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Perspective

State of Sweat: Emerging Wearable Systems for Real-Time, Noninvasive Sweat Sensing and Analytics

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ABSTRACT: Skin-interfaced wearable systems with integrated colorimetric assays, microfluidic channels, and electrochemical sensors offer powerful capabilities for noninvasive, real-time sweat analysis. This Perspective details recent progress in the development and translation of novel wearable sensors for personalized assessment of sweat dynamics and biomarkers, with precise sampling and real-time analysis. Sensor accuracy, system ruggedness, and large-scale deployment in remote environments represent key opportunity areas, enabling broad deployment in the context of field studies, clinical trials, and recent commercialization. On-body measurements in these contexts show good agreement compared to conventional laboratory-based sweat analysis approaches. These device demonstrations highlight the utility of biochemical sensing platforms for personalized assessment of performance, wellness, and health across a broad range of applications.

KEYWORDS: *health monitoring, wearable sensors, epidermal microfluidics, lab-on-chip, flexible electronics, biosensors, sweat analysis, eccrine sweat*

■ INTRODUCTION

The shifting paradigm in clinical practice to evidence-based care underscores the critical need for an expanded suite of capabilities for the rapid and continuous assessment of digital and metabolic biomarkers relevant to human health.[1,2] Traditional eminence-based approaches to patient care, which have relied on the informed opinions of medical practitioners for selection of a course of therapy, have yielded to evidence-based clinical strategies that employ quantitative metrics to inform therapeutic interventions and treatment efficacy.[3] Although recent studies demonstrate the power of this approach in assessing therapeutic benefit (e.g., surgical interventions,[4,5] off-label drug use[6−8]), evidence-based medicine remains, by nature, reactive—capable of supporting treatments for an active, symptomatic disease state. Extending evidence-based approaches that enable proactive interventions during periods of healthy living and early onset of disease requires the advent of new digital health tools and analytics that not only track physiological health status but also alert to subtle perturbations.

Skin-interfaced wearable systems offer multiparameter sensing capabilities to address these limitations by monitoring the diverse range of signals arising from natural physiological processes.[9] Novel instruments that track the biochemical (i.e., electrolytes, metabolites, hormones), biophysical (i.e., temperature, biopotentials, hemodynamics), and kinematic (e.g., movement, posture, gait) signals from the body provide critically valuable information about overall health status.[10] Conventional wearable systems support the quantitative assessment of select physiological parameters via wrist-worn (e.g., smart watches), chest-strapped (e.g., heart-rate monitors), and apparel-integrated (e.g., sun exposure monitors) device form-factors. Continuous glucose monitors (CGMs) have been commercialized and widely adopted, highlighting the enormous potential for real-time biochemical sensing of glucose levels for diabetics. For devices worn continuously, the ubiquitous nature of such systems can yield important health insights from a limited range of health markers.[11] Nevertheless, these conventional platforms typically lack the ability to noninvasively characterize multiple biomarkers and the underpinning metabolic processes essential to overall health.

Blood-based analysis is the primary approach to monitoring body chemistry via invasive sampling (blood draw) and expensive, centralized laboratory equipment.[12] Biofluids such as tears, interstitial fluid, and sweat are attractive alternatives

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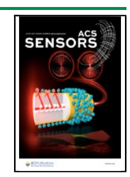

for noninvasive sampling and analysis.[13] Of these alternative biofluids, eccrine sweat is of particular interest[12,14] on account of the rich composition of biochemical information including micronutrients (electrolytes), metabolites, hormones, proteins, nucleic acids, and exogenous agents[15−20] and suitability for facile, noninvasive collection. Emerging classes of skin-interfaced wearable platforms harness recent advances in soft microfluidics, flexible/stretchable electronics, and electrochemical sensing technologies to support the continuous or intermittent assessment of sweat composition in a variety of conditions or settings.[15,21−24] The resulting time-dynamic insight these platforms offer into metabolic activity is critical for creating a comprehensive understanding of health, nutrition, stress, and wellness status.

This perspective offers an overview of the current state-of-the-art for wearable sweat biosensors, with particular emphasis on the application use cases for these sensors. The nascent field is of considerable interest with recent reviews[11,14,20,25−54] contextualizing the progress of wearable sweat sensors within the scope of skin-interfaced devices,[9,15,18,23,24,55] sensing technologies,[13,22,24,56−63] specific applications,[10,17,19,21,57,61,64,65] material systems,[66,67] and fabrication methods.[68] By contrast, this perspective highlights the most advanced translational embodiments spanning the fundamental use cases for these platforms in relationship to sensing targets. A short introductory section summarizes key considerations in terms of sweat collection and the sensing architectural constructs that form the foundation of these wearable systems. The section that follows broadly classifies the application targets according to athletic performance and clinical diagnostics with representative examples of the current approaches. The perspective concludes with a discussion of efforts to expand the overall utility of these sensors for diagnostic applications, in which clinical validation of sensor technologies will be critically important for commercialization.

