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Review

Capturing Measures That Matter: The Potential Value of Digital Measures of Physical Behavior for Alzheimer's Disease Drug Development

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Abstract. Alzheimer's disease (AD) is a devastating neurodegenerative disease and the primary cause of dementia worldwide. Despite the magnitude of AD's impact on patients, caregivers, and society, nearly all AD clinical trials fail. A potential contributor to this high rate of failure is that established clinical outcome assessments fail to capture subtle clinical changes, entail high burden for patients and their caregivers, and ineffectively address the aspects of health deemed important by patients and their caregivers. AD progression is associated with widespread changes in physical behavior that have impacts on the ability to function independently, which is a meaningful aspect of health for patients with AD and important for diagnosis. However, established assessments of functional independence remain underutilized in AD clinical trials and are limited by subjective biases and ceiling effects. Digital measures of real-world physical behavior assessed passively, continuously, and remotely using digital health technologies have the potential to address some of these limitations and to capture aspects of functional independence in patients with AD. In particular, measures of real-world gait, physical activity, and life-space mobility captured with wearable sensors may offer value. Additional research is needed to understand the validity, feasibility, and acceptability of these measures in AD clinical research.

Keywords: Alzheimer's disease, digital measure, drug development, gait, life-space mobility, meaningful aspect of health, physical behavior, physical function, wearable sensor

ALZHEIMER'S DISEASE: A LEADING CAUSE OF DEATH WITH FEW EFFECTIVE THERAPIES

Alzheimer's disease (AD) is the primary cause of dementia and the seventh leading cause of death worldwide [1]. AD is a progressive and neurodegenerative condition, which ultimately affects every aspect of daily life for patients and their caregivers. In addition, it has major economic impacts, with the cost of AD care estimated to total $321 billion in 2022 in the US alone [2]. Despite the magnitude of AD's impacts, it remains the only leading cause of death with very few therapies to prevent or slow disease progression. Between 2002 and 2012, 99.6% of AD

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clinical trials failed [3, 4]. Although this low success rate reflects many factors including AD's complex pathophysiology, a lack of validated biomarkers, and underpowered trials [5], it also reflects the failure of established AD clinical outcome assessments to guide the development of potentially valuable therapeutic interventions. Given the costs associated with drug development, which are estimated to total $42.5 billion since 1995 [6], and the lack of effective AD therapies, innovation is paramount. In this review, we articulate an approach to developing novel outcome measures reflecting functional independence that are suitable for AD drug development. First, we summarize why more sensitive and ecologically valid outcome measures reflecting functional independence are needed in AD clinical research. We then describe how wearable sensors deployed passively, continuously, and remotely have the potential to capture changes in real-world physical behavior that occur in AD and impact the ability to function independently. Finally, we outline our hypothesis that measures of real-world physical behavior provide an opportunity for the AD clinical research community to better understand functional independence in AD and summarize the research needed to develop, validate, and implement these measures.

FUNCTIONAL INDEPENDENCE IN AD: CRITICAL FOR DIAGNOSIS AND MEANINGFUL TO PATIENTS

In the progression of AD, cognitive and behavioral changes are coupled with declines in the ability to perform activities of daily living (ADLs) and to function independently. Impairments in instrumental ADLs, which include complex tasks such as performing household chores, preparing meals, and traveling outside the home, may be evident during the mild cognitive impairment (MCI) stage and intensify in disease progression [7]. Basic ADLs, such as grooming, bathing, and ambulation, decline in moderate-to-severe disease stages [8]. Accordingly, functional impairment is one criterion required for a diagnosis of AD dementia [7, 9] and is encompassed in the diagnostic criteria for MCI due to AD [10]. The ability to perform ADLs and function independently is also something that patients with AD and their caregivers want to maintain in disease progression. Across recent qualitative studies, patients have reported their desire to continue carrying out everyday behaviors such as walking, gardening, and caring for oneself [11–13]. Yet despite functional impairment being a key diagnostic criterion and something that both patients and their caregivers want to prevent, in AD drug development, less emphasis is placed on functional outcomes compared to cognitive and neuropsychiatric outcomes. For instance, among clinical trials conducted from 2004–2014, only 32% of dementia trials and 16% of MCI trials included an outcome reflecting functioning [14].

