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Mobile sensing to advance tumor modeling in cancer patients: A conceptual framework

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ABSTRACT

As mobile and wearable devices continue to grow in popularity, there is strong yet unrealized potential to harness people's mobile sensing data to improve our understanding of their cellular and biologically-based diseases. Breakthrough technical innovations in tumor modeling, such as the three dimensional tumor microenvironment system (TMES), allow researchers to study the behavior of tumor cells in a controlled environment that closely mimics the human body. Although patients' health behaviors are known to impact their tumor growth through circulating hormones (cortisol, melatonin), capturing this process is a challenge to rendering realistic tumor models in the TMES or similar tumor modeling systems. The goal of this paper is to propose a conceptual framework that unifies researchers from digital health, data science, oncology, and cellular signaling, in a common cause to improve cancer patients' treatment outcomes through mobile sensing. In support of our framework, existing studies indicate that it is feasible to use people's mobile sensing data to approximate their underlying hormone levels. Further, it was found that when cortisol is cycled through the TMES based on actual patients' cortisol levels, there is a significant increase in pancreatic tumor cell growth compared to when cortisol levels are at normal healthy levels. Taken together, findings from these studies indicate that continuous monitoring of people's hormone levels through mobile sensing may improve experimentation in the TMES, by informing how hormones should be introduced. We hope our framework inspires digital health researchers in the psychosocial sciences to consider how their expertise can be applied to advancing outcomes across levels of inquiry, from behavioral to cellular.

1. Introduction

This paper is about an unlikely relationship between digital health and basic cancer research, two fields that traditionally have little in common. Drawing them together, however, are breakthrough innovations in mobile sensing, machine learning, and tumor modeling, that collectively have the potential to revolutionize cancer treatment outcomes. The goal of this paper is to propose a conceptual biobehavioral framework that leverages patients' mobile sensing data to render more realistic models of their tumors. We hope this framework empowers digital health researchers in the psychosocial sciences to consider how their expertise can be applied across traditional disciplinary boundaries.

1.1. Digital health research: untapped potential for investigating biologically-based outcomes

Advances in digital technologies have revolutionized many aspects of health and medicine. In particular, the growing adoption in the general population of commercially-available mobile devices (i.e., smartphones, smartwatches, wearables) has led to increased efforts to use people's behavioral data to advance precision medicine (Steinhubl et al., 2015; Topol, 2014)—medical care that delivers the right treatments to the right patients at the right time (Collins and Varmus, 2015). In digital precision medicine, data related to people's heath related behaviors, such as their physical activity (Trifan et al., 2019), sleep disruption (Staples et al., 2017), and stress response (Egilmez et al., 2017) are captured unobtrusively from their mobile devices. Data from these mobile devices, or mobile sensing data, are then used to inform when and where an intervention should be delivered (Trifan et al., 2019; Aung et al., 2017; Harari et al., 2017). Reviews and meta-analyses demonstrate that people's mobile sensing data can provide a nuanced understanding of their behavior, which can then be used to optimize the delivery of behavioral interventions (Trifan et al., 2019; Harari et al., 2017; Mohr et al., 2017).

A foundational principle of mobile sensing, often referred to as 'digital phenotyping' (Mohr et al., 2020), is that people's behaviors can be approximated through data captured by their mobile devices (Mohr et al., 2017). Embedded in virtually every commercial mobile device is a multitude of sensors that measure physical properties such as geolocation, acceleration, and light. Due to unparalleled technological advances in recent years, these sensors have become more precise, more agile, and less impeded by geographical boundaries (Steinhubl et al., 2015). It is now commonplace for mobile devices to be connected to various systems and networks, allowing users to access their data almost anywhere on demand. To help guide digital health researchers, a layered, hierarchical framework is often used to provide a schematic outline of how people's mobile sensing data is related to the behavioral

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markers they are meant to inform (Mohr et al., 2017). In this framework, people's raw sensor data is transformed into low-level data features. Data features refer to the individual measurable characteristics of a dataset, often represented through variables or columns in a dataset. Low-level features, such as movement intensity and bedtime/waketime, are derived through feature extraction, which is the process of reducing the dimensionality of the data to capture the most relevant or representative features for subsequent analyses (Guyon et al., 2008; Khalid et al., 2014). Higher-order behavioral markers, such as sleep disruption, are then approximated through machine learning algorithms that use lower-level features as inputs (Kliegr et al., 2020; Turgeon and Lanovaz, 2020). This hierarchical framework is particularly relevant to digital health researchers given the unprecedented amounts of raw, unprocessed sensor data that is able to be collected via people's mobile devices. In particular, capturing mobile sensing data from patients suffering from a chronic illness has strong potential for advancing precision medicine because it offers a nuanced understanding of their daily behaviors. This can help clinicians determine when to route a patient into care, what level of care to deliver, and whether care that has been delivered is effective.

