Multimodal biometric monitoring technologies drive the development of clinical assessments in the home environment

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Quote: “The whole is greater than the sum of its parts” – Aristotle

1. Abstract

Biometric Monitoring Technologies (BioMeTs) attracted the attention of the health care community because of their user-friendly form factor and multi-sensor data collection capabilities. The potential benefits of multimodal remote monitoring for collecting comprehensive, longitudinal, and contextual datasets spans therapeutic areas, and both chronic and acute disease settings. Importantly, multimodal BioMeTs unlock the ability to generate rich context data to augment digital measures. Currently, the availability of devices is no longer the main factor limiting adoption but rather the ability to integrate fit-for-purpose BioMeTs reliably and safely into clinical care.

We provide a critical review of the state of art for multimodal BioMeTs in clinical care and identify three unmet clinical needs: 1) expanding the abilities of existing ambulatory unimodal BioMeTs; 2) adapting standardized clinical test protocols (''spot checks'') for use under free living conditions; and 3) novel applications to manage rehabilitation and chronic diseases. As the field is still in an early and quickly evolving state, we make practical recommendations to 1) select appropriate BioMeTs; 2) develop composite digital measures; and 3) design interoperable software to ingest, process, delegate, and visualize the data when deploying novel clinical applications. Multimodal BioMeTs will drive the evolution from in-clinic assessments to at-home data collection with a focus on prevention, personalization, and long-term outcomes by empowering health care providers with knowledge, delivering convenience, and an improved standard of care to patients.

1. Introduction

About a decade ago, wearable Biometric Monitoring Technologies (BioMeTs) began to attract the attention of the health care community. They were touted as solutions to gather continuous physiologic data, driven by the miniaturization of sensors that could be combined into slick and ergonomically designed hardware, with a user-friendly interface and good battery life. However, traditional medical devices for remote patient monitoring have been around for longer. They are typically unimodal (measure one type of physiologic signal (Box 1)) and often need configuration by specialized personnel. Examples include Holter monitors for ambulatory electrocardiogram (ECG) observation, home-use blood pressure (BP) monitors, and thermometers [1,2]. They can collect data in natural settings, potentially removing hospital-associated trends such as whitecoat hypertension and extend monitoring periods. Typically, they are indicated for 24-hours so their longitudinal utility is still limited and due to their unimodal nature, they do not record context measures, such as behavior, location, and type or intensity of activity prior or during a measurement.

Box 1. Definitions

Biometric monitoring technologies (BioMeTs) – Connected digital medicine products that process data captured by mobile sensors using algorithms to generate measures of behavioral and/or physiologic function [29].
Wellness devices – Devices and applications marketed directly to consumers; intended for personal recreational use; do not require a prescription and do not carry regulatory clearance as medical devices in the US. These technologies are classified as wellness devices by the FDA [34].
Medical devices – Devices cleared as medical devices; may require a prescription from a health care professional, and trained personnel to configure and deploy [35].
Unimodal BioMeT – BioMeT containing a single sensor type and associated software to derive single or multi-variable outputs from the sample-level data. For instance, a Holter monitor with the ability to record one or more ECG channels.
Multimodal BioMeT – BioMeT containing multiple sensor types and associated software to derive unimodal and multimodal outputs from the (interaction between the) multiple sample-level data streams. For instance, a bioimpedance-based wearable respiratory monitor that will not generate respiratory rate results when the user is speaking, as derived from the accelerometer sensor.

Due to technological advancements, multiple sensors can be embedded in smaller and more user-friendly form factors, enabling collection of ambulatory remote physiological data that goes beyond such simple measurements, expanding the scope of clinical applications. Additionally, newer sensors are becoming more commonplace, such as photoplethysmography (PPG) [3] for detection of pulse rate or blood oxygenation, biopotential signals (e.g., electromyography and electroencephalography) [4,5], and electrodermal activity [6]. Importantly, many of these specialized devices have adopted a user-centered development approach, blurring the line between wearables for wellness and medical applications further. Wellness wearables were the first to embrace the use of multiple sensor modalities in a single user-friendly device [7]. This enabled personalized approaches to health and wellbeing by making sure people have their data at their fingertips, potentially prompting them into making lifestyle changes. Data is collected and processed in near real-time, can be acquired for days, weeks or years, and stakeholders

