

Review

Addressing barriers to clinical translation of body-fluid-sensing devices for chronic disease monitoring

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<https://doi.org/10.1016/j.device.2026.101214>

THE BIGGER PICTURE Advances in wearable biosensing, data analytics, and device integration are reshaping how physiological information is being collected. The choice of target body fluid impacts sensor design, sampling architecture, and device placement, enabling temporal insight into biomarkers that cannot be captured through episodic laboratory testing. However, translation into viable real-world products is governed by sensing performance and by intended clinical use, which determines regulatory burden, evidentiary requirements, and benchmarking standards. Design decisions spanning body-fluid selection, biomarker assays, data-interpretation strategies, and expected clinical outputs shape whether a technology is positioned as a wellness, monitoring, or diagnostic device. By discussing biological-sensing constraints, engineering considerations, data analytics, and regulatory frameworks, this review provides perspective on biosensing platforms from proof-of-concept demonstrations to clinically deployable devices.

SUMMARY

Current diagnostic pathways rely on infrequent, laboratory-based sampling that is poorly aligned with real-time disease dynamics. Sensors for continuous or near-continuous biochemical monitoring offer a practical alternative. Wearables, integrated electronics, and lateral-flow devices enable decentralized analysis of biomarkers across body fluids, including interstitial fluid, sweat, saliva, tears, and urine. However, clinical translation remains limited by sparse validation, insufficient comparison to reference assays, and a lack of long-term performance data. Here, we discuss how specific body fluids dictate sensor architecture and performance and classify these systems as monitoring or diagnostic devices based on their regulatory claims and intended use. We further examine the role of artificial intelligence in biomarker correlation and performance optimization and outline key barriers to translating body-fluid-sensing technologies from laboratory settings to clinical and commercial deployment.



INTRODUCTION

For most chronic conditions, clinical decisions rely on intermittent laboratory measurements that provide only snapshot assessments of a patient's physiological state. This mismatch between measurement frequency and dynamic disease progression limits timely treatment adjustment and effective disease management.^{1,2} Most clinical diagnostic methods used for extracting key biomolecular information (e.g., metabolites, inflammatory markers) typically involve blood draws, lumbar punctures, and/or other invasive methods (e.g., tissue biopsies) that are conducted in a centralized health care facility requiring trained personnel, are potentially harmful, typically expensive (>\$1,000 USD), and are not suited for continuous or frequent assessments.^{3,4} Alternative technologies, such as the continuous glucose monitoring (CGM) from Dexcom and Abbott in diabetes management and lateral-flow assay (LFA) strips used for at-home pregnancy tests, demonstrate the potential for real-time, on-the-spot molecular monitoring by detecting biomarkers in biological fluids such as interstitial fluids (ISFs) and urine.^{5,6} The primary advantage of these systems lies in their ability to provide decentralized, real-time analysis for screening and early disease detection.⁷ Other alternative body fluids, such as sweat, saliva, tears, and ISFs offer an accessible window into systemic physiology, as key biomarkers tend to diffuse from the bloodstream into these fluids, as shown in Figure 1, enabling dynamic real-time monitoring of metabolic and endocrine processes central to chronic disease management.⁸

By harnessing this information, sensing technologies can potentially expand access to complex diagnostics and ensure accessibility to individuals across diverse socioeconomic backgrounds. Furthermore, monitoring markers in such body fluids are considered minimally invasive, meaning that patients avoid the risk of pain; harmful side effects, including surgical complications associated with biopsies; risk of infection; and are more likely to adopt and adhere to crucial, potentially life-long health-monitoring technologies.⁹ These advancements, along with the success of the CGM, have sparked the development of several companies focused on revolutionizing precision and personalized healthcare in chronic disease management. In spite of the development of sensing technologies such as the SunVida Platform¹⁰ by Kilele Health for remote patient monitoring and the Arma iDX carelab by ArmaBio¹¹ for at-home rapid testing, large-scale implementation in the clinical information and workflow systems still faces challenges. These include (1) robust validation of biomarkers levels against alternative body fluids and blood levels to ensure diagnostic accuracy; (2) sensor stability in diverse and harsh environmental conditions with high sensitivity and selectivity while ensuring accuracy for long-term on-body analysis; (3) improving long-term data collection and management for clinicians and improving data interpretation for end users; and (4) ongoing reliance on simulated/artificial fluids for proof of concept rather than providing meaningful patient derived clinical evidence. Few studies have conducted preclinical pilot testing, demonstrating the challenge of benchmarking these technologies against the current lab-based assays.

We examine how sensor technologies are reshaping chronic disease monitoring, highlighting studies supported by clinically

relevant data. We outline how body-fluid selection influences sensor design and performance and summarize key barriers to translation and adoption. We also discuss regulatory considerations, including how device claims determine classification as wellness, monitoring, or diagnostic tools, and we explore the potential of artificial intelligence (AI) and machine learning (ML) to enhance sensor performance. Finally, we provide perspectives on strategies to advance these technologies toward practical monitoring applications.

Design considerations and translational challenges in peripheral body-fluid sensing

Given the dynamic complexity of human physiology, single-point laboratory measurements provide a static snapshot but fail to capture how metabolic biomarkers fluctuate over time. Traditional diagnostics often miss short-term changes that are important for tracking chronic disease progression.¹² Real-time monitoring prioritizes minimal latency enabling immediate clinical decision-making, whereas continuous monitoring focuses on high-frequency longitudinal data acquisition to capture trends, variability, and disease dynamics. In this context, the former supports acute intervention, while the latter enables long-term optimization and predictive care. The need for continuous, real-time monitoring using peripheral body fluids such as sweat, saliva, tears, and ISF, which can capture metabolic changes with higher temporal resolution, is growing. Many chronic conditions display variable or episodic biomarker patterns, making isolated measurements insufficient for accurate assessment. Furthermore, no single biomarker can reflect overall physiological status, highlighting the value of sensing technologies that can monitor multiple analytes simultaneously.¹³

Sweat-based sensors

Sweat has emerged as a promising body fluid for monitoring chronic diseases due to its biomarker composition and non-invasive accessibility, enabling insights into electrolytes (e.g., Na⁺, K⁺, Cl⁻) and key metabolites such as glucose, lactate, and uric acid.¹⁴ The reliability of these biomarkers depends on sweat generation and transport mechanisms, which in turn dictate sensor design and performance. Human sweat is primarily produced by eccrine glands, originating from blood plasma and interstitial fluid, making it most relevant for sensing applications.^{15,16} Conventional stimulation methods such as exercise or heat produce variable sweat rates and are unsuitable for continuous monitoring in vulnerable populations. Iontophoresis-based (IP) stimulation addresses this limitation, but early implementations relied on bulky collection systems, restricting decentralized use.¹⁷ Recent advances in wearable platforms integrating soft electronics, microfluidics, and multiplexed sensors now enable on-body sweat generation, collection, and analysis.¹⁸ These systems leverage microfluidic architectures to control fluid transport and enable multiplexed detection of metabolites and electrolytes in low sweat volumes.¹⁹

To illustrate the potential of microfluidic systems for sweat-based monitoring, Rogers et al., in 2020, introduced a skin-interfaced sweat-based sensor that utilized microfluidics and a smartphone for processing real-time Cl⁻ levels in sweat.²⁰ The device consists of a polymeric thin-film multilayer stack with laser-cut

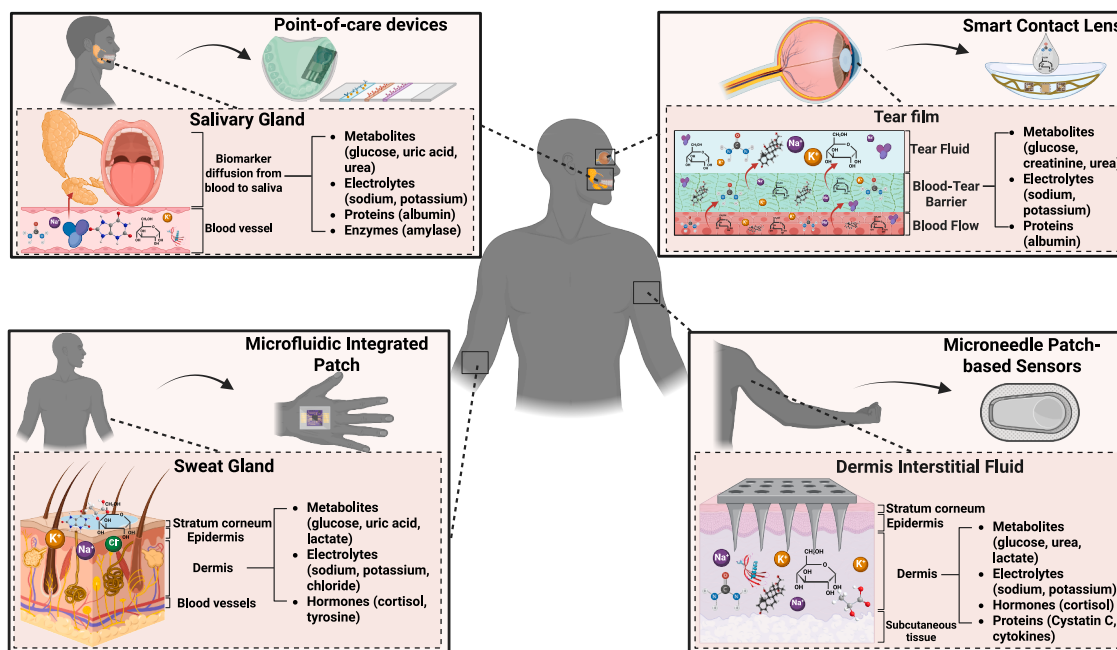


Figure 1. Emerging sensing technologies for point-of-care chronic disease management across diverse peripheral body fluids