■ SWEAT ANALYSIS: SAMPLING METHODS AND ANALYTICAL APPROACHES

Wearable, sweat-based platforms must address sweat collection for a diverse range of applications including passive sweat in fragile infants to intense physical exertion in athletes and warfighters. These sensors must function in arid, hot temperatures, under high humidity conditions, and even during aquatic activities. Across all use cases, these platforms must establish and maintain a conformal, intimate interface with the epidermis to support robust sweat collection and analysis. Soft, wearable microfluidic devices utilize biocompatible, low-modulus elastomeric (e.g., poly(dimethylsiloxane), PDMS) substrates and hypoallergenic silicone adhesives to support a robust, watertight interface for the pristine capture and clean storage of sweat. Activated eccrine sweat glands excrete sweat at a natural pressure sufficient to route sweat through networks of microfluidic channels and reservoirs.[69] As detailed in recent reviews,[15,24,43,45,62,70] the integration of optical (e.g., colorimetric,[22,71−80] fluorescent[81−84] assays) and electrochemical[22,23,30,45,85] sensors, either singularly or in tandem, enable quantitative analysis of sweat biocomposition. Constraints from operating conditions, body-interfacing locations, and time-dynamic biochemical variations in sweat composition necessitate sophisticated lab-on-chip design strategies to obtain high-quality measurements. These competing requirements define the chemical sensor performance specifications for precision, sensitivity, selectivity, operational stability, operational lifespan, methodology of data transfer, and power requirements.

Simple, adequate stimulation of sweat remains a longstanding[96] and significant[97−99] challenge for sweat-based analytical platforms. Intense physical activity, exposure to heat stress, and localized chemical inducement are the core methods for generating sufficient microliter volumes of sweat for biochemical analysis with suitability defined by target application.[16,100−104] Whereas exercise-based stimulation serves as the primary means for athletic performance monitoring[86] (Figure 1A), clinical diagnostics support on-demand analysis through the transcutaneous delivery of a cholinergic agonist via iontophoretic stimulation[87] (Figure 1B) to activate localized sweat glands. For a given sensing application, a key consideration in tandem with the mode of deployment (ambulatory vs stationary individual) is the dependence of both the rate of sweat production[105] and the biochemical composition[100,106,107] on the stimulation method. Additionally, these methods are not amenable to applications that require frequent, repeated stimulation events (as comparable to blood glucose measurements). Recent efforts to support daily health assessments demonstrate the potential for collection of sweat at a consistent flow rate[108] generated either during showering[88] (Figure 1C) or by natural perspiration processes[109−111] (Figure 1D). By virtue of the passive nature and circumvention of resource and exertion requirements, these alternative stimulation methods may significantly expand the breadth of potential applications for sweat analytics.

Emerging from early device designs[71] of simple networks of microfluidic channels and reservoirs, current wearable microfluidic platforms employ a suite of sophisticated design strategies to collect and route sweat. Valves are a key component to many fluidic platforms and thus permit the direct capture and routing of sweat from the epidermis to target regions of a device in a programmatic manner. Most demonstrations[90] (Figure 2A) are passive in nature (i.e., battery-free) relying upon fluidic resistance changes,[69] one-time chemical reactions (e.g., sodium polyacrylate, a superabsorbent polymer),[74] or surface functionalization (hydrophobic/hydrophilic surfaces)[112] to control fluid flow via a series of irreversible stop-points. A recent device embodiment[91] employs an active valve concept comprising the combination of thermoresponsive poly(*N*-isopropylacrylamide)-based hydrogel and wireless heating elements to enable dynamic control of sweat transport in response to physical actuation of hydrogel size (Figure 2B). These valve concepts offer nuanced control over fluid routing,[42] which is key both for accurate sensor performance and for correlating the time-dynamic response of sweat constituents to physiological parameters (e.g., mental state, physical activity). Valves are of particular interest for optical sensing approaches. Colorimetric and fluorescence-based sensors operate by reacting a defined sweat volume with a chemical or molecular assay to generate an optical signal proportional to target analyte concentration. Integration of networks of valves enable fully passive optical sensors to "chronosample" sweat[113] as described in Figure 2A, either in time or in fixed volumes, to provide quantitative measurements at defined intervals. By contrast, electrochemical sensors, typically employed for continuous sweat monitoring, require constant flux of sweat over the sensor surface to maintain analytical performance.[30,45,49,50,114] Integration of such sensors with networks