Using mobile sensing data to estimate people's behaviors has led to increasingly sophisticated intervention designs and behavioral detection methods. For example, just-in-time adaptive interventions (JITAIs) aim to provide the right type of support, at the right dose, at the right time, by adapting to an individual's internal or contextual state (Nahum-Shani et al., 2017). This degree of precision is often enabled by sensor data collected in micro-randomized trials (MRTs), data from which are used to construct JITAIs. MRTs can leverage the sensing capabilities of mobile devices to sequentially randomize users to types and/or levels of an intervention to determine its near- and long-term effectiveness (Klasnja et al., 2015; Qian et al., 2022). Researchers conducting MRTs have used a range of features from participants' mobile sensing data to trigger a randomization sequence such as their location, activity type, and stress level (Klasnja et al., 2015; Qian et al., 2022). This has led to the development of JITAIs targeting a range of health outcomes such as weight loss, smoking cessation, and medication adherence (Wang and Miller, n.d.).

Importantly, the power and precision afforded by mobile sensors presents digital health researchers with an opportunity to apply their expertise to advancing discovery in more basic levels of inquiry. In theory, a hierarchical framework that links people's mobile sensing data with their underlying biological processes could be used to inform outcomes at the biological level. Despite a large and robust body of literature demonstrating a direct link between people's health behaviors and their underlying biological processes, such as levels of circulating hormones (Segerstrom et al., 2014; Marketon and Glaser, 2008; Robles et al., 2006; Kyrou and Tsigos, 2009), digital health researchers have yet to explore the potential for using people's mobile sensing data to inform outcomes related to their cellular and biologically-based disorders, such as malignant tumors.

1.2. Basic cancer research: a need to better account for the impact of patients' behaviors

A goal of basic cancer research is to understand, and ultimately target, the genetic and cellular processes that drive the growth of tumors in humans. Despite remarkable advancements in cancer therapeutics that have contributed to an overall cancer survival rate of >70 % (Brenner, 2002), the five-year survival rate for the deadliest forms of cancer is <20 % (Jemal et al., 2017). These cancers tend to spread quickly and not respond well to conventional cancer treatments. To address this, cancer researchers develop tumor models to study the etiology of these cancers and how they grow and respond to different treatments in a controlled setting. This has traditionally involved the use of genetically engineered mice to derive tumor models, however, findings from these experiments often have limited generalizability to human patients (Ijichi, 2011; Borowsky, 2011; Fong and Kakar, 2009). Recent innovations, such as the three-dimensional multi-cell type tumor microenvironment system (TMES) (Gioeli et al., 2019; Roller et al., 2021), provide a rigorous and realistic platform to model the growth of patient-derived tumor cells by allowing researchers to mimic the tumor microenvironment in human patients. By leveraging the ability of the TMES to flow media (e.g., hormones) in and out of the system, cancer researchers can model the rhythm of circulating hormones, such as cortisol, that are associated with key health behaviors in patients, such as sleep and stress. By experimenting with different hormone levels in the TMES, the findings can shed light on the effect of human behaviors known to impact tumor growth and response to chemotherapy (Robertson et al., 2016; Sklar and Anisman, 1979; Thaker et al., 2006).

