Trends in Biotechnology

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TrendsTalk

Next-generation digital biomarkers: continuous molecular health monitoring using wearable devices

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On October 5, 2023, a seminar on next-generation digital biomarkers was conducted at ETH Zurich, Switzerland. A consortium of interdisciplinary experts from engineering and translational medicine discussed the emergence of wearable device-based body-fluid analysis such as for sweat, interstitial fluid, and breath, and their translation from bench to clinical application. While molecular next-generation digital biomarkers derived from these body fluids can be collected noninvasively or minimally invasively, and analyzed independently from specialized laboratories, one major asset of those innovative wearable devices is the unique ability to generate continuous molecular information of health and disease. With the increasing availability of digital health technologies, the term 'continuous' has been used increasingly recently. However, a clear definition of 'continuous' remains lacking. To foster a deeper and interoperable understanding of 'continuous' derived from the interdisciplinary perspectives, each presenter was asked about their personal conception of the term. Their valuable feedback was summarized and is discussed within this article.

Noé Brasier

Joseph Wang

Can Dincer

How do you define 'continuous' in the context of the use of digital health technologies?

Noé Brasier: Continuous may be divided into two categories: (i) explorative and (ii) clinical. Explorative continuous monitoring may be conducted in research and development at the highest sampling frequency and longest time frame possible from a technological and usability point of view (ia) to generate novel hypothesis; (ib) to validate; and (ic) to repurpose, thus aiming to generate novel added clinical value. Clinical continuous monitoring may be conducted at the sampling frequency and time frame related to the respective underlining pathophysiological dynamics to (iia) diagnose or rule out a disease; (iib) monitor treatment success; and (iic) monitor disease progression, thus, added clinical value must be derivable. In general, measuring, either single or continuous, should only be conducted when an added value and a consequence can be expected.

Joseph Wang: Continuous monitoring involves a direct contact between a wearable or implantable sensor and the target body fluid and measurement of the concentration of the target analyte (marker) at preselected time intervals based on the specific clinical needs. The goal of continuous monitoring is to provide timely feedback into the changing target concentrations. Measurements can be performed at high frequency, in real time or near real time (e.g., every 1 or 5 min), as in minimally invasive continuous glucose monitoring (CGM), or at low frequency (of 1 per hour or per day). The measurement frequency may be changed in response to sudden changes in the response.

Can Dincer: Continuous monitoring means a measurement without any interruption and is mainly defined by the time interval applied. Measuring your blood pressure/glucose level every morning for a period of time, for example, a year, is continuous monitoring. By using wearable technologies for body-fluid analysis, this time interval could be shorter, maybe every minute, second, or even less. Nevertheless, we need to be careful

Firat Güder

Ivo Schauwecker

Dietmar Schaffarczyk

Roozbeh Ghaffari

since shortening this interval leads to another important term real time, which means at the same time as events actually happen, but is still continuous.

Firat Güder: Continuous means that all information present in a biological (or chemical) signal is captured in full such that the digital approximation is lossless in the time domain. To achieve continuous monitoring in the time domain for a digital system, digital samples for the signal of interest must be taken at least twice as fast as the highest frequency component of the time domain signal to be truly continuous hence lossless, according to the Nyquist–Shannon sampling theorem.

Ivo Schauwecker: Continuous health monitoring can range from measuring every step in a patient's life, down to tracking the HIV load every 3–5 months. Importantly, measuring health continuously can only be achieved when patients' compliance is warranted.

Dietmar Schaffarczyk: Continuous monitoring in the context of digital health technologies refers to the ongoing, real-time collection and analysis of health data by software-based medical devices or *in vitro* diagnostic medical devices, typically outside traditional healthcare settings. This approach represents a paradigm shift from episodic, professional-led monitoring in clinical or near-to-clinical environments to patient-centric, home-based care, ensuring uninterrupted health data tracking. Consequently, regulatory frameworks and patient information, education, and training must evolve to accommodate this new model, where the patient is both primary beneficiary but also the healthtech-operator.

Roozbeh Ghaffari: With the framework of health monitoring and management, one approach is to define continuous from the framework of the user or patient, and determine what cadence they need to view data and receive actionable feedback. For example, Type I diabetes patients may require regular minute-by-minute intervals of glucose data and atrial fibrillation patients may require second-by-second intervals of electrocardiogram (ECG) waveforms to diagnose their condition, whereas patients living with Parkinson's disease may require stride length, gait, tremor tracking data with lesser continuity depending on when they are or off their medications. The level of continuity requirement is thus highly dependent on the patient phenotype and being able to pinpoint disease progression or effects of therapeutic progression due to an intervention.

Jörg Goldhahn: Since technology is no longer the limitation for sampling of digital biomarkers, the definition of continuous must be derived from the biomarker itself. In other words, the sampling rate has to be high enough to detect changes of the specific biomarker. This can be every hour in the case of physical activity but every millisecond in the case of fall detection.

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