attempt to make it actionable via interactive smartphone apps. The medical community realized the opportunity for collecting rich and longitudinal multimodal datasets based on habitual behaviors in diverse fields such as cardiovascular care, sports medicine, rehabilitation, and neurology [8–12]. These datasets contain information on baselines and trends over various time scales, which can complement traditional snapshot assessments made during a medical consultation [13,14]. Ongoing work seeks to better understand how to leverage remote multimodal data when it does not include contextual information typically available in a controlled clinical setting. This context during which physiologic data is collected is critically important for interpretation and clinical decision-making. Knowledge of what a person was doing the moment a digital measure changed can mean the difference between deriving meaningful clinical information or discarding it. Often, contextual data will be derived from dedicated sensors or tools, each with their own advantages and shortcomings (Table 1). Electronic forms of patient-reported outcomes (PRO) and electronic diary-like applications are an improvement over paper [15]. They can augment data derived from BioMeTs but require a conscious effort from users which are subjective, have recall biases, and are often plagued by low adherence [16]. Many contemporary BioMeTs have motion sensors on board, such as accelerometers and gyroscopes, which can provide direct measures of clinically relevant ambulation, such as stride velocity [17]. In addition, they provide measures of physical activity (total activity counts), specific periods of ambulation and classification of specific types of activities, sleep, and other behavioral contexts which can be cross-referenced with vital signs [13]. These context measures are collected passively, without requiring active or very minimal user interaction. This approach has gained wide adoption when using fitness trackers in large population strata [18] and has also been leveraged in BioMeTs with regulatory clearance [19]. Additionally, data from other Internet of Things (IoT) enabled devices can be used to augment BioMeT data. For instance, data from indoor environmental quality monitoring devices can be fused with vital sign data to better characterize the effect air quality has on people with chronic respiratory conditions [20]. Integrated wall mounted photodiodes or microphones could augment gait data in poorly lit indoor environments [21] or cough counting [22,23], respectively. Indeed, sensing modalities can be incorporated into everyday objects, such as a mattress [24,25] or car seats [26]. Finally, multimodal BioMeT data collected in the habitual environment is noisier than data collected in a controlled clinical environment. To ensure reliable data capture under a broad set of conditions, sensor redundancy is important. Two approaches exist: 1) redundancy can be achieved by using more than one sensor modality to sample a physiologic measure, e.g., measuring respiratory rate via a bioimpedance and accelerometer sensor simultaneously [27]; and 2) the same sensor modality can be measured more than once in the same BioMeT, e.g., measure two leads of ECG instead of one.

Table 1. Approaches to contextual data collection

Method	Advantages	Shortcomings
Patient diaries (paper or electronic) [36]	● Wide adoption in medical community ● Many clinically validated options available ● Relatively easy to deploy ● Easy to use for patient	● Captured information is limited and subjective ● Requires active effort from the patient
Patient diaries with prompts via an app; optionally these prompts can	● See row above	● See row above

be dictated by data from a BioMeT [37]	● BioMeT-derived data is increasingly used to prompt patients to answer a specific diary question ● This user input is increasingly used to generate labels for training machine learning algorithms	● More complex set up with increased need for validation, especially if the labels will be used to train algorithms ● Adjusting prompt frequency to ensure patient adherence is an active field of research
Activity and behavioral data derived from motion sensors (accelerometer, gyroscope, magnetometer) [38]	● Passive background collection of objective and high-resolution data ● Algorithms for deriving activities of daily living (walking, driving, position changes, etc.) exist	● Although some algorithms exist, many are under active development and definitive proof on their validity and reliability is yet to be determined for many patient groups
Location monitoring via GPS (outdoor) or other beacon-technology (e.g., based on Wi-Fi or Bluetooth) for indoor use [39]	● Passive background collection of objective and high-resolution data ● Relevant to understanding how geographical and more granular indoor locations influence BioMeT-derived data	● Pragmatic approaches to use location-tracking technologies to augment BioMeT data remain limited ● Patient privacy concerns
Environmental monitoring based on data from e.g., light, noise, or air quality sensors [40]	● Can provide a valuable additional layer of information when environmental triggers can precipitate a clinical event (e.g., asthma exacerbation or epileptic seizure)	● The number of available and validated sensors are limited ● May be limited to a patient's habitual environment and therefore limit their usefulness