To develop tumor models that are realistic and generalizable, it is essential to account for patients' day-to-day health behaviors in the tumor microenvironment system, such as their stress response, sleep disruption, exercise, and diet. Literature in cancer has documented a robust association between people's health behaviors and their tumor progression (Robertson et al., 2016; Sklar and Anisman, 1979; Thaker et al., 2006). In particular, hormones associated with these behaviors, such as cortisol and melatonin, have been found to significantly impact tumor growth (Blask, 2009; Schuller et al., 2011; Li et al., 2017). Research has found that health behaviors contribute to individual variation in cancer outcomes by activating sympathetic and neuroendocrine responses (Costanzo et al., 2011). Hormones, which are products of these responses, have downstream effects that can directly impact the tumor microenvironment, and thus tumor growth (Costanzo et al., 2011). Understanding the relationship between people's health behaviors and their hormone levels can inform cancer researchers of how they should introduce hormones in experiments using the TMES, or similar tumor model systems, to answer fundamental questions about how people's behaviors influence their tumor biology. In the TMES, this can be done by adjusting the flow and timing of hormones and other biological elements in the system, thereby allowing researchers to recreate a tumor microenvironment as found in a human patient. An obstacle to this approach is collecting enough hormone-relevant data from patients to meaningfully inform TMES experimentation. Having a way to continuously monitor patients' critical hormone levels over time could lead to ultra-realistic tumor models that accurately portray the impact of patients' health behaviors.

2. An unlikely partnership: a framework that integrates innovations in digital health and basic cancer research

Our conceptual framework (Fig. 1) extends the hierarchical sensemaking framework by Mohr et al. (2017). Our framework integrates innovations from multiple disciplines—mobile sensing from behavioral health, machine learning from data science, tumor modeling from cancer biology—to advance the role of digital health in tumor modeling. It capitalizes on the burgeoning interest from researchers to harness technology and algorithmic approaches to solve complex issues in medicine. Whereas artificial intelligence (AI) has captured the imagination of the general population, machine learning is what enables machines to mimic human-like intelligence without explicit programming (Das et al., 2015). As highlighted in recent reviews (Rajpurkar et al., 2022; Johnson et al., 2021), many aspects of health and medicine are at the precipice of being dramatically changed by AI. While this is made possible by the wealth of data collected by healthcare systems, it is spurred on by the vast amounts of data available through the widespread adoption of common networked devices like smartphones, smartwatches, and wearables. Thus, we believe our framework has strong relevance to the future of digital health applications in medicine.

Our framework leverages widely accepted approaches to approximating health behaviors, such as insomnia and stress reactivity, by transforming data captured by sensors into low-level data features through handcrafted and/or automatic feature engineering methods