ESTABLISHED ASSESSMENTS OF FUNCTIONAL INDEPENDENCE IN AD CLINICAL RESEARCH

When functional independence is assessed in AD clinical research, it is traditionally captured through informant-based assessments of a patient's competence at performing basic and/or instrumental ADLs. ADL assessments used commonly in clinical trials include the AD Cooperative Study – ADL Scale (ADCS-ADL) [15], the instrumental subscale of the ADCS (ADCS-iADL), and the version of the ADCS for use in MCI (ADCS-MCI-ADL) [16]. Other commonly used ADL assessments are the Amsterdam Instrumental ADL Questionnaire [17] and the Integrated AD Rating Scale (iADRS), a composite assessment that combines items from the widely-used AD Assessment Scale – Cognitive Subscale and the ADCS-iADL [18].

Although these assessments capture some of AD's impacts on functional independence, there are limitations associated with their use. For one, the majority of these assessments are dependent on informant reports [19, 20], which increases caregiver burden and introduces bias [21]. In addition, established assessments of ADLs only capture a limited scope of activities and are assessed in the clinic, limiting their ability to capture the complexities of patients' experiences, such as the pace and diurnal patterning of behavior [22]. Finally, these assessments are prone to ceiling effects at early disease stages, when changes in day-to-day function may be challenging to quantify [21]. These effects are especially relevant as most current clinical trials target individuals early in disease progression, with 45% of Phase III and 59% of Phase II trials enrolling individuals with MCI due to AD or mild AD, and a subset of trials enrolling individuals who are cognitively normal but at risk for AD [23]. In these stages, episodic assessments of ADLs may therefore fail to detect subtle, but

important, clinical changes over time. Together, these challenges necessitate innovative approaches to measure functional independence in AD more holistically and with greater sensitivity.

CHANGES IN PHYSICAL FUNCTION IN AD

AD has a significant impact on physical function, which we define here as an individual's ability to perform physical tasks such as locomotor behaviors [24]. The changes in physical function that occur in AD, together with cognitive and behavioral changes, contribute to patients' ability to perform ADLs [25–27]. Historically, physical function in AD has been evaluated in laboratory- or clinic-based settings. Compared to otherwise healthy older adults, individuals with MCI and AD exhibit slower and altered gait patterns when assessed in the clinic [28–34]. Furthermore, gait parameters differ significantly in individuals with MCI compared to those with overt dementia [35, 36], suggesting that changes in physical function progress as cognitive function declines. Declines in physical function assessed with in-clinic physical performance tests are associated with risk of developing AD, and among individuals with MCI, motor function impairment is related to risk of progressing to overt dementia [37–39]. Furthermore, AD-related changes in physical function may be detectable prior to the onset of cognitive changes; for instance, among those who develop AD, declines in grip strength measured in the clinic and a history of falls may be evident more than 5 years prior to diagnosis [40]. Although these findings have been generated largely from cross-sectional studies, they support the clinical relevance of changes in physical function in patients with AD.

There are limitations in translating evidence from in-clinic physical function tests to the real-world. For instance, gait speed and stride regularity are lower when measured with accelerometry in older adults' real-world environments than when measured in the laboratory [41–43]. Accordingly, there has been an increase in the use of digital health technologies to quantify physical function through the remote monitoring of patients' real-world physical behavior. In the sections below, we provide evidence that assessing real-world physical behavior may offer value for capturing functional independence in AD clinical research.

THE POTENTIAL FOR DIGITAL MEASURES OF REAL-WORLD PHYSICAL BEHAVIOR TO CAPTURE FUNCTIONAL INDEPENDENCE IN AD

Under the umbrella of digital medicine [44], digital health technologies can be deployed remotely in clinical research to capture health information continuously, characterize disease manifestation and progression, enable decentralized clinical trials, and facilitate recruitment of diverse and underrepresented populations [45–47]. One class of digital health technologies with significant potential for AD clinical research is wearable sensors such as accelerometers and Global Position System (GPS) trackers. These tools can be deployed to assess real-world physical behavior passively, remotely, and continuously. In the case of AD, digital measures of real-world physical behavior, derived from wearable sensors, have the potential to provide rich insights into functional independence throughout disease progression [22, 48]. In particular, we hypothesize that digital measures of real-world physical behavior have the potential to capture meaningful aspects of functional independence and to complement established assessments to improve monitoring of functional independence in AD clinical research [48–51].