Rapid proliferation of BioMeTs and realization of how these technologies can address unmet clinical needs raised expectations for development of digital solutions to "*democratize medicine... enabling each individual to generate their own real-world data*" [28]. Steps have been taken to encourage rigorous evidence-based validation to assess if a particular BioMeT is fit-for-purpose [29,30] but work remains to move measurements into the home environment, and the ability to capture multimodal data is a critical component of this transition. A first wave of multimodal device deployment focused on the engineering challenges, including data processing and interpretation [31,32]. Those efforts resulted in several pilot experiments [33] along with a few examples of digital "snake oil" [28] raising the question: What has been achieved by the field after a decade of trial and error, and what challenges need to be addressed to leverage the full potential of multimodal BioMeTs? We review the state of art for use of multimodal BioMeTs, describe a number of unmet clinical needs that would benefit from a wider adoption of these technologies, and make practical recommendations to drive patient care delivery.

2. Unmet Clinical Needs

Potential benefits of multimodal remote monitoring for collecting robust, comprehensive, longitudinal, and contextual datasets spans therapeutic areas and includes a broad range of acute and chronic disease settings, like rehabilitation. We identify three high-level unmet needs that progressively build on each other (Box 2).

Box 2. Unmet clinical needs

Expand the capabilities of existing ambulatory diagnostic BioMeTs – Ambulatory diagnostic tests are often unimodal and limited in scope due to low usability. Contemporary BioMeTs could improve many of these tests due to their greatly improved usability and could expand their clinical scope as physiologic data can be recorded over longer periods of time and cross-referenced with contextual data. Example: remote cardiac monitoring supplemented by physical activity data recorded by body worn accelerometers [13,41].
Adapt standard clinical test protocols ("spot checks") for use under free-living conditions – Multimodal BioMeTs can replicate many clinical measures typically measured inside the clinic during standardized test protocols, and therefore provide an opportunity to make these protocols compatible with the real-world, moving away from occasional spot checks. Example: measure blood oxygenation after a physiologic or physical challenge [42].
Develop novel applications to manage rehabilitation and chronic disease management – Multimodal BioMeTs are ideally suited to guide people with chronic conditions, post-surgery, or post-trauma, moving essential but non-life-threatening care to the home environment. Example: cardiopulmonary disease rehabilitation [8,43,44].

First, the use of ambulatory diagnostic devices, such as Holter monitors, is usually limited in time and clinical scope due to the low usability and limitations in how much data can be reviewed (Box 2, row 1). Modern BioMeTs (e.g., ECG patches) exist that drastically improve usability and can even be used in a two-step approach: a simple wellness BioMeT performs an initial screening on a large population, followed by a more rigorous screening with a specialized BioMeT for people that show certain risk factors [45]. The improved usability makes it possible to record data for longer periods of time, potentially expanding the clinical scope [41]. When adding the ability to collect contextual data, that scope can be improved further, e.g., by quantifying the relationship between certain types of physical activity and ECG features, allowing physicians to make more granular assessments on the collected data [13]. However, this approach has raised concerns about false positives and the societal benefits of these types of mass screenings remains to be determined [46].

When staging the severity of heart failure, a key parameter is occurrence of symptoms such as fatigue, heart palpitations, and dyspnea during physical activity [47]. Often, a patient will undergo a standardized exercise and physiological function test in a clinic, such as a cardiopulmonary exercise test (CPET [48]) or 6-minute walk test (6-MWT [49]). During these tests, multimodal data on cardiovascular performance is correlated to a well-defined physical exertion. Similar testing approaches also have utility for neurodegenerative disorders such as Parkinson's disease (PD) which generally manifests through rigidity and slowness of movement. In PD, gait assessment during a 6-MWT is important to examine reduced gait speed or fluctuations in the gait cycle which may limit functional abilities during everyday life [50]. Additionally, dual task 6-MWT can be used to examine the mechanistic interaction between gait and cognition (e.g., number recall) [51]. These types of diagnostic or prognostic snapshot assessments occur under highly controlled circumstances. Although many current multimodal BioMeTs could objectively assess the same or similar measures, they require significant validation to replicate them under non-controlled (free-living) conditions [52], illustrating the second unmet need: not every prolonged walk (e.g., 6-minutes) in daily life can be compared to the controlled result of supervised 6-MWT, especially as the

environment and any additional tasks that person may be performing, can influence gait pattern (Box 2, row 2). Studies have already shown the ability of BioMeTs to gather relevant data in controlled conditions, but their true utility lies beyond the clinic or lab, where patients can wear BioMeTs for long periods of time, enabling clinicians to better understand disease trajectories [53,54]. It is also important to keep in mind that many conventional assessments, such as 6-MWT, have serious limitations, e.g., a lack of specificity [55], can be impacted by personal motivation and are therefore highly variable [56], and were sometimes found not useful by both patients and clinicians [57].