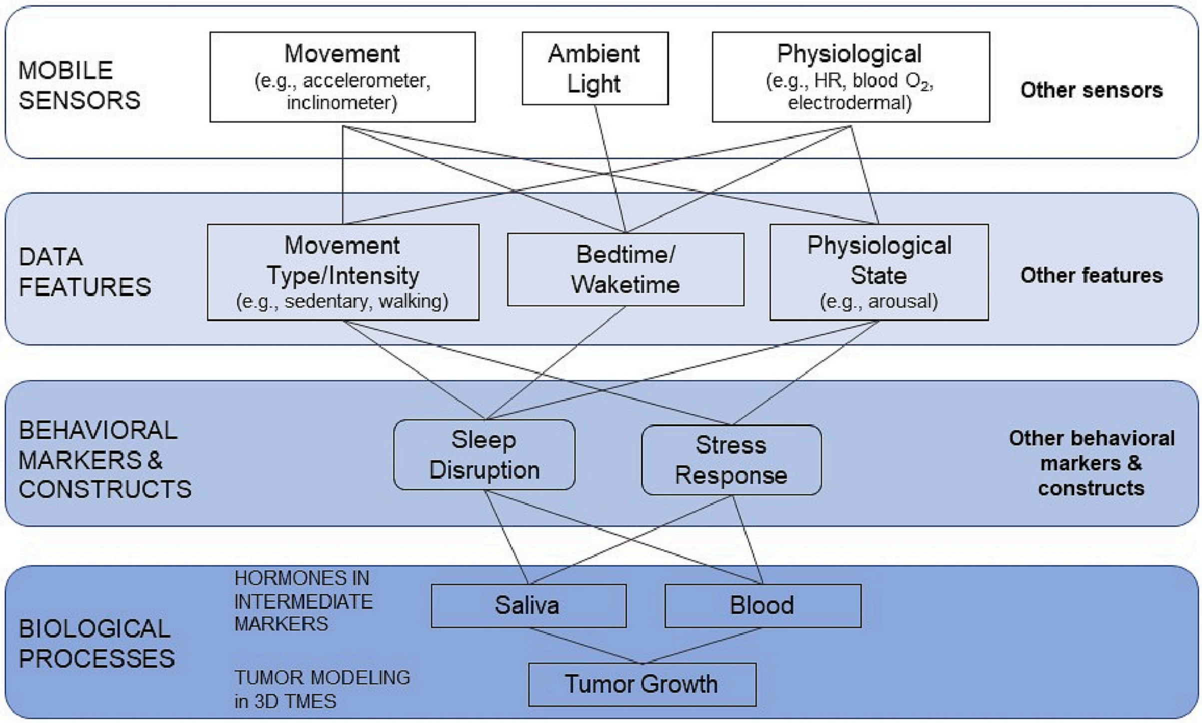

Fig. 1. The framework below depicts how data gathered from mobile devices can be used to inform underlying biological processes. A laboratory study of tumor cells in a tumor modeling system is necessary to understand the impact of sensed behaviors on tumor growth through hormones in an intermediate biological marker, such as circulating cortisol levels in saliva.

(Trifan et al., 2019; Mohr et al., 2017; Sheikh et al., 2021), which can in turn be used to approximate more complex behaviors and constructs. Although a detailed review of machine learning and feature extraction approaches in health behaviors is beyond the scope of this paper, interested readers are encouraged to seek out the many excellent resources that exist on these topics (Jiang et al., 2020; Bzdok and Meyer-Lindenberg, 2018; Hoogendoorn and Funk, 2018).

Our framework establishes a connection between mobile sensing data and the underlying biological processes by leveraging data features extracted from individuals' mobile sensing data to detect hormone levels such as melatonin and cortisol. This linkage may also involve higher-order behavioral markers and constructs, analogous to latent constructs in psychological research, which cannot be directly observed but can be approximated by combining lower-level data features. It is important to note that there may be robust support for the use of various data features in directly approximating hormone levels, depending on the feature in question. For instance, numerous studies have demonstrated a strong association between physiological arousal and underlying cortisol levels across different populations (Peifer et al., 2014; Rief et al., 1998; Evans et al., 1994). Therefore, researchers may discover that aggregating lower-level data features into higher-order behavioral markers or constructs is not always necessary for approximating different hormones. However, further studies are warranted to explore this in greater detail.

Establishing a process for using people's mobile sensing data to automatically assess hormone levels has multiple advantages over taking serum or saliva samples. Namely, it is less burdensome to collect, cheaper to analyze, and can offer nearly continuous monitoring. In our framework, estimates of hormone levels in actual patients are then used to inform how hormones should be introduced in the TMES or a similar tumor model system. This could lead to the widespread adoption of using commercial devices to continuously approximate a patient's hormone levels or other biological markers, with the goal of developing tumor models that more accurately reflect the impact of patients' health related behaviors on their tumor growth.

Critically, two things are necessary to demonstrate the feasibility and potential usefulness of this framework. First, it is necessary to demonstrate the feasibility of using people's mobile sensing data to detect their underlying hormone levels. Second, it is necessary to demonstrate that detecting people's hormone levels through their mobile sensing data can meaningfully impact TMES experimentation to produce more realistic tumor models.

2.1. From mobile sensing to hormones: studies demonstrating the feasibility of using mobile sensing data to detect hormone levels

Two published papers demonstrate the feasibility of using people's mobile sensing data to detect their underlying hormone levels. In a recent study, Castaldo et al. (2021) found that healthy participants' mobile sensing data can be used to monitor their melatonin-onset. They used a chest-worn commercial medical-rated device (Zephyr BioHarness™ 3.0; Medtronic, Inc., Annapolis, MD, USA) to collect electrocardiogram signals for 24 h. Deep learning of the mobile sensing data demonstrated that patterns of heart-rate variability, physical activity, and skin temperature could precisely and reliably detect melatonin-onset assessed through people's saliva samples.