As previously described, established assessments of ADLs often rely on informant reports, require active participation from patients and/or their caregivers, may rely on recall, and are captured infrequently. In contrast, wearable sensors can provide remote and passive assessments and offer the potential to capture everyday physical behavior with high granularity and low patient and caregiver burden [52]. As such, deploying these measures could increase sensitivity to detect subtle changes in functional independence over time [53, 54], especially at early disease stages, which could lower sample size requirements and costs in AD clinical trials [55]. Furthermore, mobility and walking behavior are key aspects of functional independence. Since wearable sensors allow for monitoring of the mobility and physical challenges encountered by patients in their real-world environments, digital measures of real-world physical behavior may provide rich insights into aspects of ADLs that are meaningful for patients and their caregivers. Below, we outline specific domains of real-world physical behavior with potential value for assessment in AD: gait, physical activity and sedentary behavior, and life-space mobility. The exact concept(s) of interest

that these measures reflect must be systematically investigated.

Gait

Assessments of real-world gait have confirmed findings from the clinic, demonstrating that individuals with MCI and AD exhibit slower gait speed and shorter stride length relative to cognitively normal older adults [56, 57]. Variability in step velocity and cadence assessed from real-world accelerometry is also higher in individuals with mild AD compared to cognitively normal older adults [58]. In addition, stride time variability and within-bout stride regularity in real-world walking patterns is lower in individuals with MCI relative to controls [34, 56], suggesting that real-world gait patterns are sensitive to clinical change in early disease stages. Real-world gait speed, stride length, and stride regularity have also been associated with cognitive performance in MCI [56, 59]. Collectively, this evidence suggests that assessing real-world gait parameters such as gait speed, gait variability, and stride length, or a composite set of these metrics with wearable sensors [60, 61] may capture clinical changes across the AD continuum.

Physical activity and sedentary behavior

Assessments of real-world physical behavior have also demonstrated that physical activity and sedentary behavior are affected in the progression of AD. Compared to controls, individuals with MCI and dementia take fewer steps per day [57], spend less time walking [34], and spend more time in sedentary activity bouts [62]. There is also evidence that AD is associated with changes in diurnal physical activity patterns measured using accelerometry. In one study, individuals with AD were less active in the morning compared to controls [62], and in another investigation, individuals with MCI exhibited lower levels of physical activity during both the morning and evening hours compared to otherwise healthy older adults [63]. Further, diurnal distributions of physical activity may provide novel insights into ecologically relevant symptoms. For instance, based on a 1-week observation in older adults' home environments, fragmentation of physical activity patterns was more strongly related to subjective memory complaints than physical activity volume alone [64]. Finally, assessing the patterns and variability of physical behavior with wearable sensors may also provide insights into habitual activity engagement [65], a component of functional independence for individuals with AD. Many habitual ADLs, such as washing dishes, brushing teeth, and folding laundry, are performed in a standing position, with occasional stepping, for extended periods of time. Wearable sensors that can differentiate sitting from other upright behaviors could be used to infer performance characteristics of ADLs. This possibility opens the door to the discovery of metrics which could provide insights into how functional independence is affected in the progression of AD.

Life-space mobility

Investigations utilizing wearable GPS trackers have also provided evidence for AD-related changes in life-space mobility, defined as the geographic area in which life is carried out [66]. In one study, GPS-derived area and mean distance traveled from home were both lower for individuals with AD compared to otherwise healthy older adults; these measures were also associated with accelerometer-derived measures of physical behavior [67]. In addition, combining wearable sensors with ensembles of non-wearable sensors may enable more holistic assessments of life-space mobility than a wearable sensor alone [68, 69]. In one study, spending less time outside the home, as captured by in-home motion sensors, predicted major transitions in care among older adults [70]. In another investigation, distributions of time spent in different rooms, as captured with non-wearable motion sensors, detected MCI with high accuracy [71]. This suggests that incorporating objective measures of how a person moves throughout their life space may add an important dimension to the assessment of functional independence and have clinical value.