COVID-19 pandemic amplified the need for remote monitoring and created pressure to advance the field of digital medicine, including novel assessments often combining multiple measures [13,58]. The DETECT study by the Scripps Institute found that the data from multiple BioMeTs when combined with patient-reported symptoms can be a reasonable predictor of a SARS-CoV-2 infection [18]. Data suggests that the combination of remote monitoring of the cardiorespiratory system with physical exercise can be important for remote monitoring in post COVID-19 recovery [43,44], essentially replicating certain aspects of an in-person physician spot check on a more continuous basis. These examples highlight incremental steps in adapting more traditional in-clinic tests for real-world usage.

The third category relates to the prevalence of many chronic conditions like diabetes, obesity, and cardiovascular and respiratory conditions suggests an increased demand for rehabilitation services [10], which is recognized by the U.S. National Institutes of Health (NIH) Research Plan on Rehabilitation [59] (Box 2, row 3). Specific examples include disease prevention, monitoring and condition management for atrial fibrillation, heart failure, stroke, and myocardial infarction [8]. Use of BioMeTs to guide and improve rehabilitation and management of chronic conditions is a logical next step in the trend towards a decentralization of health care but much work remains to develop fit-for-purpose devices and applications for specific patient groups [60].

3. Recommendations to drive adoption of multimodal BioMeTs for clinical assessments in the home environment

We have reached a point where, in many cases, the technology is no longer the limiting factor [31] but rather the ability to integrate fit-for-purpose BioMeTs reliably and safely into existing and novel clinical care pathways for various chronic and acute conditions. As discussed in the previous section, selecting the right BioMeTs is not trivial but just the starting point (Figure 1). Collected data will need to be ingested, processed, interpreted, and visualized appropriately in a technology environment that is compatible with the safety, privacy, and data governance requirements of health care providers. Below, we discuss three categories of practical recommendations to deploy successful clinical applications that run on data derived from multimodal BioMeTs. These recommendations were identified in conversations between industry, regulators, and nonprofit organizations [61] as well as peer reviewed literature, and require collaboration between device vendors, service providers, and health care providers.