Each fluid exhibits a distinct biomarker profile and unique diffusion partitioning mechanisms. A comprehensive understanding of these fluids, their distribution profiles, and the challenges they present is essential for designing effective sensing platforms tailored to decentralized chronic disease management. Figure created using [biorender.com](https://www.biorender.com).

microfluidic channels that were assembled using roll-to-roll processing allowing for rapid, low-cost, large-scale manufacturing ($\sim 1,000$ patches/min), as shown in Figure 2A. The microfluidic channels were coated with hydrophobic materials to exploit the eccrine sweat generated by natural pressure for efficient sweat transport, as shown in Figure 2Ai. For the colorimetric analysis of sweat, the system consisted of orange dye that mixes with the transported sweat sample (Figure 2Aii and iii) allowing for rapid assessment and measurement of Cl^- . For on-body analysis, assessment of 312 athletes was conducted under various settings and was compared to lab-confined methodologies (absorbent-pad measurements in a controlled lab environment), yielding a good agreement ($r^2 = 0.86$), demonstrating the potential of these sensors for personalized health management. Fueled by the success of this prototype, in 2021, the Gx Sweat Patch was developed by Epicore Biosystems in partnership with Gatorade.²¹

The use of microfluidic integrated wearable sensors for on-body analysis has shown promise for metabolic analysis of key biomarkers such as uric acid, xanthine, and alcohol in the management of chronic disease such as gout, chronic kidney disease (CKD), type 2 diabetes (T2D), and cardiovascular diseases (CVDs), as shown in Figure 2B.²² To address the challenges associated with immunoprecipitation for multiday detection such as, drug dosage of pilocarpine, skin irritation, and hydrogel stability, these devices used bioinspired microfluidic design. The microchannels were structurally tailored based on the lotus leaf and pitcher plant trichomes for transport and refreshment of sweat sample, as shown in Figure 2Bi. The nature-inspired microchannels facilitate rapid transport during low-flow sweat conditions, as shown in Figure 2Bii.

The device was employed to monitor the key biomarker xanthine and uric acid, metabolic by-products of purine-rich diets that are linked to elevated risk of metabolic disorders, including CVDs, T2D, CKD, and gout, as shown in Figure 2Biii. For on-body validation the fabricated device (Figure 2Biv) was used for multiday monitoring in a healthy participant wherein data were collected 8, 24, and 48 h post IP. The results demonstrated that the system could accurately track uric acid and xanthine levels, capturing dynamic fluctuations associated with dietary intake (including red meat, fish, and soda) as well as day-to-day activities such as exercise, movie watching, and office work. The findings showed that consuming purine-rich foods increased uric acid concentrations in participant's sweat with similar trends confirmed in two other healthy participants, demonstrating the potential of this device for long-term longitudinal monitoring.

Capturing daily fluctuations of key biochemical markers while accounting for circadian rhythm remains a challenge for precision and personalized monitoring. To address this, researchers have developed a time-resolved, wearable, sweat-based system for capturing the dynamic fluctuations of cortisol, a key biomarker for monitoring stress.²³ For on-body validation, participants ($n = 3$, male 32 and 34 years old, female 24 years old) cortisol levels were tracked before and after long-haul trips and under the influence of jetlag. Sensor measurements demonstrated inverse morning and afternoon cortisol profiles, with cortisol levels progressively normalizing over days in accordance with physiological rhythms, highlighting the potential of this time-triggered sequential wearable sensing device for multiday measurements.

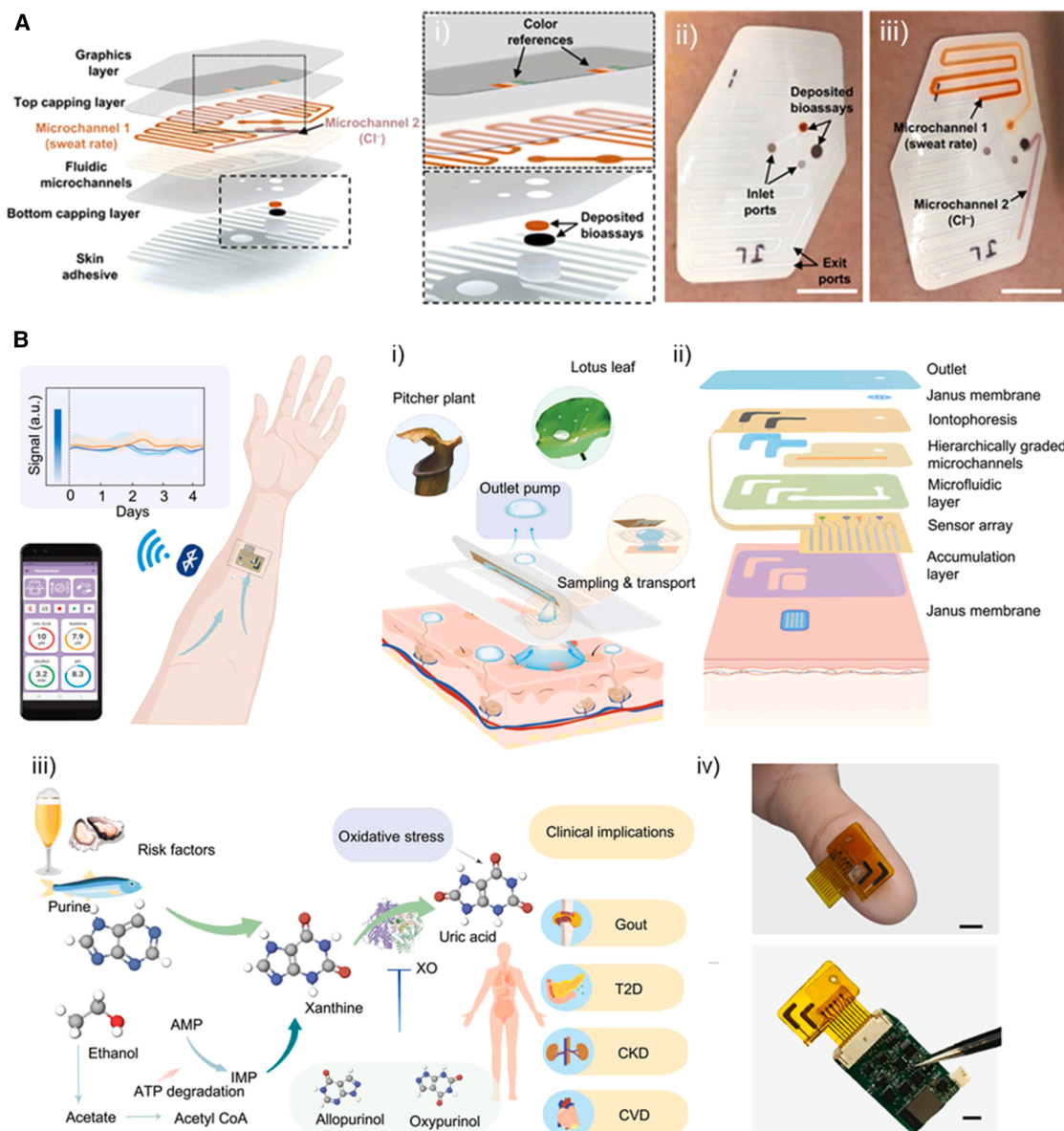


Figure 2. Sensor architect and design based on the different strategies for biomarker monitoring using sweat as the medium

(A) The fabrication of the Gx Sweat Patch developed by Epicore Biosystems for monitoring hydration levels in sweat.²⁰ (i) The microfluidic pathway and the deposited bioassay for the colorimetric quantification of Cl⁻ in sweat. (ii) and (iii) How the orange dye interacts with sweat as the sweat is being transported through the microfluidic channel. Adapted with permission under the CC 4.0 open access agreement,²⁰ copyright 2020, Science.

(B) The development of a microfluidic integrated wearable sensor for multiday monitoring of key biomarkers.²² (i) The nature-inspired microfluidic channel based on lotus leaf for efficient sweat sample collection and transport, (ii) the overall design of the device, and (iii) the metabolic pathway in which the consumption of purine-rich diet can increase the risk of metabolic diseases such as gout, CKD, and CVDs. (iv) The prototype worn by the participants for on-body validation. Adapted with permission under the CC 4.0 open access agreement,²² copyright 2025, Science.

Although IP enables controlled sweat induction at rest, its composition may differ from naturally produced sweat.¹⁵ To address this, alternative strategies leverage naturally occurring sweat for continuous sensing, using capillary-driven microfluidics and hydrogel-based materials to extract sweat passively via osmosis.²⁴ While these innovations have pushed the boundaries for sweat-based sensing, factors such as compensating for

sweat-rate variability and improving sensor calibration should be considered for passive sweat monitoring.²⁵ Active sweat-based monitoring must address wear-time constraints such as housing the sensing device on a skin-compatible substrate and utilizing a self-powered system for long-term monitoring.²⁶ Sweat-based sensors suffer from reduced performance, as biofilm formation on the sensing electrode reduces the sensitivity, accuracy, and