In a recently published paper, our team demonstrated the feasibility of using cancer patients' mobile sensing data to detect their cortisol levels over time, using a less invasive device and over a longer duration (Dong et al., 2021). In a study of ten newly diagnosed pancreatic cancer patients with self-reported moderate insomnia symptoms, patients' mobile sensing data (accelerometer, inclinometer, light) was captured by a wrist-worn actigraph that was worn on their non-dominant hand for 5 days. We focused on the impact of disrupted sleep on pancreatic cancer, which has one of the lowest 5-year survival rates of all cancers at approximately 5 % (Ilic and Ilic, 2016). Cortisol, a marker of disrupted sleep and a known cancer agonist (Harari et al., 2017; Guyon et al., 2008), was measured in saliva samples collected by patients three times each day for five days (Dong et al., 2021). Handcrafted features were extracted from the raw sensor data based on the literature. Automatic feature engineering using Graph Representation Learning was used to extract additional features. Machine learning of both handcrafted and automatic features was able to detect patients' salivary cortisol levels with low Mean Absolute Error (MAE). Our paper indicates that machine learning of patients' mobile sensing data composed of can be used detect their salivary cortisol levels over a 5-day period with good performance. Collectively, these studies strongly suggest the feasibility of using cancer patients' mobile sensing data to detect their underlying hormone levels.

2.2. From hormones to tumor models: a study demonstrating the potential usefulness of using patient-derived hormone values to inform experimentation in a tumor modeling system

No studies have used cancer patients' assessed hormone levels to inform experimentation in a tumor modeling system. Showing this is not only possible, but useful for advancing cancer science, is needed to support the feasibility and potential usefulness of our framework. Our team conducted a proof-of-concept TMES experiment to study the impact of patient-derived cortisol levels on tumor growth. We used cortisol data from our previously reported observational study of ten pancreatic cancer patients. A detailed description of our study participants, inclusionary/exclusionary criteria and saliva collection procedures, can be found in Dong et al. (2021).

The supplemental material contains detailed information about the technical aspects of the TMES setup. We found that when cortisol was cycled through the TMES based on patients' actual cortisol levels, there was a significant increase in pancreatic tumor cell growth compared to when cortisol levels were at normal healthy levels based on values in the literature (Konishi et al., 2012; Rodenbeck et al., 2002), as seen in Fig. 2. These findings suggest that cortisol levels in pancreatic cancer patients with disrupted sleep contribute to increased pancreatic tumor growth versus patients without disrupted sleep. Consistent with our framework, in conjunction with the previous studies demonstrating the feasibility of detecting patients' hormone levels from their mobile sensing data, these findings support the feasibility of ultimately using people's continuously detected hormone levels from their mobile sensing data to inform experimentation in the TMES to produce more realistic models of their tumors.

2.3. From mobile sensing to personalized tumor modeling: a hypothetical integrated system

To meaningfully improve the modeling of tumors using cancer patients' mobile sensing data, the design of a comprehensive system is crucial. Our envisioned system comprises several interconnected components: data collection, hormone level approximation, tumor experimentation and prediction, and a feedback loop for personalization. In this system, cancer patients would wear a smartwatch connected to their smartphones through a dedicated app. This app would securely transmit encrypted data to a reliable computing platform, such as Amazon Web Services, ensuring data storage and privacy. This combination of hardware/software connected integration is commonplace for popular tracking devices. Artificial Intelligence (AI)-assisted technology would automatically compute individual hormone levels using validated machine learning algorithms. These hormone levels would be displayed in patients' electronic health records or another secure platform accessible to clinicians and researchers. To project tumor growth and response to anticancer treatments, a patient's tumor cells would be experimentally studied within a 3D Tumor Microenvironment System (TMES), considering their respective hormone values. This integration of hormone data into tumor models facilitates personalized predictions and treatment recommendations tailored to the patient's specific cortisol dynamics and tumor characteristics. The integrated system would also incorporate a feedback loop to continuously refine and improve the cortisol approximation and tumor models for future patients. As more data becomes available from smartwatches and tumor experimentation, the system