PRECEDENCE FOR THE DEPLOYMENT OF DIGITAL MEASURES OF REAL-WORLD PHYSICAL BEHAVIOR IN CLINICAL TRIALS

Although there is evidence supporting AD-related changes in real-world measures of gait, physical activity, and life-space mobility, the majority of evidence supporting the value of such measures comes from cross-sectional studies in laboratory or clinic settings [60]. As such, to date, these measures have not yet been deployed in drug development studies. However, there is precedent for deploy-

ing digital measures of real-world gait and physical activity as outcome measures in clinical trials for Parkinson's disease [72], osteoarthritis [73, 74], and Major Depressive Disorder [75]. Furthermore, stride velocity 95th centile, captured continuously with a validated ankle-worn device, was recently qualified by the European Medicines Agency for use as a secondary efficacy endpoint in clinical trials for Duchenne Muscular Dystrophy [76]. This was the first regulatory qualification of a digital clinical measure and serves as a precedent for the development of novel endpoints in other therapeutic areas. For instance, wearable sensor-derived gait speed, collected in patients' real-world environments, is undergoing qualification procedures with the FDA and European Medicines Agency for use as a measure of walking behavior in sarcopenia and multiple sclerosis, conditions in which mobility is affected [43, 77, 78]. In alignment with this effort, the Mobilise-D clinical validation study is being conducted to understand the construct validity, predictive capacity, and sensitivity of real-world measures reflecting walking behavior across a number of therapeutic areas, with the aim of identifying outcomes that can be deployed for regulatory decision-making [77]. Similar efforts are needed to understand whether measures of real-world gait, physical activity, and life-space mobility can also provide relevant information about the efficacy of novel therapeutics targeting AD.

THE POTENTIAL FOR DIGITAL MEASURES OF REAL-WORLD PHYSICAL BEHAVIOR TO ENRICH COGNITIVE ASSESSMENTS

Beyond providing standalone insights into functional independence, digital measures of real-world physical behavior may enrich established measures of cognition in individuals with AD. Current evidence suggests that combining assessments of cognitive and physical function may provide richer insights into disease progression than either type of assessment alone. For instance, combining assessments of cognition and instrumental activities of daily living outperforms cognitive assessments alone for predicting conversion from MCI to overt dementia [79]. Supplementing established cognitive outcomes with digital measures of real-world physical behavior could also be a means of demonstrating the meaningfulness of an identified cognitive change [80, 81]. In addition, this approach may also help to address limitations of established assessments such as ceiling effects. For example, the Cognitive-Functional Composite, which combines items from existing assessments probing memory, executive function, and ADLs, has fewer range restrictions compared to established cognitive assessments and therefore offers greater sensitivity to clinical progression [82].

A ROADMAP TO DEVELOP AND VALIDATE DIGITAL MEASURES OF REAL-WORLD PHYSICAL BEHAVIOR IN AD

We have summarized evidence that measures of real-world physical behavior captured with wearable sensors may be capable of complementing established assessments in AD clinical trials to better capture aspects of functional independence that matter to patients with AD and their caregivers. However, developing, validating, and implementing these measures in regulated clinical trials comes with challenges. Broadly, a digital clinical measure requires substantial evidence demonstrating that it: 1) represents something meaningful to patients, 2) can be derived accurately and reliably with a specific digital health technology, 3) is feasible to derive with that digital health technology in the relevant clinical setting, and 4) is linked to gold-standard clinical outcomes, such as clinical events or survival. Frameworks for generating such evidence have been established in recent years [83–85]. Based on these frameworks, we outline a roadmap of steps required to develop and validate digital measures that can be deployed in clinical trials and highlight challenges specific to the case of developing measures of real-world physical behavior in AD.

