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Perspective

Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer's disease clinical trials

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Abstract Digital technology is transforming the development of drugs for Alzheimer's disease and was the topic of the Alzheimer's Association's Research Roundtable on its May 23–24, 2017 meeting. Research indicates that wearable devices and unobtrusive passive sensors that enable the collection of frequent or continuous, objective, and multidimensional data during daily activities may capture subtle changes in cognition and functional capacity long before the onset of dementia. The potential to exploit these technologies to improve clinical trials as both recruitment and retention tools as well as for potential end points was discussed. The implications for the collection and use of large amounts of data, lessons learned from other related disease areas, ethical concerns raised by these new technologies, and regulatory issues were also covered in the meeting. Finally, the challenges and opportunities of these new technologies for future use were discussed.

Keywords: Alzheimer's disease; Digital technology; Cognition; Function; Clinical trials; Biomarkers

1. Introduction

Recent advances across a range of digital technologies, including wearable devices, unobtrusive sensors, and passive data collection applications, along with improved computational power and analytic approaches have the potential to provide a more nuanced and comprehensive understanding of the presentation and progression of Alzheimer's disease (AD) and other neurodegenerative diseases. Moreover, the potential ability of digital technologies to detect subtle changes in cognition and function across the disease spectrum may improve the sensitivity and specificity of diagnosis, help identify appropriate participants for clinical

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trials, and improve the assessment of therapeutic responses. Digital technologies may also enhance the care and safety of patients by promoting aging in place and facilitating the development of precision medicine approaches to therapy. Yet, digital technologies also introduce many challenges ranging across scientific, clinical, technological, business, ethical, and regulatory domains.

On May 23rd and 24th, 2017, the Alzheimer's Association Research Roundtable convened a meeting of researchers from academia, the pharmaceutical industry, and health agencies, along with digital technology and data analytics experts, representatives of patient advocacy organizations, and a patient and caregiver to discuss how digital biomarkers are transforming clinical trials in other disease areas and emerging efforts to apply lessons learned in these areas to the AD clinical trial space.

2. Transforming clinical trials with new technologies

Interest in developing novel technological approaches to aid in the clinical diagnosis and assessment of AD cognitive and functional progression in response to treatment has grown in recent years as interventional trials have moved into earlier stages of disease. Current testing paradigms have proved to be poor at identifying meaningful ecologically valid changes in individuals with early stage disease. For example, high variability in scores of existing cognitive tests at baseline and over the course of a trial has produced false signals in phase 2 studies that contributed to costly failures in phase 3 [1]. Other problems with existing tools include the questionable accuracy of self- [2] and clinician-reported measures, substantial variability among individuals administering tests, and appropriateness for diverse groups of patients.

To address these well-known issues, a range of validated digital technologies are being applied to clinical trials. Electronic or direct data capture represents an interim step on the path toward digital biomarkers. Digitized forms have been shown to improve data quality and enhance guidance during the administration of a test by proactively responding to errors, calculating results automatically, managing branching rules, checking for consistency of responses, and responding immediately to missing data. They also enable the management of translations and the integration of audio and video data capture into assessments. The end result of using electronic or direct data capture is an increase in both accuracy and precision, both of which are necessary to detect anything other than large effect sizes.

Meanwhile, new tools that provide sensitive, frequent or continuous, objective, and multidimensional measurement of changes in function or behavior are being incorporated into clinical trials in multiple disease areas. For example, daily activity assessments with accelerometers were used as a primary end point in a study testing the ability of nitrates to enhance activity tolerance in patients with heart failure [3]. In AD, ankle-mounted wearable accelerometers have also been used to measure changes in everyday motion behavior even in the absence of major behavioral impairments [4]. High-frequency, in-home monitoring data have also been shown to distinguish individuals with mild cognitive impairment from those with normal cognition [5,6], suggesting that such data could reduce sample sizes needed for clinical trials and thus reduce exposure of participants to potentially harmful drugs [7]. To evaluate personalized/precision medicine approaches in clinical trials, digital tools with continuous measurements may also enable detection of individualized behavioral profiles, susceptibility to placebo responses, or be used as run-in data to reduce regression to the mean effects.

A range of sensors, software, and smart phone applications ("apps") can provide passive remote monitoring across a range of settings including the home, community, automobiles, and health-care settings to name a few. These sensors can measure behaviors (e.g., in sleep, mood, physical activity, social activity, and eating behaviors) from which we may be able to infer cognitive and functional status and changes therein. Platforms consisting of a network of diverse sensors may be needed to effectively measure and identify biomarkers of change; and interfacing these devices with other data streams such as electronic medical records will be needed to facilitate communication and sharing of data. However, as the number and range of devices increases, it will be important to maintain a focus on outcomes that are clinically meaningful. For some outcomes such as sleep, a single sensor may be sufficient; whereas for other outcomes affected by subtle cognitive decline, multiple sensors may be needed. Redundancy will be initially necessary to validate novel devices and analyses, and clear data and metadata annotation will also be essential, particularly at early stages of development.

To investigate the transition from current practice to real-time, continuous, home-based, objective, unobtrusive, ambient measures, researchers at the Oregon Center for Aging and Technology developed a platform of sensors and devices to capture data in the home or in simulated home environments [8,9]. This technology-agnostic platform uses pervasive computing wireless technologies and data analytics to assess a range of functional and behavioral activities, including time and location of sleep, patterns of movement around the home, taking of medications, use of a phone or computer, opening and closing of doors and refrigerators, and driving. The platform has been deployed in free-standing single-family homes and retirement communities and has been incorporated into several observational and clinical studies. Data from these studies are being used to identify behavioral biomarkers that can be used to phenotype populations and stratify potential participants in clinical trials by identifying persons who are progressing more rapidly.

Another platform, EmPowerYu, uses a variety of sensors to detect motion within a fixed space, appliances being turned on and off, doors being opened and closed, and entry or exit from a room to build a multidimensional understanding of