Digital Biomarkers

Editorial

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The State of Digital Biomarkers in Mental Health

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Introduction

Untreated mental health conditions are a leading cause of disability in the world [1, 2], accounting for more than 30% of years lived with disability [1]. However, the staggering impact of mental health likely extends far beyond this statistic [3]. Mental health problems, if left untreated, predict the development of some of the most significant physical ailments impacting society including obesity, diabetes, heart disease, and stroke [4–6]. With a global shift in healthcare practices from reactive models of care to more preventative, wellness-focused models, we have a unique opportunity to address mental health as a key, upstream determinant of morbidity and mortality [3]. Societal acceptance of mental health is at an all-time high. Shifting healthcare incentives and improved mental health acceptance combine to provide a unique opportunity for systemic change in the way we practice mental healthcare. If successful, there is a chance that we can build healthier societies, with equitable and early access to mental healthcare, that are better prepared to address the pressing problems of our age.

However, to realize this vision for societal health through improved mental health, there are several significant challenges that we must overcome. For example, there is a critical shortage of mental healthcare providers. Large geographic areas (e.g., rural and urban medical deserts [7]) and patient groups (e.g., children [8]) do not have access to effective mental healthcare options. These access challenges are further compounded by a lack of demographic representation in current mental health services leaving many patients from underserved and underrepresented groups without culturally tailored resources, negatively impacting participation and outcomes [9].

Digital health technologies (DHTs) that move mental health assessment and treatment outside the footprint of traditional brick-and-mortar healthcare infrastructure may provide compelling solutions to many of these challenges [10]. With the COVID pandemic, treatment approaches that leverage telehealth strategies to connect patients with providers have been accelerated, enabling access to care even in medical deserts [11, 12]. Prescription digital therapeutics have been developed that can augment this virtual care model or even, for some conditions, allow effective mental health management without direct oversight from a healthcare provider [13]. With broader access to digital mental health treatments, there are now opportunities to match patients with providers (e.g., Spring health [14]) which has been shown to dramatically improve outcomes while also reducing costs [15].

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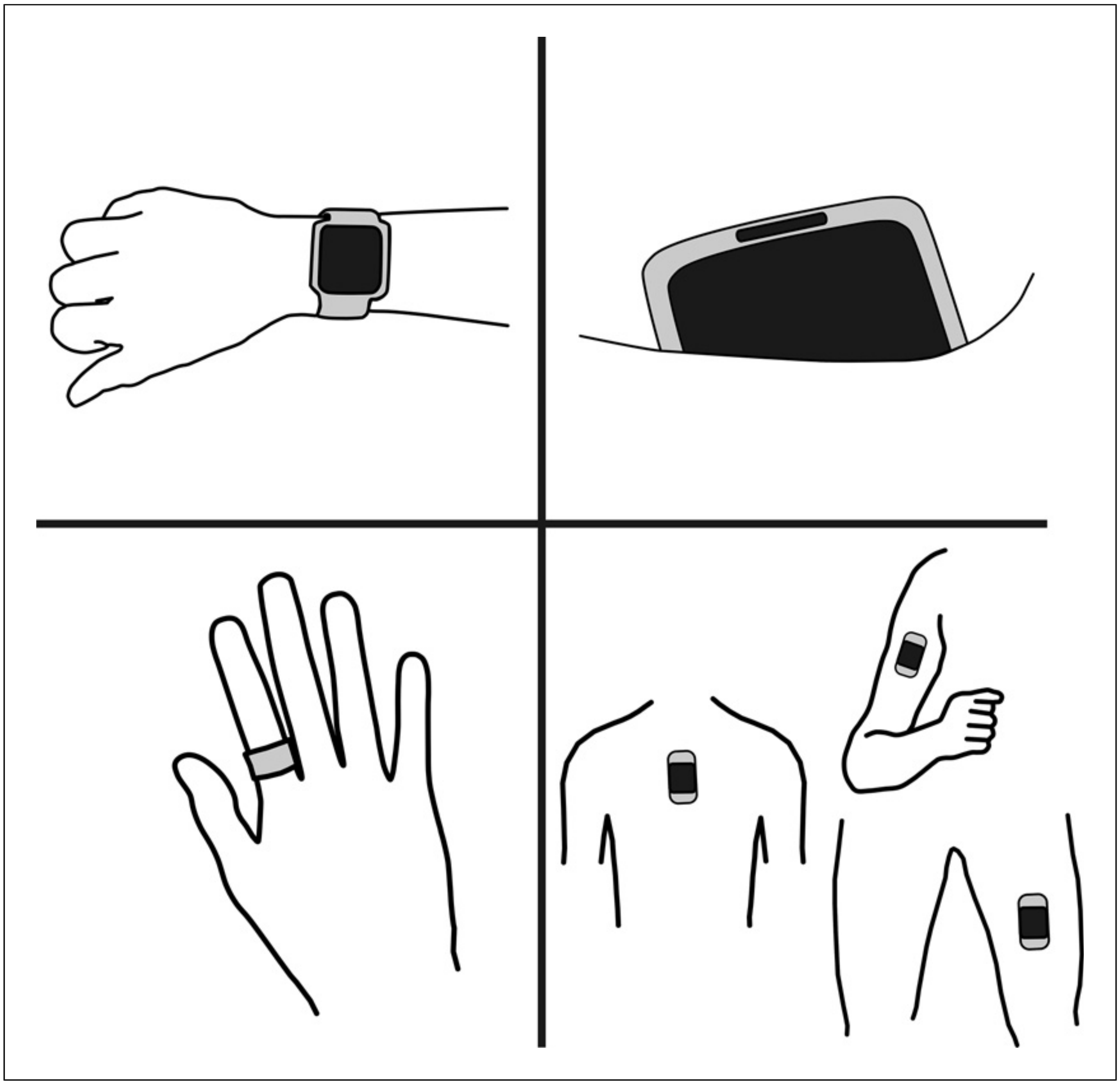