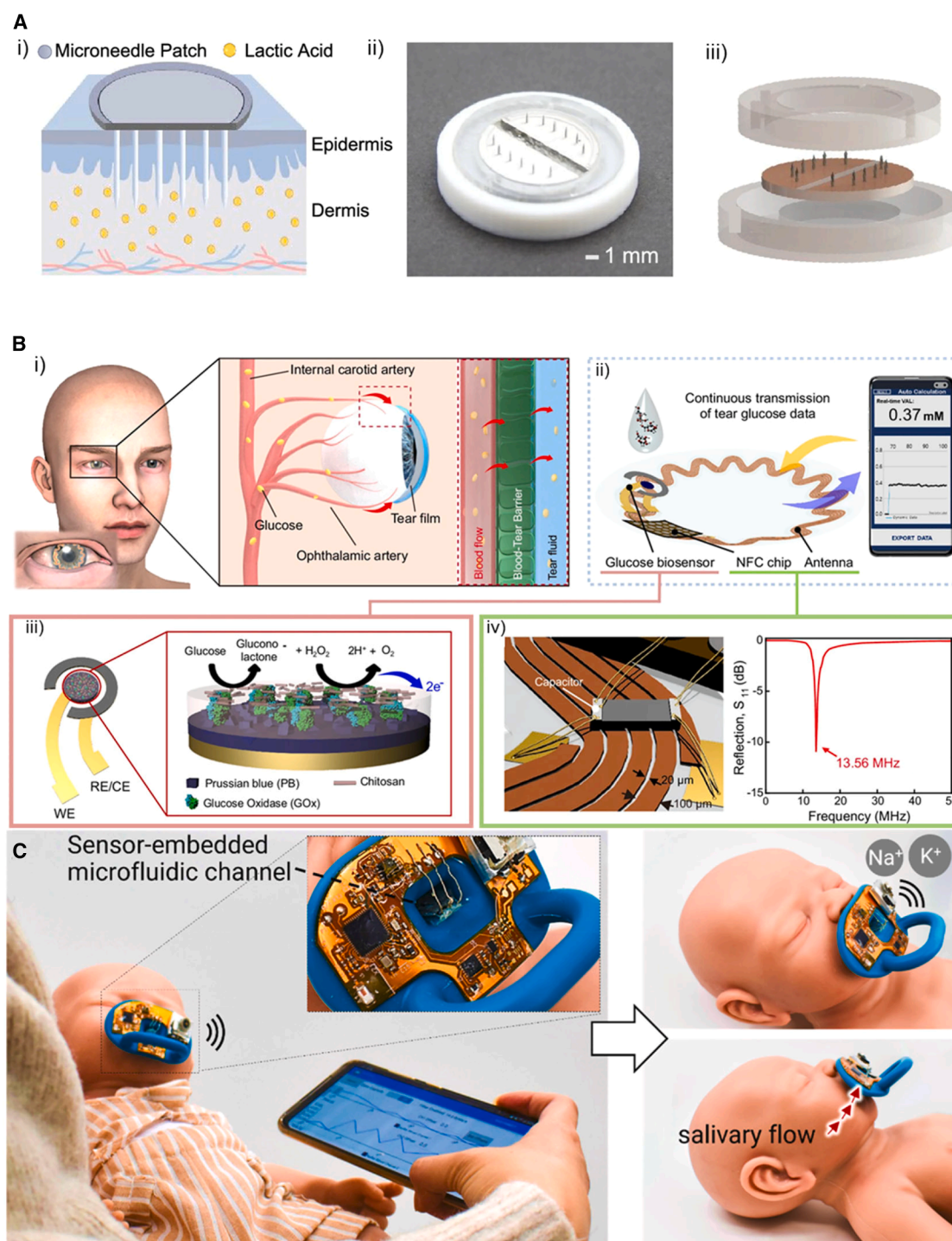


Figure 3. Device integration strategies for monitoring biomarkers in body fluids such as ISF, tears, and saliva

(A) ISF-based MN sensor. (i) The development of an ISF-based sensor for monitoring lactic acid in critically ill patients. (ii) The integrated MN sensor encased in a PDMS soft casing. (iii) Exploded view of the integrated ISF-based wearable sensor. Reproduced (adapted) with permission,³⁷ copyright 2026, American Chemical Society.

(B) The development of a smart contact lens for detecting glucose in tears with personalized lag time.³⁸ (i) The partitioning mechanism of glucose from blood to tears. (ii) The smart contact lens design consisting of a soft silicone-based biocompatible material integrated with a glucose biosensor and an NFC (near-field communication) chip and antenna for data acquisition and data transmission. (iii) The glucose biosensor consisting of chitosan, glucose oxidase, and Prussian

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functionality of the device over time due to accumulation of skin cells, lipids from the sebaceous glands, proteins, and bacteria.²⁷ Addressing biofouling is paramount for the development of next-generation biosensors that can match the reliability and diagnostic accuracy of the current lab-based gold-standard assays, enabling their integration into the clinical workflow.

ISF-based sensor

ISF has gained prominence for minimally invasive management of chronic disease, as its composition resembles blood plasma.²⁸ Dermal ISF (within the skin) has markers such as metabolites (glucose, uric acid, creatinine, lactate), electrolytes (Na^+ , Ca^{2+} , K^+ , Cl^-), proteins (cystatin C, cytokines), xenobiotics (antibiotics), and hormones (cortisol) present in abundance compared to other body fluids (e.g., sweat).²⁹ These biomarkers flow from the blood to the ISF via capillary exchange, and factors such as capillary area-to-volume ratio, pressure, and flow rate can skew the concentration of these biomarkers in ISF.³⁰ To access this source of information, skin-mounted devices consisting of microneedle (MN)-integrated sensors offer a minimally invasive and relatively pain-free alternative while avoiding clotting risk associated with the current lab-based venous blood draws. These devices penetrate through the skin using MNs and extract ISF by using techniques such as reverse iontophoresis, micro-dialysis, electroosmosis, or by using hollow MNs.³¹ To reduce the risk of infection and localized inflammation associated with piercing the dermal skin layer, the design of the MNs is important.³² Parameters such as needle length, needle spacing, and needle tip diameter must be taken into consideration. Deep penetration can lead to localized inflammation, which skews the biomarker concentration and can cause user discomfort.³³

The current challenge with MN sensors is that the previous generation were limited to detecting a single analyte, with the most successful example being the CGM device that showed good correlation between ISF and blood glucose levels.³⁴ To achieve this, a study focused on combining MN with an integrated circuit consisting of four working electrodes and a low-energy Bluetooth system for data transmission for constraint-free, real-time, multiplexed monitoring of analytes (glucose, lactate, and alcohol) in ISF.³⁵ Simultaneous monitoring of these three markers provides a more comprehensive insight into understanding and better controlling the glycemic load, especially in individuals with type 1 diabetes. As proof of concept, healthy participants ($n = 5$) were asked to wear the device and were subjected to identical meals, alcohol consumption, and exercise protocols to trigger lactate, glucose, and alcohol spikes. The correlation between the fabricated sensor and the gold-standard assays was 0.92 for lactate, 0.81 for glucose, and 0.94 for alcohol, demonstrating high potential for this device for on-body analysis.

A study focused on advancing MN sensing by integrating chemical (glucose, lactate, alcohol) and physical (blood

pressure, arterial stiffness, heart rate) marker detection enabling comprehensive evaluation of glycemic load while capturing physiological patterns associated with CVDs and warn the wearer if they are at risk of developing the disease.³⁶ Multiple on-body assessments were performed, including a continuous test for 7 h. The results showed a strong correlation compared to the gold standard for both chemical and physical markers with coefficients 0.98 for alcohol, 0.98 for lactate, 0.97 for glucose, and 0.98 for blood pressure, demonstrating this system's ability for on-body chronic disease management. Building on this, researchers presented the development of an MN-integrated wearable patch for continuous monitoring of lactate levels in critically ill patients at risk of sepsis, as shown in Figure 3Ai.³⁷ The device consists of a modified platinum working electrode with lactate oxidase as the enzymatic recognition element for monitoring lactate in real time. To reduce the potential effect of biofouling, the MNs were coated with a polyvinyl-chloride antifouling membrane, while a skin-conforming flexible potentiostat was used to relay the data generated by the enzyme-target interaction via Bluetooth communication, and the entire system was encapsulated in a soft polydimethylsiloxane (PDMS) casing, making the device lightweight at ~20 g, as shown in Figure 3Aii and iii.

For the on-body proof of concept, the device was worn by patients across diverse clinical conditions, including patients in the intensive care unit (ICU; $n = 9$), patients in the emergency department (ED; $n = 4$), and participants under cardiopulmonary exercise to monitor lactate levels ($n = 4$). To benchmark the performance of the device, simultaneous blood lactate readings were taken at a 30-min time interval for 65 paired measurements. The results obtained from patients in the ICU and ED showed blood lactate level in the range of 1.5–12.3 mmol/L with a mean average ($n = 13$) of 4.5 mmol/L. The readings from the ISF device were compared with the blood lactate levels and showed a strong linear regression correlation of $r = 0.94$ for patients in ICU. Statistical evidence using Bland-Altman analysis revealed a mean bias of -0.028 mmol/L and 95% limit of agreement between blood and ISF lactate readings. These results highlight the potential of the device for continuous monitoring of lactate levels. However, the clinical data generated from this study are not rigorous enough to state with certainty that the wearable sensor could replace current lab assays for monitoring and treating patients at risk of developing sepsis, nor were interventional studies conducted to demonstrate the system's role in impacting clinical outcomes.

Factors such as biofouling induced from foreign-body response due to accumulation of proteins and lipids on the surface of the MN lead to increased signal drift, reduced selectivity, and, in most cases, device failure, hindering the long-term clinical implementation of ISF-based sensors.⁴⁰ Integrating anti-fouling coatings based on zwitterions, hydrophilic polymeric brushes, and functionalized hydrogels onto the surface of the MN could help reduce non-specific protein binding and improve

blue as the recognition element. (iv) The serpentine antenna and its resonant frequency for data transmission. Reproduced (adapted) with permission based on the open access agreement CC 4.0,³⁸ copyright 2024, Springer Nature.