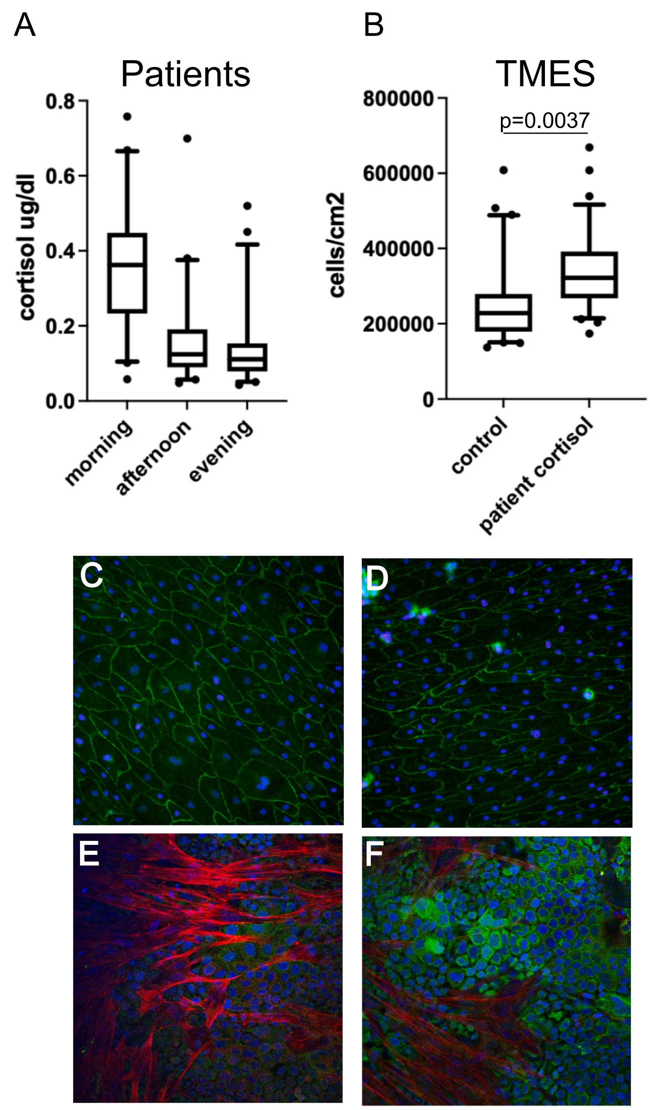

Fig. 2. Modeling effects of cortisol in the TMES. (A) Patient cortisol levels. (B) Quantitation of growth of tumor cells in the TMES under control and sleep disrupted hormone conditions derived from patients. Compared to cells under normal healthy sleep conditions (Panels C and E), the elongation of endothelial cells was similar under sleep disrupted hormone conditions (Panel D), while images of tumor and stromal cells suggested increased tumor growth (Panel F).

can update the machine learning algorithms and refine the cortisol estimation process. This iterative process ensures that the system evolves with new insights and data, enabling ongoing personalization for improved modeling and treatment strategies.

3. Discussion

Our conceptual biobehavioral framework is the result of breakthrough innovations in digital health, machine learning, and cancer tumor modeling. We anticipate that researchers in digital health and machine learning may be unfamiliar with innovations in cancer research such as the TMES. Similarly, it is expected that basic cancer researchers may be unfamiliar with how mobile sensing and machine learning can be used to advance their scientific agenda. This highlights an exciting aspect of our framework. By integrating innovations from disparate fields, it expands the reach of digital health and highlights its ability to inform outcomes at different levels of inquiry, from behavioral to cellular. In addition to previous papers that support the feasibility of using people's mobile sensing data to detect their underlying hormone levels, findings from our TMES experiment suggest that patients' sensed hormone levels can ultimately be used to render more realistic models of their tumors. Although this research is preliminary, findings from these studies support the feasibility and potential usefulness of our framework. We hope it serves as a launching pad for future studies at the intersection of digital health and cancer biology.

We believe our framework has immense potential for advancing both digital health and basic science in cancer. Data from wearables may improve the precision of tumor models by more accurately accounting for the impact of health-related behaviors. We envision that mobile sensing data collected from individual patients may one day be used to inform experiments in the TMES or other similar tumor model systems. This could generate 'patient avatars' that clinicians can use to tailor treatments based on their patients' health behaviors. To realize this potential, future studies need to obtain stable and robust estimates of patients' hormones through their mobile sensing data. This may lead to new innovations in machine learning or a better understanding of how people's behaviors influence their hormone levels.