Fig. 1. DHTs capable of providing accurate real-time digital biomarkers are increasingly coming in a variety of form factors, including smartphones, smartwatches, smart rings, and wearable patches.

Digital mental health assessment has, to some extent, lagged advances in digital mental health treatment. This is most likely due to inherent challenges in how mental health diagnoses are defined, based on how people present and not underlying etiology, thus creating inherent problems with reliability of assessment [16]. The emergence of digital medicine frameworks and the explosive growth in smartphone and wearable device ownership now enable objective measurement of patient physiology and behavior at an unprecedented scale. Digital biomarkers extracted from these technologies (shown in Fig. 1) are increasingly being combined using advanced artificial intelligence and machine learning approaches into digital phenotypes that could hold the key for improving mental health assessment [17, 18]. Despite a small handful of early examples, digital biomarkers and phenotypes of mental health are still in their infancy. In this editorial, we make the case for why digital biomarkers and phenotypes should be a key component of mental health assessment and highlight several compelling areas for future work.

The Case for Digital Biomarkers and Phenotypes of Mental Health

Recent efforts and more long-term trends have primed the community of mental health researchers, providers, and patients for a shift to assessment inclusive of objective data. Psychologists and psychiatrists have been studying the physiology and behavior of mental health disorders for decades. In fact, nearly 15 years ago, the US National Institute for Mental Health advanced a new model for studying mental health based on Research Domain Criteria [19, 20]. This model takes a translational approach to identifying the mechanisms underlying mental health conditions. Operationalization of Research Domain Criteria includes behavioral and physiology units of measurement that can serve as key targets for DHTs.

However, the context for those measurements is key. Under very specific laboratory conditions, we know that affected individuals react differently to stimuli [21–28], and those reactions are mechanistically linked to their mental health conditions [29]. Mental health researchers have painstakingly trained teams for months to perform behavioral coding of reactions considered "behavioral fear responses" in young children as they are administered a series of brief fear inducing tasks [30]. Researchers have also had preteens wait 30 min in a laboratory so their stress levels normalize enough from the novelty of coming into the laboratory to detect stimuli reactivity, and then wait 60 min after the stimuli to assess recovery [31], and have instrumented participants to detect eyeblink magnitude within milliseconds after acoustic startle probes [32, 33]. We need to exercise this level of control because, unlike a height or a weight, the physiology and behavior underlying mental health is highly variable within individuals over years, months, days, and even minutes; is highly variable across individuals in terms of symptomology and impairment even within the same diagnosis; and is often context dependent such that other people, situations, and spaces can significantly alter impairment in the moment.