(C) The pacifier-integrated sensor consisting of a flexible circuit and microfluidic channels for transporting the salivary flow of the neonate into the sensing element.³⁹ Reproduced (adapted) with permission, copyright 2022, Elsevier.

signal reliability and sensor accuracy.⁴¹ Continued innovation into antifouling coatings and biocompatible materials will ensure reliable and stable performance of ISF sensors, improving reliability and enabling integration into clinical workflows. Other challenges, including limited and inconsistent sampling due to low fluid volume and skin variability from person to person, can affect effective monitoring. Additionally, biomarker concentrations in ISF suffer from lag due to biomarker diffusion from the bloodstream and can complicate real-time monitoring and accuracy, making standardization a challenge.³³

Tear-based sensors

Tears have potential for non-invasive management of chronic diseases such as diabetes, CVD, CKD, and neurodegenerative disease such as Parkinson's disease due to their rich biomarker composition.^{42,43} Several markers, such as glucose, cortisol, creatinine, and alpha-synuclein, can traverse the blood-tear barrier, reducing the matrix effect, as shown in Figure 3Bi.⁴⁴ Despite these advantages, factors such as low analyte concentrations, uneven tear production, fast evaporation rate, and lag time make tear monitoring a challenge. Companies such as Google attempted to harness tear fluids for glucose monitoring through the development of a smart contact lens for real-time diabetes management. However, variation in the lag time, unreliable correlation between blood glucose and tear glucose levels, compounded with wearer discomfort led to the project being discontinued.⁴⁵

To address these limitations, newer sensing devices must focus on integrating biocompatible soft polymeric materials for user comfort with flexible electronics and microfluidic channels that transport the fluid to the recognition element for data acquisition in real time.⁴⁶ A recent study focused on developing smart contact lens for diabetes management by monitoring glucose levels in basal tear.³⁸ The device architecture consisted of a glucose-recognition element with a flexible printed antenna, and an NFC chip for continuous data transmission, and the entire system was housed on a soft biocompatible silicone elastomer for user comfort as shown in Figure 3Bii–iv.

To validate the device, glucose levels in healthy participants ($n = 10$) and diabetic patients ($n = 10$) were monitored. The results showed that the system was able to track tear glucose levels in real-time, while also estimating the lag time for each individual participant during the test due to sub-minute data acquisition intervals. The correlation between the device reading and blood glucose showed a high correlation (r) of 0.97 and 0.95 for healthy and diabetic participants, respectively, showcasing the potential of this smart contact-lens technology for personalized diabetes management.

The traditional approach of monitoring biomarkers in tears utilizes point-of-care sensor technology wherein tear samples are collected using the Schirmer tear test.⁴⁷ It consists of a paper strip that is placed in the lower eyelid for a few minutes while it is being wetted by the sample, also allowing the measurement of tear production. The sample can be extracted from wet paper with extraction buffers to be analyzed later by standard laboratory methods such as ELISA. Researchers used those strips to evaluate patient improvement for dry-eye syndrome, based on increased tear production, against me-

chanical non-invasive stimulation and oral supplementation, respectively.^{48,49}

In this context, paper-based devices such as LFA strips have a high potential for tear sensing. LFA paper strips, also known as rapid diagnostic tests, are advantageous tools for point-of-care sensing since they are inexpensive to produce, portable, equipment and battery free, robust, provide a fast response (between 3 and 5 min), and are very simple to use (the patient itself can self-test without any previous training).⁵⁰ Although there exist reports on LFA tests for tear-sample analysis,⁵¹ including even patented technologies,⁵² and hybrid systems integrating the Schirmer test on LFAs,⁵³ commercial clinical translation has yet to be achieved.

Saliva-based sensors

Saliva presents a distinct set of physiological and engineering challenges and has been used for a while in psychological research.⁵⁴ While saliva is rich in biomarkers such as hormones, proteins, enzymes, and antibodies that are key in detecting and managing various chronic diseases such as diabetes, gout, CVDs, and neurological disorders, its viscous nature, variable flow rate, and complex oral microflora complicate microfluidic designs.⁵⁵ Circadian rhythm adds to the dynamic nature of salivary-based biomarker concentrations. Systems designed for continuous salivary monitoring must deal with reduced sensing performance due to the accumulation of salivary proteins, such as mucin, enzymes such as amylase, lysozyme, oral bacteria, along with food debris, which ultimately leads to device failure due to biofouling.⁵⁶

Given these challenges, saliva-based monitoring has pivoted toward point-of-care, intermittent monitoring platforms that prioritize ease of use, portability, and rapid detection over continuous data acquisition. These include LFAs,⁵⁷ mouth-guard-integrated sensors,⁵⁸ and pacifier-based platforms.⁵⁹ One study focused on developing a pacifier-based salivary sensor for determining dehydration in neonates by monitoring electrolyte levels (Na^+ and K^+),³⁹ as shown in Figure 3C. As proof of concept, the electrolyte readings of the sensor were compared to blood samples taken from the neonates' feet. The results demonstrated that the pacifier sensor tracked electrolyte concentrations within healthy physiological ranges and showed strong correlation with blood-based measurements, highlighting the promise of pacifier-integrated platforms for non-invasive salivary diagnostics.

Regarding LFA tests, clinical studies detecting COVID-19⁶⁰ biomarkers have been reported. For detecting COVID-19 biomarkers, researchers focused on developing a dual lateral-flow device that combines gold-nanoparticle-labeled anti-human immunoglobulin A (IgA) for colorimetric detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific IgA coupled with a chemiluminescent substrate to achieve a higher sensitivity in saliva samples.⁶⁰ The addition of this substrate directly onto the test and control was done to reduce the signal-to-noise ratio and assay time to just 15 min. For its clinical proof of concept, samples from four COVID-patients were analyzed and used to determine IgA. The platform was able to detect salivary IgA in three out of four patients' samples, including those with low serological responses, underscoring

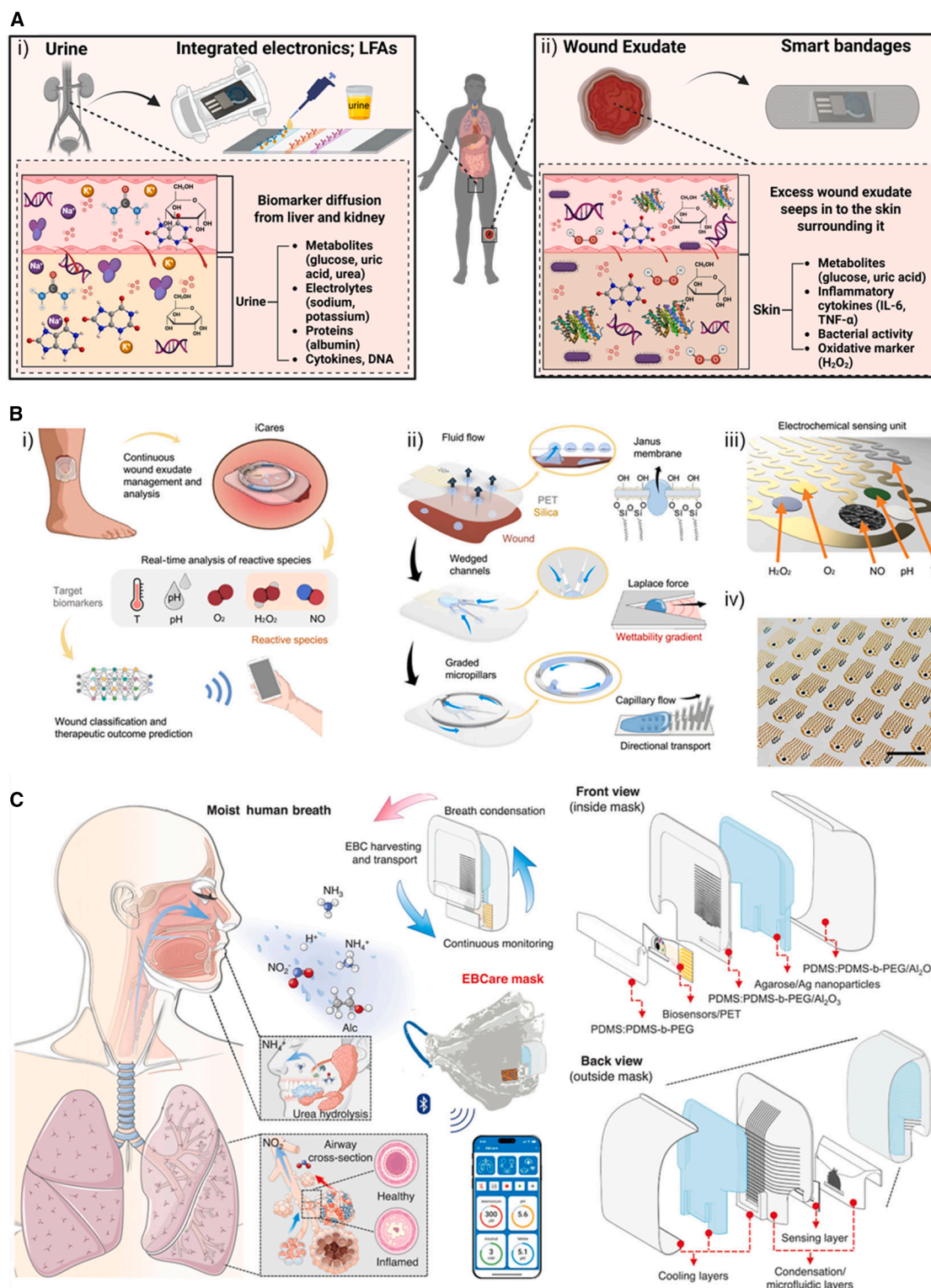


Figure 4. Alternative body fluids for chronic disease management

(A) The key biomarkers and the partitioning mechanism in key alternative body fluids such as (i) urine and (ii) chronic wound exudates for chronic disease monitoring and management. Figure created using [biorender.com](https://www.biorender.com).

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the performance of this device. However, the device also demonstrated high false-positive rate for serum IgA levels, indicating that the system still requires further improvements to improve its clinical utility.