A novel aspect of our framework is the use of people's mobile sensing data from commercial devices to approximate their hormone levels. The studies referenced in this paper use commercially-available devices to capture people's mobile sensing data, using hormone levels in their saliva samples as ground truth. A strength of this approach is the potential for scalability in the long-term. Using widely accessible mobile devices to track patients' hormone levels could be a breakthrough solution to better understanding, and treating, their tumors. However, a drawback of this approach in the short-term is the need to collect patients' saliva or blood samples in large validation studies to serve as the ground truth for training machine learning models. An alternative yet attractive approach is to use transdermal devices that unobtrusively monitor hormone levels. This new and exciting technology is being pioneered by researchers in the chemical, biofluidic, and materials sciences, who have begun testing prototyping biochemical sensors that can measure people's cortisol levels through their sweat and other bodily fluids (Kaushik et al., 2014; Ku et al., 2020; Bandodkar et al., 2019; Zhao et al., 2019). This technology is still being developed and currently no commercial products exist. However, it has strong potential for unobtrusive hormone monitoring for improving treatment outcomes for large populations of cancer patients. Of particular relevance to our framework, using transdermal devices to unobtrusively monitor people's hormone levels would replace the need to validate hormone detection through people's mobile sensing data from currently available commercial devices (i.e., smartphones, smartwatches, wearables). Because repeatedly collecting saliva or blood samples is impractical for clinical decision making, wearable biochemical sensors may one day replace the need for specimen collection while providing a source of continuous data from patients to improve their care.

Although the purpose of this paper is to propose a conceptual framework, it should be interpreted in light of several limitations. Although there are now at least two published papers using mobile sensing data to approximate people's hormone levels using widely available consumer products (Castaldo et al., 2021; Dong et al., 2021), more studies are needed to replicate these findings and validate this approach. Findings from our own observational study are based on ten cancer patients, most of whom are White, which may limit their generalizability. While the TMES experiment described in this paper used cortisol values based on actual patient values, we used mean values which ignores potentially important individual differences in cortisol fluctuation. Future studies aimed at developing a process for using people's mobile sensing data to detect their hormone levels may also want to cluster patients based on their hormone trajectories. Although our framework focuses on cancer outcomes, researchers may also investigate whether the proposed framework has relevance to other biologically based disorders, such as endocrine disorders and disorders of metabolism. In spite of these limitations, we believe our framework can be useful for guiding future research at the intersection of cancer and digital health. It is important to note that our framework is still in an early conceptual stage. We encourage researchers to propose changes to our framework, based on their own findings and emerging innovations in their field of study.

As sensors and data analytic approaches become increasingly sophisticated, there is a need to ensure the privacy and security of people's data. This is particularly relevant to the proposed framework that uses people's mobile sensing data to approximate an intimate aspect of their biology, their underlying hormone levels. As noted by others (Mohr et al., 2020; Shilton, 2009; Ulrich et al., 2020), trust between researchers/clinicians and patients is critical to fulfilling the potential of mobile sensing. This can only be achieved if researchers are clear and transparent about the risks and benefits of their research to participants. This includes ethical practices in data collection, such as following the principle of least privilege (Saltzer and Schroeder, 1975), which in a research context calls on researchers to collect no more data from participants than is necessary. As mobile sensing capabilities, data analytics, and tumor modeling systems continue to evolve, making data repositories attractive targets for cyber-attack, researchers must be prepared to adopt increasingly stringent practices to preserve the public trust.

4. Conclusions

With the continued advancement of mobile sensing capabilities, machine learning, and novel technologies in other fields (e.g., TMES), digital health researchers may soon find themselves at a crossroad between familiar and unfamiliar paths. A focus of digital health researchers has been to use people's mobile sensing data to approximate their behaviors to inform the delivery of biobehavioral interventions. This work, which is still being developed, has immense potential for improving people's mental and behavioral health. We believe there is also opportunity for digital health researchers to consider how their expertise, in conjunction with their colleagues in the basic sciences, can be leveraged to advance research in outcomes beyond the realm of people's mental and behavioral health. We hope our framework provides some guidance and inspiration for those who are interested in exploring off the beaten path.

Declaration of competing interest

The authors declare no competing non-financial interests but the following competing financial interests: DG has equity in HemoShear Therapeutics, which holds the license for commercial use of the TMES.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.invent.2023.100644.

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