Identifying aspects of functional independence that matter to patients with AD and their caregivers

A key tenet of patient-focused drug development, the US Food and Drug Administration's framework for incorporating the patient perspective into all phases of drug development [86], is the notion that what matters to patients should inform the development of outcome measures and, in turn, the evaluation of novel therapeutics [87]. In practice, this occurs by directly engaging patients to identify meaningful aspects of health, which are the symptoms and impacts of disease that patients want to improve, prevent, or protect from becoming worse [88]. Recent

studies aimed at understanding meaningful aspects of health in AD have demonstrated that functional independence is something that patients and their caregivers wish to maintain in disease progression [89–92], but few studies have systematically examined how specific aspects of functional independence change along the AD continuum [89]. Additional research in this domain will be critical for the development of digital measures of real-world physical behavior with clinical utility across the AD continuum. Once these aspects of functioning are identified, a conceptual framework should be developed which maps those aspects to concept(s) of interest that can be measured with a specific wearable sensor [88, 93–95].

Evaluating analytical validity to derive outcome measures of interest

Once outcome measures and measurement technologies are identified, evidence should be generated to demonstrate that the measure(s) of interest are analytically valid—that is, that they can be captured accurately and reliably with the selected measurement technology [84]. In the case of generating digital measures of real-world physical behavior in AD, this step is especially important, as many existing algorithms to derive measures of physical behavior have been developed and validated in healthy populations. When these algorithms are applied to clinical populations with slow or altered gait patterns, such as individuals with AD, algorithmic bias may exist [96]. Therefore, it is critical that analytical validation and reliability studies are conducted in representative samples of patients with AD.

Establish feasibility of wearable sensors in an aging and forgetful population

Understanding the feasibility and acceptability of a digital health technology that will be used to derive an outcome measure is an essential step in the process to establish that technology is fit-for-purpose [97]. Wearable sensors can be used to derive digital measures of real-world physical behavior, but their feasibility and acceptability in AD is not well understood. A number of studies have demonstrated that the short-term use of wearable sensors among older adults with MCI and AD is both feasible and acceptable [98–102]; for instance, one study demonstrated the feasibility of using wearable sensors to assess gait over a 7-day period in individuals with mild AD [103]. However, other studies have documented challenges with using wearable sensors among individuals in this population, including ease of device use, the need for assistance from a caregiver, and forgetting to charge the device [101, 104]. Studies examining barriers and facilitators to using wearable sensors in patients with AD for extended periods of time will be important for understanding their applicability for capturing measures of real-world physical behavior.

Determining clinical validity of measures of real-world physical behavior in AD

Once it is established that the measure of interest is analytically valid and feasible to capture, a critical step is establishing evidence of the measure's clinical validity—that is, its relationship with gold standard clinical outcomes of interest [84]. In the case of AD, generating this evidence will require long-term wearable sensor deployment in individuals with AD to assess relationships between digital measures of real-world physical behavior and clinical benefit over time. Within this step, collecting data from representative samples of individuals with AD, across the AD continuum, will be also critical to ensure that digital measures found to be clinically valid also reflect patients' collective experiences [48]. Although generating the evidence along this roadmap will require significant investment from many stakeholders [97], this investment is necessary to realize the potential value of digital measures of real-world physical behavior in AD and to promote their appropriate deployment in AD clinical research.

CONCLUSION

In the case of AD, where disease-modifying therapies are in high demand, there is mounting pressure to move away from the status quo in drug development. Amid a digital revolution in clinical research, digital measures of real-world physical behavior captured with wearable sensors have the potential to advance AD drug development. Because they can be captured passively, continuously, and remotely, these measures have the potential to complement established outcomes of functional independence in AD clinical trials. In particular, measures of real-world gait, physical activity, and life-space mobility may provide novel insights into aspects of functional independence that matter to patients with AD. Additional research is necessary to understand the analytical and

clinical validity, feasibility, and acceptability of digital measures of real-world physical behavior in AD clinical research and drug development.

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CONFLICT OF INTEREST

SLB, JMB, KL, and IC are employees of VivoSense, Inc. IC is on the Editorial Board of Karger Digital Biomarkers and the Scientific Advisory Board for IMI IDEA FAST, and has received fees for lectures and consulting on digital health at ETH Zürich and FHNW Muttenz. All other authors have no conflict of interest to report.

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