Engineering and translational challenges of urine-, wound-, and breath-based sensors

Urine, due to ease of sample accessibility, low contamination during sample collection, along with higher analyte concentrations and simple-collection mechanism, is a strong candidate for non-invasive disease management (Figure 4Ai).⁶¹ Urine is useful for monitoring health in neonates, the elderly, and individuals who require long-term care (in comas, restricted to bed rest) by utilizing a catheter to monitor kidney functions of the patient, track their metabolic activity, and personalize treatment protocols based on these trends. However, the long-term use of urethral catheters is not conducive to sustained patient care due to the risk of biofilm formation, which can lead to recurrent urinary tract infections and other complications.⁶²

Sensor-integrated diapers have emerged as a non-invasive alternative, enabling continuous monitoring of urinary biomarkers without compromising patient comfort or increasing infection risk and have been used to monitor biomarkers such as albumin, creatinine, electrolytes (Na^+ , K^+ , Cl^-), and glucose.⁸ Several sensor designs have shown promising potential for urine-based disease management.^{65–67} Factors such as intermittent urine production and being a reservoir with changing hydration status, uneven sampling, and the accumulation of high concentrations of proteins, lipids, extracellular DNAs, and polysaccharides on sensor electrodes leads to biofouling and reduced performance, which have ultimately hindered their integration into the clinical workflow.⁶⁸

Researchers developed a self-locking expansion valve using superabsorbent polymer; the valve inlet remained open when the diaper was dry and, during urination, the valve would gradually close, allowing precise sampling.⁶⁹ The system monitored glucose and uric acid, along with a portable device that transmits data via Wi-Fi. Urine samples from participants ($n = 5$) were collected at five different time points that included premeal and postmeal glucose and uric acid level readings compared to serum levels. The system showed a coefficient variation of 3.06% and 5.45% for glucose and uric acid, respectively. Furthermore, the system accounted for both male and female anatomy, indicating the potential of this system for urine-based monitoring.

Wound exudate

Wound exudate supports monitoring wound healing due to its availability and rich biochemical content, which is directly associated with systemic inflammatory processes such as interleukin-6 (IL-6), oxidative stress markers such as hydrogen

peroxide (H_2O_2), oxygen (O_2), nitrogen oxides (NO), and metabolites such as glucose and uric acid, as illustrated in Figure 4Aii.⁷⁰ The fluid has shown promise in managing chronic conditions in patients suffering from diabetic-related chronic wounds due to high blood sugar levels, leading to poor blood circulation, nerve damage, and an impaired immune system. Various challenges, such as changes in biomarker composition based on each healing stage, changes in pH and temperature, fluctuations in wound fluids, and the need for a highly moist environment to promote wound healing, act as roadblocks for developing systems for long-term continuous monitoring of wound exudate. An ideal sensor for monitoring this body fluid must be flexible, biocompatible, have breathability, able to remove wound exudate, and offer protection against secondary infection.⁷¹

To this end, a wearable sensing device called iCares demonstrated that it could collect precise quantities of wound fluid released by the body for multiplexed sensing of oxidative stress markers (H_2O_2 , NO, and O_2), pH, and temperature required for real-time wound monitoring and management, as shown in Figure 4Bi.⁶³ To ensure precise sampling, the device utilizes a microfluidic module consisting of a superhydrophobic-superhydrophilic Janus membrane with bioinspired wedge channels for efficient exudate collection, transport, and refreshing with a unidirectional flow (Figure 4Bii). To ensure long-term continuous monitoring, the multiplexed sensing system was integrated onto a single printed circuit board and encapsulated using medical-grade PDMS due to its compatibility with wound-dressing applications, as shown in Figure 4Biii. Importantly, the entire device was fabricated using established manufacturing approaches, such as laser patterning and advanced printing techniques, highlighting its potential for scalable and up-stream manufacturing (Figure 4Biv).

A clinical trial involving participants with chronic wounds ($n = 20$) was considered, out of which two participants had their chronic-wound fluid measured before and after surgery. For the patients who underwent surgeries, their levels were monitored 7 days before the surgery and $\sim 7/14$ days after surgery for 90 min to assess biomarker concentrations. The results showed that the system was able to detect biomarker concentrations; however, factors such as age of the patient and diabetic progression can affect these biomarkers and contribute to the time required for the wounds to heal. For clinical adoption, the platform will require extensive validation, as current correlations between biomarkers and wound status remain preliminary. Although flexible, the device cannot accommodate wounds with varying depths or irregular contours, limiting its practical applicability. Incorporating therapeutic functions could further enhance patient outcomes and overall utility. Addressing these limitations over time may ultimately enable a fully integrated,

(B) The development of a smart sensor for monitoring chronic wound exudate.⁶³ (i) Schematic of the iCares sensor system for multiplexed detection of key biomarkers for wound healing, with ML integration for understanding which biomarkers are essential for classifying wound healing status. (ii) The development of the superhydrophobic-superhydrophilic Janus membrane with the wedge channels for efficient collection, transport, and sample refreshing of the chronic wound fluid. (iii) The electrochemical sensing unit of the iCares device along with the ability to mass produce these sensors using inkjet printing.⁶³ Reproduced (adapted) with permission, copyright 2025, Science.

(C) Schematic illustration of the development and architecture of the EBCares smart mask for harvesting and analysis of EBCs in real time.⁶⁴ Reproduced (adapted) with permission, copyright 2024, Science.

closed-loop system for personalized wound monitoring and management.

Exhaled breath analysis

Exhaled breath and its condensates represent a rich, underutilized biological matrix for continuous, non-invasive monitoring by offering real-time insights into systemic and pulmonary physiology. Their potential for monitoring chronic diseases lies in their ability to reflect metabolic, inflammatory, and oxidative stress markers that are key for monitoring diseases such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, and cancer.⁷² By leveraging these insights, face-mask-integrated sensors can provide real-time information on wearers by analyzing their respiratory patterns and harnessing these molecular condensates. The main challenge lies in the inability to harvest these exhaled breath condensates (EBCs) without using a commercial condenser in tandem with laboratory-grade mass spectroscopy machines.

To overcome this shortcoming, researchers proposed and developed an EBCare mask-based device, as shown in Figure 4C.⁶⁴ To showcase the EBCare's potential, a clinical trial consisting of five healthy participants, 12 participants who were newly recovered from COVID-19, 10 individuals who were smokers, nine patients with COPD, and 10 patients with asthma were considered, and they were monitored over a 12-h window. The results demonstrated that the EBCare device effectively captured dynamic fluctuations in key biomarkers from exhaled breath, reflecting the user's physiological condition and highlighting its potential for personalized health monitoring and real-time disease tracking.

To address factors such as unstable moisture harvesting and short sensor lifespan of the EBCare system, researchers proposed the development of EBClite, a newer battery-free mask capable of multiday biomarker tracking with lactate as the target analyte.⁷³ The system consists of a porous polyacrylamide hydrogel doped with a hygroscopic salt, namely lithium chloride, to improve the moisture retainability and improve condensation efficiency of the system while maintaining structural integrity of the system over repeated wet-dry cycles. To make the device battery free, the authors integrated quasi 2D-perovskite solar cells, with a bent geometry and power conversion efficiency of 30%, which was sufficient to support sensor operation and device communication.⁷⁴ The sensing module included an enzymatic recognition element embedded into a matrix of chitosan-albumin to withstand the wet-dry breathing cycles while maintaining the enzyme activity for multiday testing. On-body analysis consisting of a cohort across different age ranges ($n = 10$, ages 20–65 years) and tracked lactate levels during different low- and high-intensity exercise sessions. The results demonstrated that sensors were able to monitor lactate levels of each individual with high temporal resolution while also accounting for the interindividual variability. To evaluate the EBClite robustness for multiday monitoring, the module was worn by the participants for 4 days and their lactate levels across different day-to-day activities were monitored. The results demonstrated that the system changes in lactate levels detected by the system were consistent with changes in lactate levels under different physiological condi-

tions, highlighting the potential of this system for long-term monitoring.

Implications of body-fluid choice in chronic disease monitoring

As shown in the above sections, no single body fluid is universally optimal for longitudinal monitoring; rather, suitability is context dependent on whether the primary objective of tracking key biomarkers is for systemic trends, localized pathology, or therapeutic response over time. Peripheral and alternative body fluids all differ in their biological origin, transport mechanism, biochemical composition, accessibility, and temporal fluctuations.^{7,16} A meaningful comparison across different body fluids should not be framed as a single “best-performing” medium but as a design trade-off that links device location and biomarker transport pathway from body fluid of choice to achieve optimal sampling rate, signal stability, biomarker correlation, and clinical interpretability.

For systemic longitudinal monitoring, ISF offers the closest physiological relevance to blood and is well suited for continuous tracking of metabolic trends when paired with minimally invasive MN-integrated patches. The key trade-off is that continuous ISF monitoring relies on repeated/prolonged penetration of the dermis (skin), which introduces user discomfort and localized tissue inflammation that may affect signal stability and skew biomarker concentration over time.¹⁶ Sweat, saliva, and tears support non-invasive sampling and are well suited for integration with microfluidic-based sensing platforms. However, their applicability to longitudinal monitoring is fundamentally constrained by secretion-rate variability, circadian rhythms, and hydration status, while matrix complexity degrades measurement accuracy. These factors complicate signal normalization, the establishment of standardized biomarker concentration ranges (e.g., healthy vs. diseased), and interindividual comparability.^{14,16,75}

In contrast, urine reflects accumulated excretory products, providing an episodic snapshot of physiological changes integrated over a defined time window. This characteristic makes urine more suitable for episodic assessment or frequent sampling in which disease-specific biomarkers are monitored for near-term clinical evaluation rather than for continuous or long-term trend tracking. Wound exudate represents a highly localized sensing environment that enables continuous or near-continuous monitoring of key biomarkers supporting longitudinal tracking of local disease progression and therapeutic response, albeit within a tissue-specific rather than systemic context. Challenges associated with wound-exudate sensing arise from confined sampling volumes, variable biofluid availability, and wound depth, all of which impose constraints on sensor performance and device integration.⁶³ EBCs offer a non-contact modality for monitoring volatile biomarkers over time, but challenges related to analyte specificity and baseline biomarker concentration variability stemming from inter and intra-individual physiology limit its quantitative reliability for longitudinal clinical monitoring.³ Taken together, Table 1 summarizes these longitudinal monitoring trade-offs by linking each body fluid to (1) its biomarker composition and transport mechanism, (2) compatible sensor archetype used to access these fluids, (3) key advantages and trade-offs, and (4) monitoring the objective it best

supports (systemic trends vs. localized pathology vs. disease-specific episodic monitoring).