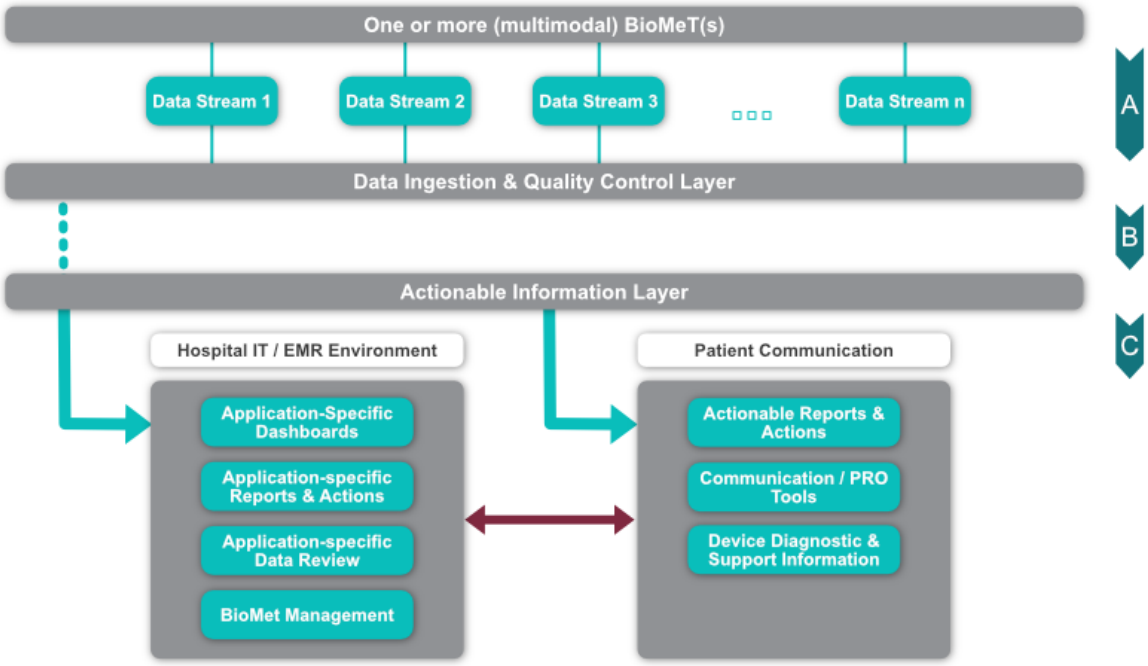

Figure 1 – Data flow considerations for deploying clinical applications with multimodal BioMeTs
A: Each BioMeT generates one or more data streams that are collected in a Data Ingestion layer. **B**: The quality of ingested data is evaluated, and the data streams are processed further into information that supports the intended application. **C**: The Actionable Information Layer connects to various applications for health care professionals and patients to delegate different levels of processed data to the right stakeholders. **Red arrow**: in many cases, functionality to securely exchange information between a patient and the provider-side of the application is needed. For instance, to provide technical support.

3.1 Selecting the right BioMeT(s)

Before trying to select one or more BioMeTs of interest, it is imperative to understand the clinical application and context-of-use, and then determine if a fit-for-purpose BioMeT is available [3]. Guidance on the latter is available elsewhere [29,64]; here we focus on clinical use of one multimodal or multiple BioMeTs (Figure 1, step A):

1. The selected BioMeTs could be medical devices, consumer devices, or a combination. This depends on the application's requirements and thus the context of use [61]. Relevant information may be available from the manufacturer or potentially a third party [3]. If not, or additionally, public clinical validation data may exist [65]. Assessing whether additional validation work is warranted is dependent on the potential risks associated with the application and the validation status of the BioMeT(s) [41]. Hospitals may not be equipped with the knowhow and resources to make this assessment, and often research and commercial providers will step in to provide these specialized services.
2. One should determine if the collected data streams provide the right information for the intended health care professional to make an informed decision on the status of a patient. In this context, "right" refers to the ability of a trained health care professional to use the data for its intended purpose (for instance, as defined in the FDA Guidance on Clinical Decision Support software [66]), while at the same time ensuring that review of the data fits in a clinical workflow and the required

time investment is appropriate. Note that we refer to “raw” data to mean data generated directly by the BioMeT: this could be sample-level sensor data, a processed version of the sample-level data, or both. If only processed data is provided by a BioMeT, assessing its quality and face validity may be difficult, which should be taken into consideration when assessing if the output generated by the BioMeT is fit-for-purpose [29,30,67].

3. If any of the used BioMeTs provide device diagnostic information, e.g., to make sure it is operating as expected or measure if the user is operating it correctly, and that information is relevant to the clinical application under development, it should be available as another data stream [68].
4. The privacy, data security, and data governance principles of the BioMeT should be compatible with the intended application [69].

As an example of these recommendations, consider a clinical care path to discharge COVID-19 patients early from the hospital with a telemonitoring application. Body temperature as measured by a thermometer, and oxygen saturation and heart rate as measured by a PPG sensor, are well understood and home use devices are readily available. Similarly, respiratory rate (RR) is an important measure, which is often still assessed by manual counting in the hospital [70]. For RR, the choice of BioMeT is less clear and may need to undergo additional validation to demonstrate accuracy for this use case. At this stage, it is also important to consider if the use of more than one BioMeT is appropriate for the intended patient population and duration of monitoring to ensure adherence. If such a telemonitoring system is used to monitor hundreds if not thousands of patients sent home during a pandemic, early warning scores (EWS) such as the NEWS, are often used to rank patients on a digital dashboard [71]. Regardless of EWS or other ranking algorithms, an assessment needs to be made about its appropriateness and whether data used to calculate it needs to be immediately available to the health care professional or if it can be obfuscated. All these factors may and should influence the choice of BioMeT to ensure that a modification of an existing care path or the introduction of a new one results in an improvement in the standard of care.