Digital biomarkers extracted from DHTs give us the ability to capture the inherent variability of mental health symptoms, behavior, and physiology in a way that a single office visit or clinical interview cannot while also tagging and integrating important contextual features. DHTs such as smartphones and wearables are a gateway into what's happening inside the body and how mental health impacts behavior and functioning. These technologies allow us to isolate specific stimuli as we do in controlled laboratory experiments, to examine baseline, reactivity, peak, and recovery [21–28]. For instance, we can answer questions like, how does your body react when you receive an urgent text message? Do affected individuals recover differently from a poor night of sleep, or a period of louder than typical ambient noise? By isolating naturally occurring clinically relevant stimuli and engineering digital features that represent stimuli reactivity, we can investigate how the outcomes of years of research in the laboratory can extend to remote settings with more ecological validity (Fig. 2). With these naturalistic experiments enabled by DHTs, we can ensure that we are studying the right constructs for discovering mechanistic biomarkers and phenotypes of mental health.

Importantly, DHTs allow more equitable representation in research and access to clinical resources. We no longer need to require laboratory visits with administrator interaction. If we are trying to understand lethargy in chronic depression, there is significant burden put on individuals affected by requiring them to drive into a laboratory and be administered hours of testing. DHTs can reach participants in their homes, enabling longitudinal access to better examine fluctuations of symptoms and impairment over time [34], and for more people than can realistically be achieved through in-person laboratory experiments. For example, a recent study demonstrated the ability to deploy Oura Rings to capture longitudinal HRV and sleep metrics nearly every night for over 6 months from more than 900 college students in less than 2 years [35–37]. As another example, researchers have used accelerometer data collected from over 100,000 individuals as part of the UK Biobank study to better understand links between physical activity and mental health conditions [38, 39]. There is a compelling opportunity to unravel the physiology and behaviors underlying mental health conditions with DHTs, but doing so requires that we ensure representation extends beyond those who already own smartphones and wearables. Recent efforts have suggested hybrid study designs that are intentional about recruitment and device provisioning to ensure adequate representation [40–42]. DHTs are enabling large scale, representative studies of mental health-relevant physiology and behavior, and the discovery of mechanistic mental health biomarkers and phenotypes that generalize outside their studies of origin and provide compelling targets for translation to clinical practice.

By providing ecologically valid measurements of the physiology and behavior underlying mental health conditions, and the mental health-relevant context from which they are sampled, from large representative samples of participants over long periods of time, DHTs promise to revolutionize mental health research. The outcomes of this research, which can provide nearly continuous monitoring of fluctuations in mental health symptoms through digital biomarkers and phenotypes, provide endless possibilities for a paradigm shift in clinical practice where mental healthcare can work to predict symptom changes, and suggest interventions to reduce symptoms and prevent negative outcomes.

