at-home measures of motor or

cognitive function, but also typing is itself an activity important to patients and important to function in the modern world. With proper processing the variability of digital signals can be controlled and outweighed by the near continuous, remote assessment (5).

Brief Focus on Early Detection

Increasing evidence suggests identification of patients early in neurodegenerative disease is a major limitation to drug development (7). Taking AD as an example, multiple failures in clinical trials over the past decade are likely due to incorrect patient selection (e.g., screening and testing on advanced dementia instead of early/prodromal disease) because recognisable symptoms often do not appear to the patient until brain pathology has progressed to an advanced state over many years (11). It is quite possible that efficacious compounds have been shelved after being tested in advanced disease patient segments where the compound had little chance of therapeutic efficacy. Digital biomarkers may allow researchers and clinicians to identify patients (directly or by enrichment for other more invasive/expensive testing) earlier in disease before phenoconversion (12-13).

Conclusion

The adoption of cost effective, reliable, and massively scalable tools able to broadly and sensitively assess impairments in daily function promise improved patient recruitment, retention, and outcome measurement in modern clinical trial designs. Of course, new technologies used for clinical purposes need rigorous validation similar to other medical devices and biomarkers before adoption into medical practice. Furthermore, patient privacy and data protection must be addressed proactively and ethically by the entire field for these technologies to be trusted and their potential realised. Reflection on a patient's lived experience is necessary not only for diagnosis, but is also vital in determining disease burden, disease progression, and the efficacy of treatment regimens. This is the promise from digital biomarkers that can seamlessly integrate into daily life.

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