3.2 Composite digital measures

In the previous example, EWS was used to illustrate composite scores that summarize several vital signs to expedite the review process and focus attention of a health care provider on the most urgent cases. Selecting one or more fit-for-purpose BioMeTs is just the start for most clinical applications. Often, there will be a need to implement existing or develop novel sensor-based composite digital measures [72] to facilitate efficient review of complex longitudinal data in a fast-paced (virtual) clinical care environment. In other words, raw data needs to be transformed into actionable information (Figure 1, step B). This presents an additional challenge as these composite measures may need to go through another validation process, including signal quality control for which clear standards may be lacking [73]. If the composite measure is well known and validated in the same or similar context-of-use, a straightforward implementation may be possible which should still adhere to appropriate international software standards for medical applications. Alternatively, if the composite measure is new, validation studies are required [58]. The rigor of those studies will again depend on the risks associated with the application, use environment, and role of health care professionals in their day-to-day use [61]. Composite measures can progressively obscure the underlying clinical decision process that a physician is trained to make, potentially speeding up the interpretation time needed but also hampering its clinical utility, and degrading trust. Whenever possible, our recommendation is to ensure a health care professional can always refer back to the original data sources (Figure 1) to verify the data points summarized by a composite measure.

Consider a digital medicine application that intends to pre-screen people at home who may need to undergo a full in-hospital polysomnography (PSG) to identify those who would likely benefit from the full expensive and labor-intensive test. The selected BioMeTs monitor records several data streams that can be transformed into information commonly reported for sleep studies, e.g., as defined in the AASM sleep scoring manual [74]. Use of commonly reported sleep scoring measures will facilitate the review by health care professionals, and the availability of the underlying data allows for a more detailed review of the data. However, this may still present a time bottleneck, especially if the target population needs to be expanded. Alternatively, consider the case where all the collected data streams are transformed into a single risk score that attempts to indicate the need for a full PSG. This may facilitate faster data review and thus the scale at which the application can be used, but the upfront validation requirements would be much higher, and it may not extrapolate well to uncommon cases, resulting in false negative and false positive results. Both approaches are valid, but they represent a fundamentally different sleep-screening application with different development and validation requirements.

3.3 The need for interoperable software to ingest, process, delegate, and visualize data

Collected and processed (composite) data needs to be securely stored in a software system to present actionable information to health care providers and patients (Figure 1, step C). This will typically require the developer to adhere to many regionally specific regulatory, security, and data privacy and governance standards. Interoperability with an Electronic Medical Record (EMR) system is most likely required to ensure health care providers can tie collected data into patient records, clinical workflows, and care pathways [75]. This may include health care provider specific communication applications. Not providing that is no longer an option as it leads to fragmentation and creation of data and ownership silos, hampering collaboration. Although this requires specific technical expertise, the involvement of clinicians is imperative to ensure the application is fit-for-purpose. Finally, BioMeTs can experience failures, and user error may also hamper the ability to always record high quality data. Access to BioMeT performance and user error data when the devices are in use outside the hospital can be valuable and provides an opportunity to send feedback to the patient to improve BioMeT usage.

In addition to these software and BioMeT integration steps, making sure relevant data can be summarized and visualized for health care professionals and patients is important. Providing an exhaustive description of the considerations for data visualization is beyond the scope of this paper but we summarize a number of key-points: 1) software usability is equally important as hardware usability, and should be considered at all stages of the design process; 2) information should be organized hierarchically, with the most pertinent information on top while providing a way to access lower-level data if needed (e.g., to evaluate an aberrant result), as required by the risk analysis of the application and the intended user (e.g., actionable data for a patient or health care provider are very different things); 3) how frequently data is updated for the health care and patient user is dictated by the targeted clinical workflow and has repercussions for the design of the application; 4) if the application informs the decision making process of a health care professional, that decision making process should be mapped onto software workflows; 5) to improve adherence and keep friction for using the patient application low, any need for application-specific communication between the patient and health care provider should be handled through the patient-facing app; and 6) data portability should always be considered [76].

4. Summary

We discussed that a growing ecosystem of BioMeTs facilitates longer-term assessment of many objective health-related parameters in habitual environments, which will have far-reaching implications for the management of many acute and chronic diseases. The increasing availability of powerful multimodal BioMeTs is enabling the replication and improvement of standardized clinical spot checks into the home environment, as well as driving development of completely novel applications. With greater data collection capabilities comes the need to make it actionable in a way that is compatible with clinical workflows and care pathways, which requires multidisciplinary collaboration. Digital medicine is leveraging multimodal BioMeTs to change the way health data is collected with a focus on prevention, personalization, and long-term outcomes.

5. Author contributions

BV, ESI and AG created the concept for the manuscript. BV and ESI were responsible for creating the first draft of the manuscript. BV, ESI and AG were involved in redrafting the manuscript and discussing content. BV, ESI and AG all contributed to writing and approved the final version.

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