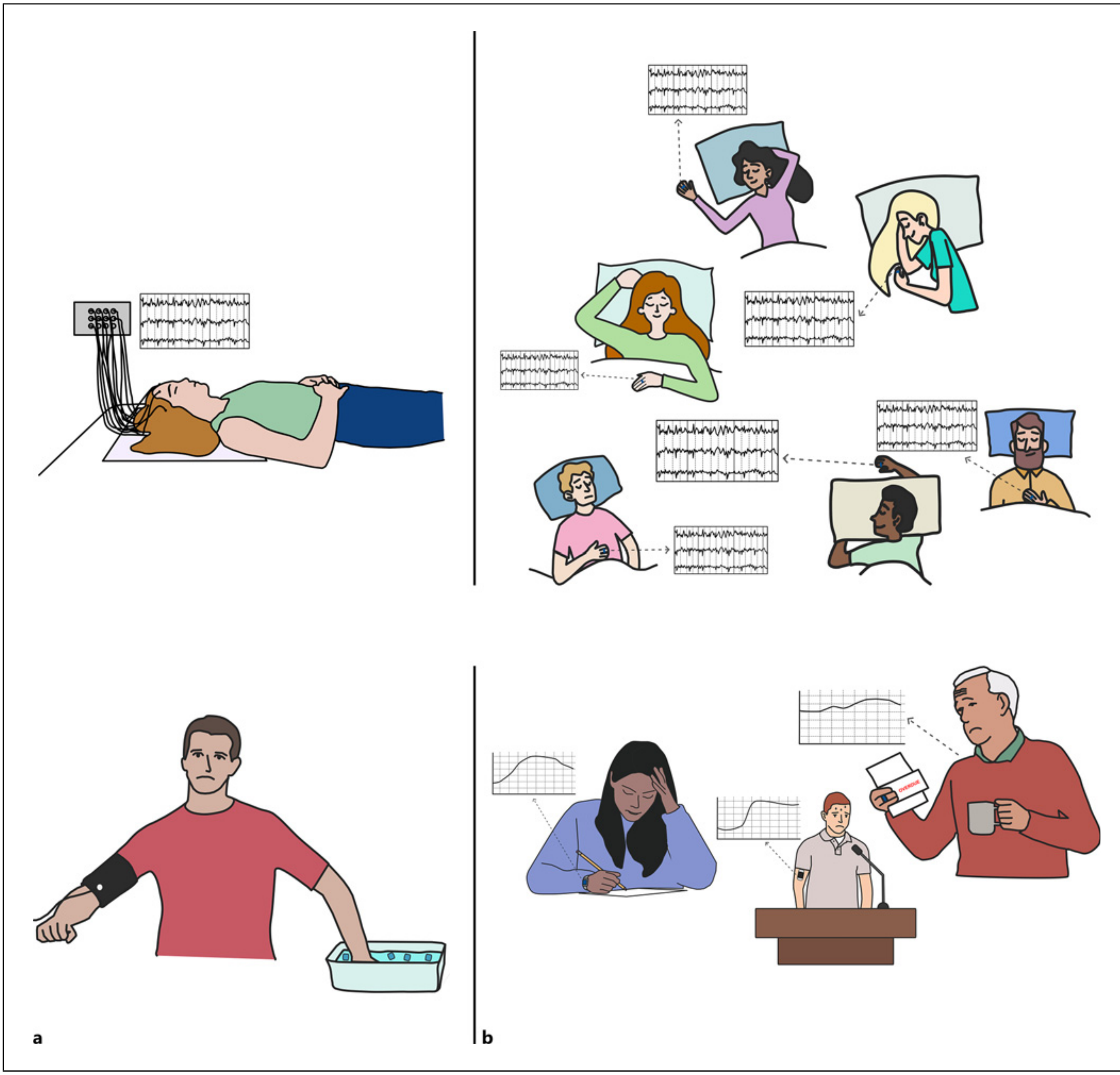

Fig. 2. a Historically, researchers interested in collecting biological signals have had to rely on specialized equipment and participants coming into a laboratory environment, a process that is time consuming and not conducive to collecting longitudinal data from many participants. **b** As DHTs have become more affordable and ubiquitous, they have allowed researchers to employ an alternative paradigm in which they are able to collect a large amount of data from many participants over long periods of time with the added context of real-world settings.

The Future of Digital Biomarkers in Mental Health

As we push toward the future of digital biomarkers in mental health, there are several areas where critical investment is needed. These include the consideration of multi-modal phenotypes, advancing new mental health-relevant sensing modalities, including historically understudied groups in research, using the right types of AI, and embracing new approaches for intervention.

Digital phenotypes must be built from multi-modal biomarkers. Especially in remote, unstandardized settings, we must understand biomarkers in relation to one another as they can provide additional context. Take, for example, an elementary school child taking a math test. Even when we have isolated a clinically relevant stimulus (the test) and examine relevant features underlying anxiety (heart rate reactivity), we still have other biomarkers to control for and other possibilities to rule out. For instance, a child may have heightened heart rate reactivity because they just saw a bird outside the window and jumped up out of their chair. By examining the ratio of the child's heart rate reactivity to the child's motion, we may better detect the likelihood of anxiety than heart rate reactivity alone. We must better understand the relationship between biomarker modalities to provide situational context and improve precision of assessment.

New sensing modalities could provide even more salient data. For instance, new technologies are capable of measuring cortisol in sweat [43]. Prior to this innovation, there were decades of promising data relating cortisol reactivity to mental health disorders [44]; however, methods were mixed, yielding challenges in summarizing interpretation across the literature. Methods changed to accommodate challenges to data collection feasibility which required multiple or continuous blood, urine, or saliva samples and to analyze as samples required to be assayed-often sent to specialized laboratories to do so. Additionally, there were many unmodeled drivers of cortisol that were not always accounted for (i.e., time of day, food intake, exercise recency). New sweat sensing patches that provide more continuous and passive measures of cortisol levels could help resolve many of these measurement challenges when paired with DHTs for providing measurement context and potentially at scale.