Device classification and compliance for clinical use

Translation of sensor technologies into products requires an understanding of the regulatory pathways and compliance requirements. Sensor technologies for point-of-care applications are developed through either the technology-push approach, where innovations are created first and later aligned with clinical needs, or a market-pull approach, in which clearly defined clinical demands drive the development of targeted technological solutions.⁷⁹ As the demand for clinically relevant data, precision, and personalized healthcare continues to rise, there is a push to translate sensor technologies for healthcare settings. However, this push has led to high failure rates and frequent misclassification of devices regarding their intended use as diagnostics, monitoring, or wellness tools based on claims.⁸⁰ In the USA, the Food and Drug Administration (FDA) is the responsible regulator and, in the European Union (EU), several EU regulations come into play for regulatory approval, including the medical-device regulation (MDR) and *in vitro* device regulation (IVDR), which apply for both sensor devices and their software as a medical device, as most sensors need underlining software for signal and data analysis as well as interpretation.

Understanding the type of information a device provides to users is essential for correct regulatory classification, particularly when clinical claims are made. A recent example is the WHOOP lifestyle band, which was marketed as a wellness product yet advertised a “medical-grade” blood-pressure feature, a key diagnostic marker for hypertension. This claim prompted an FDA warning letter directing the company to either revise its claims or pursue appropriate clearance through the 510(k) pathway.⁸¹ This case illustrates that classification depends on stated claims and on whether device functions align with regulatory definitions. The FDA defines wellness devices as low-risk products intended solely to promote general well-being without diagnosing, monitoring, treating, or preventing disease and therefore subject to minimal regulatory oversight. However, the distinction between wellness and medical devices often blurs when functionality targets clinically relevant parameters. Devices that harness body fluids such as sweat, ISF, exhaled breath, and saliva, especially those measuring recognized clinical biomarkers, may trigger medical-device scrutiny depending on their invasiveness and intended use.⁸²

To understand how sensor technologies are regulated for clinical use, it is first important to know what qualifies as a medical device. The FDA defines a medical device as something that is intended to diagnose, monitor, prevent, or treat a disease. Because this definition is broad, the FDA groups devices by their level of risk, the way they work, and the type of clinical marker they measure. For example, a sweat sensor that measures electrolytes may seem low risk, but, because chloride is a key diagnostic marker for cystic fibrosis, the device is classified as a class II medical device, as illustrated in Figure 5.⁸³ Similarly, ISF-based glucose monitors are also class II, but they face stricter oversight because they are invasive and may pose long-term risks. These devices often require pathways such as 510(k), *de novo*, or pre-market approval depending on

what the company claims the device can do (see Table S1).⁸⁴ While regulatory pathways vary internationally, most follow a risk-based framework that considers device invasiveness and clinical purpose. For specific cases where the monitoring is in relation to high-risk chronic diseases such as CVDs or cancer, the regulations are escalated. It requires defining their clinical purpose, the patient group, and the stage of disease they apply to. This requires developers to understand the clinical need and basic medical terminology.⁸⁵

A clear understanding of basic medical terminology such as the difference between detection, diagnosis, and monitoring is essential when designing next-generation healthcare sensors and avoiding problems related to incorrect device claims. Detection devices can flag the presence of symptoms or abnormal signals, but they cannot confirm a disease. Diagnosis requires a device that can identify a medical condition, usually by meeting strict clinical accuracy standards. Monitoring devices track a patient’s health over time, often to guide treatment decisions or check disease progression. In clinical practice, both diagnostic and monitoring devices can inform therapeutic actions, such as starting or adjusting medications. In contrast, a detection-only device cannot trigger treatment on its own; it must be followed by an approved diagnostic test before any therapy is initiated. Although these device types work together within healthcare, they face different levels of regulatory scrutiny. Diagnostic devices require strong clinical evidence, comparison against gold-standard tests, and validation across large and diverse patient groups to ensure accuracy. Monitoring devices generally face fewer requirements, depending on how invasive they are and what they claim to measure. As sensing technologies evolve, regulatory frameworks must also adapt, updating classification rules and approval pathways to reflect the growing complexity and clinical roles of modern biosensors.

Integrating AI and ML

As regulatory frameworks evolve to accommodate the increasing complexity of modern biosensors, there is a parallel need for analytical frameworks capable of managing the scale, heterogeneity, and temporal dynamics of the data these devices generate, particularly for long-term continuous monitoring. Single-analyte biosensing approaches provide limited physiological insight and are insufficient to capture the multifactorial and time-varying signatures associated with chronic disease, motivating a shift toward multiplexed sensing platforms. These high-dimensional datasets are often characterized by temporal variability, leading to false responses arising from lag effects; overlapping output signals; interindividual variability; and progressive loss of accuracy due to biofouling, changes in the interfacial chemistry, sensor aging, and dynamic changes in the local physiological environment, thereby challenging conventional analytical and computational approaches.¹³

AI and ML are increasingly being used to analyze the large and complex datasets generated by modern biosensors. These tools can detect anomalies, uncover hidden patterns, and improve sensor performance (Figure 6).⁸⁶ A recent study focused on how different factors such as diet, gut microbiome, sleep, exercise, and genetics can lead to type-2 diabetes in a cohort of 1,137 participants to study glucose spike, rather than relying

Table 1. Design and performance implications of body-fluid choice for longitudinal chronic disease monitoring

Body fluid	Biomarker transport mechanism	Biomarker composition	Device type	Key advantages	Primary design and translation trade-offs	Monitoring suitability
Sweat ^{7,14}	secreted from the eccrine glands and is influenced by thermoregulation	electrolytes (Na ⁺ , Cl ⁻ , K ⁺), metabolites (glucose, lactate, uric acid), hormones (cortisol)	Utilizes skin-mounted microfluidic integrated wearable devices	non-invasive sampling, useful for tracking multiple analytes simultaneously	variable secretion, biomarker concentration affected by hydration and environmental factors, normalization challenge due to interindividual variability	suitable for continuous contextualized metabolic monitoring
Interstitial fluid (ISF) ²⁹	biomarker diffuses through blood via capillary action	electrolytes (Na ⁺ , Cl ⁻ , K ⁺), metabolites (glucose, lactate, uric acid), plasma derived proteins (albumin, immunoglobulins, apolipoproteins), hormones and inflammatory biomarkers	utilizes MN-integrated patches	closest physiological relevance to blood; supports continuous monitoring; stable temporal dynamics	MNs are still invasive, can cause user discomfort; tissue inflammation from long-term wear, affecting biomarker concentration	systemic longitudinal monitoring; personalized metabolic trend tracking
Saliva ^{30,76}	glandular secretion with transport from blood via diffusion and active transport	glycoproteins (IgA), enzymes (amylase), metabolites (urea, glucose, uric acid) electrolytes (Na ⁺ , Cl ⁻ , K ⁺)	integrated electronic devices, LFAs, point-of-care test strips	ease of access, repeated sampling, and low user burden	matrix interference is high, circadian rhythm affects biomarker variability, hydration dependence	more suitable for frequent episodic sampling over continuous longitudinal monitoring
Tears ^{38,77}	biomarker diffuses via the blood-tear barrier and via local secretion through the tear ducts	metabolites (glucose, urea), proteins, electrolytes	soft materials based smart ocular lenses, LFAs	non-invasive sampling process, tightly controlled microenvironment	low volume; reflex tearing, wearability constraints	personalized short-term monitoring; more suitable for context-driven disease monitoring
Urine ⁶⁹	biomarker is excreted through the waste fluid which reflects cumulative metabolic activities	proteins, metabolites (urea, creatinine)	integrated electronics (e.g., sensors integrated into diapers)	non-invasive sampling, ease of access, and low user burden	sampling variability, dependent on hydration status, biomarker concentration is skewed due to dilution variability	suitable for context-drive disease monitoring and episodic monitoring
Wound exudate ^{63,70}	localized fluids from wound sites reflecting inflammation and tissue response	inflammatory and oxidative biomarker (IL-6, H ₂ O ₂ , O ₂), pH	integrated electronics (e.g., smart wound dressing, bandages)	supports continuous local monitoring; therapy response tracking	confined volume; biofluid variability; sensor design can be constrained by wound depth and placement	localized disease progression and therapeutic monitoring; not suitable for systemic monitoring
Exhaled breath ^{64,78}	gas-phase exchange via alveolar diffusion	volatile organic compounds (VOC) (e.g., ammonia, acetone), oxidative stress markers (H ₂ O ₂), and inflammatory markers (cytokines)	integrated electronics (e.g., sensors integrated into masks)	non-invasive sampling, rapid sampling, repeated measurements	low analyte levels; specificity challenges; interindividual variability	can be used for metabolic trend monitoring

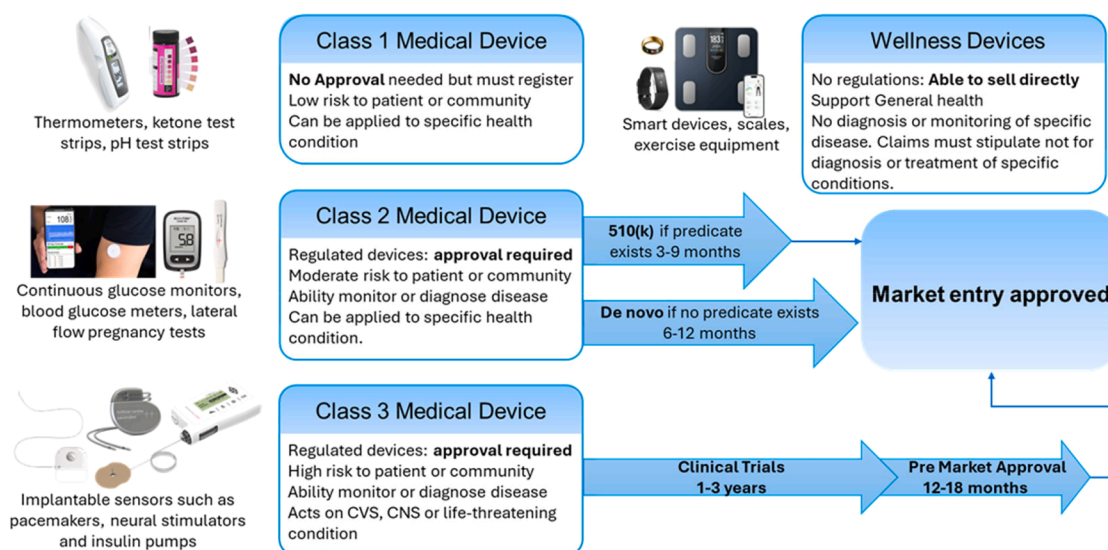


Figure 5. Schematic illustration of the device classification and compliance steps required for a product to be marketed as either a wellness or as a class 1, class 2, or class 3 medical device

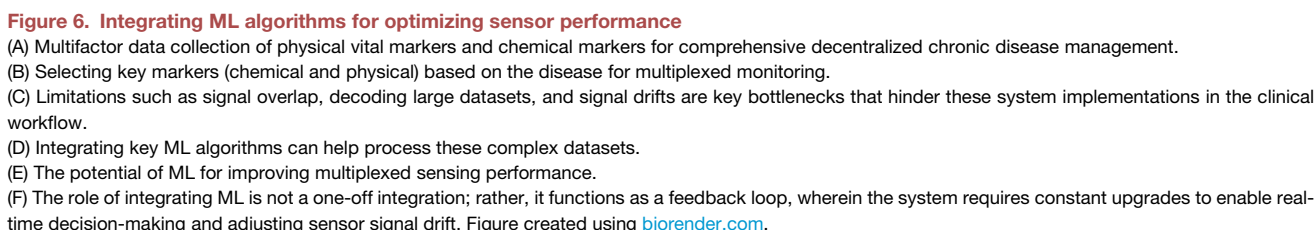
on the current clinical diagnostic assay (hemoglobin A1c [HbA1c] levels), which does not capture the complex nature of the glucose spike.⁸⁷ To assess such a large dataset and find correlations, the authors of this study relied on integrating multi-modal AI and ML with statistical analysis to formulate glucose-spike metrics, correlation between the multimodal factors, and its causes in glucose spike. By using this binary multimodal classification model, the system was trained to differentiate and separate normoglycemic individuals from individuals that are at risk of developing diabetes based on their day-to-day activities rather than just relying on HbA1c levels by pinpointing these behavioral factors, showcasing how ML and AI could be trained for early detection and intervention of chronic diseases. The role of AI and ML has been further utilized for precision medicine and monitoring by developing a closed-loop sensing system that can administer levodopa in real time for Parkinson's management.⁸⁸ To identify niche correlation and to discover biomarker correlation, studies combined supervised k-NN algorithm with unsupervised principal-component analysis (PCA) to identify unseen relations between key markers for contact dermatitis (CD) that arises due to direct skin contact with allergens and account for 90% of all occupational skin disorders.⁸⁹ The study was able to identify some key markers that could determine whether the skin inflammation arose from allergic CD or irritant CD, thus improving diagnostic accuracy and improving treatment protocols.

While AI/ML is utilized to improve biomarker correlation and health management, their impact on improving sensor performance is equal for translating these devices into real-world products. Beyond *post hoc* data analysis, AI/ML frameworks are now being adopted to address current sensing bottlenecks such as long-term signal drift, calibration instability, biofouling, accounting for lag time, and interindividual variability. Devices that focus on monitoring key biomarkers in peripheral body fluids often suffer from biofouling due to non-specific adsorption leading to

overlapping and distorted electrochemical signals that cannot be eliminated by simply changing the surface chemistry alone.

Introducing AI-driven multivariate analysis as a complementary feature can help improve target-specific signal response while suppressing false signals. A non-enzymatic, electrochemical, wearable sweat sensor for tyrosine and tryptophan monitoring suffered from overlapping electrochemical signals that limited real-time quantification.⁹⁰ Integration of a supervised k-nearest neighbor (k-NN) algorithm enabled separation of overlapping peaks and correction of local pH-induced signal distortions, allowing accurate real-time detection of both biomarkers. Sensor outputs showed strong agreement with laboratory-based high-performance liquid chromatography (HPLC) measurements, achieving correlations (r^2) of 0.98 for tyrosine and 0.988 for tryptophan, highlighting the role of AI-assisted signal processing in enhancing wearable sensor performance.

Environmental variation and biological matrix effects remain a dominant roadblock for continuous monitoring of metabolites. Static calibration approaches fail to account for time-dependent variations, leading to progressive drop in accuracy. ML-based adaptive models such as self-calibrated biosensing platforms that utilize deep learning in conjunction with convolution neural network models have been shown to improve the sensor's accuracy of determining sweat glucose, Zn^{2+} , and Ca^{2+} levels secreted from six participants (three male and three female) with ~91.7%–97.2% accuracy when benchmarked against participants' sweat samples using UV-visible (UV-vis) spectrophotometry, effectively demonstrating the role of ML.⁹¹ Researchers demonstrated that theory-guided ML models can extract accurate analyte concentrations from early transient responses rather than relying on steady-state data acquisition.⁹² By combining their ML model with algorithms such as support vector machines, gradient boost, random forest, and decision trees, they achieved prediction accuracies, precision, and recall of ~93% while reducing the data



Translating these devices for real-world applications accounting for interindividual variability in physiology, body-fluid composition, and body-sensor coupling adds to the challenges for a unified population-averaged calibration strategy. AI-enabled personalization approaches address this issue by learning user-specific baselines and response patterns over time to improve classification reliability and maintain consistent performance across heterogeneous devices and users.⁹³ The authors of this study tested over 200 devices for accurate detection of

As multiplexed sensing platforms are integrated into chronic disease management, ML-driven analytics will be essential

not only for interpreting dynamic biomarker fluctuations but also for enabling real-time, adaptive clinical decision-making. Despite rapid advances in algorithms, distinguishing clinically meaningful signals from transient interference remains a major challenge, largely because many models are trained and validated on synthetic or controlled datasets. Rigorous validation through high-quality prospective studies is therefore critical to establish reliable, adaptive AI systems capable of addressing the physiological complexity and heterogeneity inherent to chronic disease.¹²

Conclusions and outlook

Despite rapid academic progress in wearable and body-fluid-based sensing, translation into clinical use remains limited. Only a small number of devices, most notably CGM systems and selected sweat-based hydration tools, have achieved widespread adoption.⁹⁴ The gap is driven by insufficient clinical validation, limited long-term stability, and incomplete integration into clinical workflows. However, current-generation body-interfaced sensors face further issues such as limited long-term performance and stability and inefficient power and data management over a longer period, hindering their translation.⁹⁵ Addressing these challenges will be key to unlocking their large-scale clinical impact.

Biomarker correlation in body fluids versus blood

Establishing a reliable correlation between biomarkers in body fluids and those in blood remains challenge for the acceptance of minimally invasive sensor platforms. This requires measurements in healthy individuals for the generation of normative data but for diseased patients with, for example, atherosclerosis, where biomarker diffusion from blood into tissue can be restricted. Although sweat, saliva, ISF, and tears offer promising avenues for decentralized, real-time monitoring, factors such as circadian rhythm, uneven fluid production, hydration status (saliva, tears), and individual physiology add to the dynamic variability of biomarker concentrations in these fluids.⁹⁶ For continuous monitoring, it is important to compensate for the time lag that results as biomarkers diffuse into these body fluids from the bloodstream, as this can also affect concentration, leading to interindividual variability making standardization a challenge.³⁸

Stimulation methods used for artificial secretion also impact biomarker concentration and composition of the fluid. For instance, sweat varies based on whether it is induced naturally or using techniques such as IP. Saliva samples collected via buccal swabs or through passive drooling, depending on the time of the day, may lead to changes in biomarker concentrations.⁹⁷ Similarly, fluctuations are seen in ISF and urine, depending on the time of the day, and in chronic wound exudate based on its healing stage. Currently, most devices are primarily designed for long-term, longitudinal monitoring aimed at personalization, trend detection, and disease management rather than acute clinical intervention. In this context, lag time between blood biomarkers and their appearance in peripheral body fluids has not been a limiting factor, provided temporal trends and relative changes are preserved.

However, as sensor data are integrated into the clinical workflow, accounting for biofluid-specific lag and rapid response time becomes critical for monitoring and detecting acute conditions

such as hypoglycemia, epileptic events, or acute heart failure. This temporal lag is dictated by the transport pathways and the diffusion mechanism for different body fluids. For instance, biomarkers in sweat have a typical delay range from 3 to 30 min, depending on the type of analyte, the sweat rate, and the sampling method, making real-time sweat sensing and intervention a challenge. Biomarkers such as cortisol typically have a lag time of 8–16 min,⁹⁸ while lactate may have lag time of 12–31 min, and these reference ranges are heavily dependent on the activity during which the sweat sample is being collected.⁹⁹ Accounting for these variations adds complexity to developing a device suitable for rapid clinical decision-making, underscoring the need for clear contextualization of lag time across body fluids, and the challenges associated with it have been summarized in Table 2.