Mental health, like many health conditions, has not always been studied with representative samples, limiting the generalizability of conclusion. There are many hard-to-reach populations wherein getting into a laboratory is not feasible, including for those without geographic access to research laboratories, physical ability, or trust in research or healthcare systems [45]. One example for which mental health biomarker work has been historically challenging is in childhood. Equipment is rarely developed for children, and studies with high data missingness demonstrate the reality of getting kids to be behaviorally compliant with cumbersome technology for long periods of time in a laboratory setting [46]. Wearable technologies open research opportunities with young children by increasing feasibility. However, user-centered design for child wearables should be a focus [47–49]. Once more pediatric DHTs are available, we are poised to accelerate the accumulation of digital mental health knowledge in early childhood and better understand digital phenotype differences from adults due to factors like symptom presentation, level of insight, autonomy over schedules, and accommodations, many of which may be better captured outside a laboratory environment.

Discovering digital phenotypes of mental health is an ideal use case for explainable artificial intelligence, and particularly machine learning [50]. These techniques excel at resolving complex relationships, like those linking longitudinal measures of digital biomarkers, their context of measurement, and mental health conditions and symptoms. However, because of the sensitive nature of the resulting phenotypes and their potential use in managing mental healthcare, it is critical that we do not fall victim to black box techniques that do not allow us to leverage those models to also advance our understanding of mental health. Moreover, we need to focus on engineering features that are clinically relevant, so that the conclusions that these models enable are clinically interpretable. Investment in explainable AI techniques in the context of mental health is thus a critical area of future work and can be most readily leveraged by multidisciplinary teams inclusive of those with domain and AI expertise.

Finally, it is critical that we undertake future work in digital biomarker and phenotype development that enables advanced approaches to intervention [51]. DHTs provide a compelling opportunity to capture a better picture of a patient's mental health, but they also enable remote delivery of intervention wherever and whenever it is needed. Mental health disorders are ripe for just-in-time adaptive interventions delivered via DHTs because of the contextual fluctuations over time, to be alerted, within moments of your reactivity, to intervention recommendations such as additional supports during a depressive episode [52], when faced with a trigger for alcohol use disorder [53], or when experiencing a panic attack [54–56]. DHTs grant users access to data, but also services when they are most useful to them. It is very challenging to have the insight to engage in even known interventions at the moment when our conditions are most activated (e.g., [54]), thus interventions (e.g., alerts, reminders) based on personalized metrics that are grounded in human-computer interaction research [57–61], could help remind us when to deploy the management strategies we already know.

Digital Biomarkers to Help Enable Mental Healthcare for All

We are at a unique moment in time where strategic investment in the development of DHTs for mental health could lead directly to dramatic health improvements. DHTs that provide objective measurement of mental health related physiology and behavior, as well as the context of the measurement are most likely to lead to effective digital mental health assessments. Investment in multi-modal phenotypes, advancing new mental health-relevant sensing modalities, enhancing the representation of historically underrepresented groups in research, and using the right types of AI are likely to help us accelerate the development of new digital mental health assessment even further. These new assessments can open the door for further innovation in intervention and ultimately lead to a paradigm shift in the way we practice mental healthcare and a healthier society as a result.

Conflict of Interest Statement

R.S.M. is an inventor on patents and patent applications related to digital health technologies; has advisory relationships with Epicore Biosystems, Pfizer, and Solid Biosciences; is co-founder of PanicMechanic and Biobe; reports research funding from NSF, NIH, Solid Biosciences, Medidata Systems, Kern Family Foundation, and MassMutual; has affiliation with Stanford University and the University of Hawaii at Manoa; and is associate editor at PLOS Digital Health, and npj Digital Medicine. E.W.M. is an inventor on patents and patent applications related to digital health technologies; is co-founder of PanicMechanic and Biobe; reports research funding from NSF, NIH, and MassMutual. J.C. declares no conflicts of interest.

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Author Contributions

R.S.M. and E.W.M. contributed to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; drafting the manuscript and reviewing it critically for important intellectual content; and final approval of the manuscript. J.C. contributed to acquisition, analysis, and interpretation of data for the work; drafting the manuscript and reviewing it critically for important intellectual content; and final approval of the manuscript.

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