Improving sensor performance

Next-generation sensors must demonstrate durable performance under physiological conditions.^{24,36} This entails robust antifouling strategies tailored to the biochemical composition of each fluid, long-term calibration stability, and power architectures that support multiday operation without user intervention. Bench testing should increasingly mirror clinical reality, including variable temperatures, motion artifacts, and complex biofluids rather than ideal laboratory conditions.

Wearable sensors for continuous monitoring will require the development of breathable, flexible, and stretchable units to allow applications such as monitoring wound healing that may have different depths and irregular contours. For long-term continuous monitoring in fluids such as sweat and ISF, substrates used to house the sensor device must be biocompatible and mitigate issues such as skin irritability and hypoxia.¹⁰⁷ Novel bioreceptors (e.g., aptamers, enzymes) used for sensitive and selective detection of analytes must undergo modifications to improve their performance in complex settings.¹⁰⁸

Biofouling remains a major hurdle for implementing long-term sensors in the clinical workflow.⁶⁸ Each body fluid of interest contains a unique mix of proteins, salts, enzymes, and other biomolecules that lead to biofouling. For instance, sweat is rich in electrolytes, and this salt content can lead to bacterial growth and salt crystallization, especially in humid and warm conditions, leading to biofouling,¹⁰⁹ whereas saliva consists of enzymes, mucins, and a diverse microflora that contributes to biofouling.⁶⁸ It should be noted that anti-biofouling strategies would depend on the body fluid of choice; for instance, sweat-based sensors would need to integrate strategies such as ion-repelling surface, salt-tolerant hydrogels, and breathable membranes, while tear, saliva, and ISF-based devices would require zwitterionic coatings, hydration layers to repel proteins, and nuclease-resistant coatings (to reduce sensing-element degradation).¹⁶

Another limiting factor is power management, wherein limited battery capacity, energy-intensive data transmission, and bulky electronics make 24/7 monitoring a challenge. These constraints have limited the clinical adoption of wearable sensors for long-term continuous monitoring. Solutions such as utilizing either enzymatic biofuels or solar cells have demonstrated the potential of making the device self-powered, but these require further upgrades, such as improving energy-conversion efficiency to improve their life cycle.^{24,26}

Table 2. Lag time implications and compensation strategies

Body fluid	Lag time relative to blood	Key factors influencing lag	Possible compensation strategies	Implications on biomarker monitoring
Sweat ^{98,99}	~5–30 min	variability in sweat rate; hydration status; physical activity; environmental conditions	context-dependent normalization and baseline corrections (e.g., accounting for physical activity/temperature variations/hydration status) when developing the reference range for biomarker concentration	suitable for developing long-term continuous longitudinal monitoring; not suitable for acute disease monitoring or intervention
ISF ^{33,100,101}	~5–15 min	capillary diffusion; tissue perfusion; increased skin temperature changes capillary diffusion	utilizing mathematical modeling for predictive analysis during interpretation for lag between blood and ISF; patient-specific lag time calibration (e.g., using CGM)	suitable for near-real-time longitudinal-trend monitoring with the potential for acute biomarker change intervention, provided lag time is accounted for
Saliva ^{102,103}	~5–15 min	saliva flow rate; circadian rhythm; oral activity and hydration status; size of biomarker (e.g., metabolites/proteins) influences the delay	time window averaging; accounting for circadian rhythm for baseline adjustment	suitable for episodic biomarker monitoring and disease-specific monitoring
Tears ³⁸	~5–20 min	hydration; tear turnover reflex secretion; individual physiology	personalized baseline calibration; trend-based relative interpretation using mathematical modeling	suitable for longitudinal monitoring for personalized trends, not suitable for acute disease intervention
Urine ¹⁰⁴	~1–6 h	depends on the renal function; hydration; voiding frequency; variability in sample volume	time-stamped episodic sampling; normalizing sample testing volume; utilizing sequential sampling and early-time points to predict biomarker trend	episodic or frequent assessment rather than continuous tracking for disease-specific monitoring and not for acute diseases
Wound exudate ^{70,105}	>30 min	wound depth; exudate volume; local inflammatory state	developing a mathematic model that accounts for wound depth for baseline referencing; continuous intra-wound trend comparison	suitable for localized pathology and therapeutic response, rather than systemic monitoring
Exhaled breath ^{78,106}	~ seconds to hours (highly variable)	depending on the type of biomarker, the time taken for diffusion can vary; ventilation rate and metabolic state can affect the variation	breath-cycle standardization; multi-analyte pattern recognition	can be used for longitudinal trend monitoring on how VOC concentration changes based on metabolic activities

From correlation to clinical relevance: Defining statistically meaningful performance

Most wearable biosensor studies in the literature report correlation between biomarker concentrations measured in body fluids and blood, and they commonly express their agreement in terms of linear regression (r^2 or r). Although these metrics are useful for proof-of-concept validation, they are derived mainly from studies that differ in sampling time, method of sample collection, normalization approaches, and cohort size and control for inter-individual variability.⁷ As a result, reported correlations cannot be used interchangeably between different studies, nor should they be assumed to reflect clinical equivalence between body-fluid and blood measurement.¹¹⁰ In most cases, these results reflect the ability of the device to track the dynamic changes in

concentration under controlled conditions without accounting for systemic bias or robustness of the cohort. Consequently, reliance on these correlation coefficients generated from sensing devices focused on personalization is insufficient for defining clinical applicability specifically for integration into the clinical workflow and decision-making.

To strengthen the translation capabilities, future validation must consider adopting a limited set of standardization, context-dependent statistical criteria that can differentiate trend-based monitoring from clinically actionable datasets. Regression-based analysis (r or r^2) still remains the gold-standard statistical data for longitudinal and personalization-based analysis, wherein datasets with $r > 0.80$ – 0.85 are sufficient for capturing meaningful trends.¹¹¹ However, for clinical decision-making or for potential

therapeutic adjustments, agreement-based data analysis should be preferred. In this context, Bland-Altman analysis provides a more comprehensive benchmark, as it predefines the limit of agreement, minimal systemic bias, and confidence intervals of capturing at least 95% of measurements within clinically tolerated error margins for analytes of interest.^{112,113} Complementary analysis must also consider dynamic conditions to ensure temporal consistency during physiological fluctuations of the analyte rather than relying solely on steady-state comparisons. Establishing a statistical framework and case-specific validation thresholds will be essential for benchmarking across different studies, enabling reproducibility and evaluation for clinical-based decision-making.

Navigating translation and regulatory barriers for clinical adoption of biosensing devices

Regulatory bodies increasingly expect early engagement, defined intended end use, and clinical studies powered by decision-relevant endpoints rather than focusing on analytical performance alone. Early involvement of clinicians and regulatory experts is therefore critical. Comprehensive technical documentation, capturing design decisions, development data, and key performance indicators, is essential for regulatory approval and for maintaining device validation when manufacturing processes change. In the absence of this documented development history, regulators often require extensive additional clinical testing to account for environmental conditions, patient variability, and batch-to-batch performance. Verification and validation data, coupled with a clear risk-benefit analysis, are central to translating sensing technologies from bench to bedside.⁸

Biosensor commercialization must adopt a regulation-first strategy, ensuring that early designs and validation decisions align with at least one viable regulatory pathway. Without this, developers risk exhausting resources on technologies that must undergo redevelopment. Such misalignment frequently results in cost overruns during the regulatory phase, delaying market entry and commercial viability. Beyond approval, clinical adoption of wearable devices introduces additional regulatory and operational challenges. Data privacy, security, and usability depend on integration with clinical workflows, electronic health records, and hospital information systems, where interoperability remains limited.¹¹⁴ Although device-independent platforms are emerging to enable secure data streaming and third-party analytics within clinical environments, their implementation raises further considerations, including API accessibility, data governance, and competing commercial interests.¹¹⁵

Clinical adoption will depend on usability. Continuous sensing can intrude into daily life and, when poorly designed, often leads to user abandonment. Future systems must minimize user burden through intuitive interfaces, low-maintenance operation, and seamless integration with clinical information systems capable of supporting secure, high-frequency data streams. Equally important is the early and sustained involvement of end users including patients, clinicians, and caregivers as co-creators in the device design and evaluation to ensure technologies fulfill their intended purpose. Remote and home-based health sensing extends beyond hardware and software as it enters a patient's private space and may introduce discomfort or reduced adherence.^{8,12} Addressing design considerations along

with regulatory and technical requirements will be critical for durable clinical uptake.

The development of biosensing technologies capable of decentralized, continuous monitoring in peripheral body fluids marks a paradigm shift in chronic disease management. These devices have the potential to improve patient health and help us better understand how these diseases progress as well as how key biomarkers influence disease outcomes at all stages. By identifying these key nodes, clinicians can develop precision and personalized treatment protocols tailored to an individual's physiology and metabolic profile. Realizing the clinical value of body-fluid biosensing will require coordinated progress across material science, clinical research, data infrastructure, and regulation. The next phase should prioritize large, disease-specific validation studies, interoperable data architectures, and co-design with patients and clinicians. Only through such multidisciplinary efforts can wearable biochemical sensing become a routine component of chronic disease management.

ACKNOWLEDGMENTS

R.J.R., D.P.L., G.W.G., and S.M.S. acknowledge support from the Australian Research Council Research Hub for Molecular Biosensors at Point-of-Use (MOBIUS) (IH240100013). The ICN2 is funded by the CERCA programme/ Generalitat de Catalunya. The ICN2 is supported by the Severo Ochoa Centres of Excellence programme, grant CEX2021-001214-S, funded by MCIU/AEI/10.13039.501100011033. A.S. and F.G. acknowledge the Bill & Melinda Gates Foundation (Grand Challenges Explorations scheme, OPP1212574 and INV-038695). F.G. and A.S. also acknowledge Research England International Science Partnerships Fund (reference G08288) and Innovate UK BMC (reference PA2131).

DECLARATION OF INTERESTS

J.A.R. is a co-founder, consultant, and unpaid board member of Epicore Biosystems.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.device.2026.101214>.

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