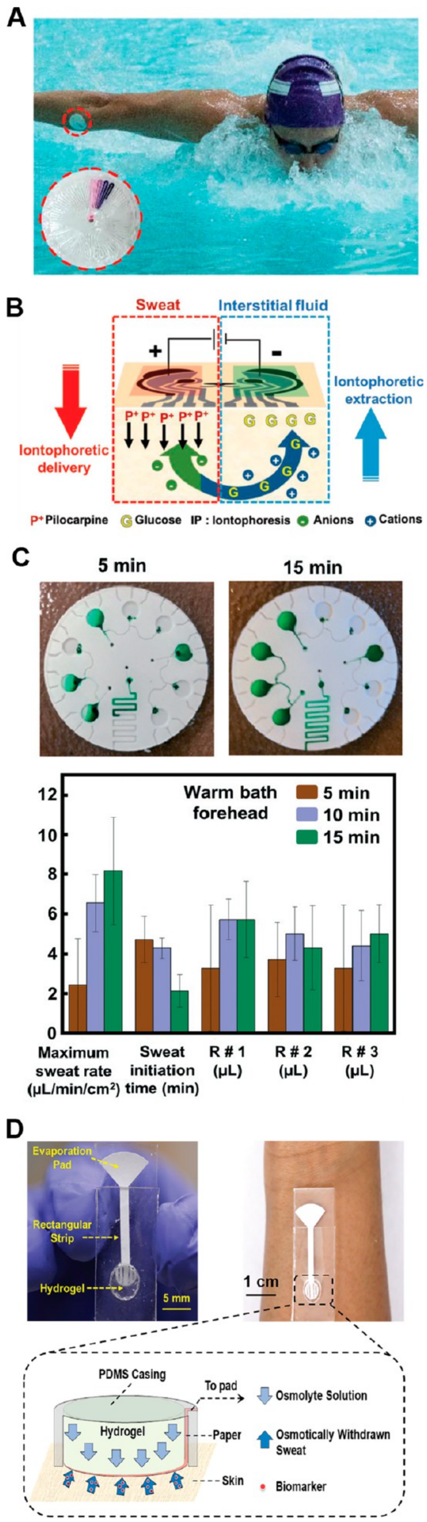

Figure 1. Methods for sweat stimulation. Typical methods for sweat stimulation include (A) physical activity[86] or (B) pharmacological stimulation.[87] Adapted with permission from ref 86, Copyright 2019 American Association for the Advancement of Science, and ref 87, Copyright 2018 John Wiley and Sons, respectively. Alternative approaches seek to collect sweat passively using (C) thermal stimulation via showering[88] or (D) wicking materials.[89] Adapted with permission from ref 88, Copyright 2019 The Royal Society of Chemistry, and ref 89, Copyright 2021 American Chemical Society, respectively.

of active or passive valves enables discrete activation of sensors, deconvolution of flow-rate effects, and programmed sensing at selected time intervals.

The expanding library of valving approaches, in combination with other emerging design concepts such as integrated mixing systems,[115] facilitates the development of devices capable of high-precision sensing of sweat biomarkers. Research efforts seek expanded sensing capabilities to support the long-term, real-time monitoring of sweat biomarkers in a battery-free manner. Use of smartphone-based image analysis offers a simple, direct mode for biomarker analysis;[75,86,88,116,117] however, this analytical pathway is ill-suited for assessing time-dynamic information in demanding applications (i.e., during active physical exercise). One recent embodiment[92] employs sweat-activated galvanic cells to serve as a series of "stopwatches" to establish time stamps for passive colorimetric measurements during an activity period (Figure 2C). Other approaches harness sweat-based biofuel cells[93] to generate sufficient power to record and store measurements from electrochemical sensors during an activity to be retrieved via a wireless data transfer at the conclusion of the testing period (Figure 2D). Implementation of such strategies[118−120] enables epidermal microfluidic devices to support multiple sensing modes (optical/electrochemical) in a battery-free form factor.

As described elsewhere,[9,13,15,16,24,55,121−123] eccrine sweat contains a wide range of metabolites, electrolytes, and xenobiotics that offer detailed clinical insight into disease states and valuable information regarding overall health. Many target sweat biomarkers are present only in extremely low concentrations.[20] Transduction of meaningful signals from these low-concentration species requires careful consideration of strategies to mitigate sample loss, biofouling of sensor surfaces, sample contamination, and deconvolution of interfering factors.[46] Optimizing device and sensor geometries yields powerful advantages in this context. Figure 2E highlights a recent strategy[94] to reduce sample loss from device deformation with a device construct that directly integrates impermeable, rigid channels within a soft, compliant polymer matrix. Resistant to deformation from physical impact, the optimized device geometry maintains a robust, conformal interface with the epidermis to support sweat collection and analysis. A similar approach[124] offers improvements to the robustness of integrated sensors such as in the utilization of novel material designs to circumvent biofouling on the surface of electrochemical sensors. Both examples reduce or eliminate interference effects for devices during operation; however, certain biomarkers (sweat chloride for cystic fibrosis) may require ex situ analysis necessitating consideration of external contamination factors. Eliminating operator interaction through utilization of custom extraction hardware[95] represents one such strategy for obtaining a "clean" sweat sample free of interfering contaminants (Figure 2F). In all cases, obtaining meaningful insight from wearable sweat sensors requires operational performance to remain invariant to external environmental factors.[13] To this end, recent efforts[125] seek to decouple target signals from interfering species, codependent biomarkers (e.g., pH, temperature), and other sources of noise (e.g., motion, biophysical signals). Further technical progress necessitates sophisticated sensing strategies and complex device designs to address these expanding challenges of sweat stimulation, fluid handling, and contamination. Such developments are critical for obtaining meaningful physiological insight from sweat in a variety of potential use cases.

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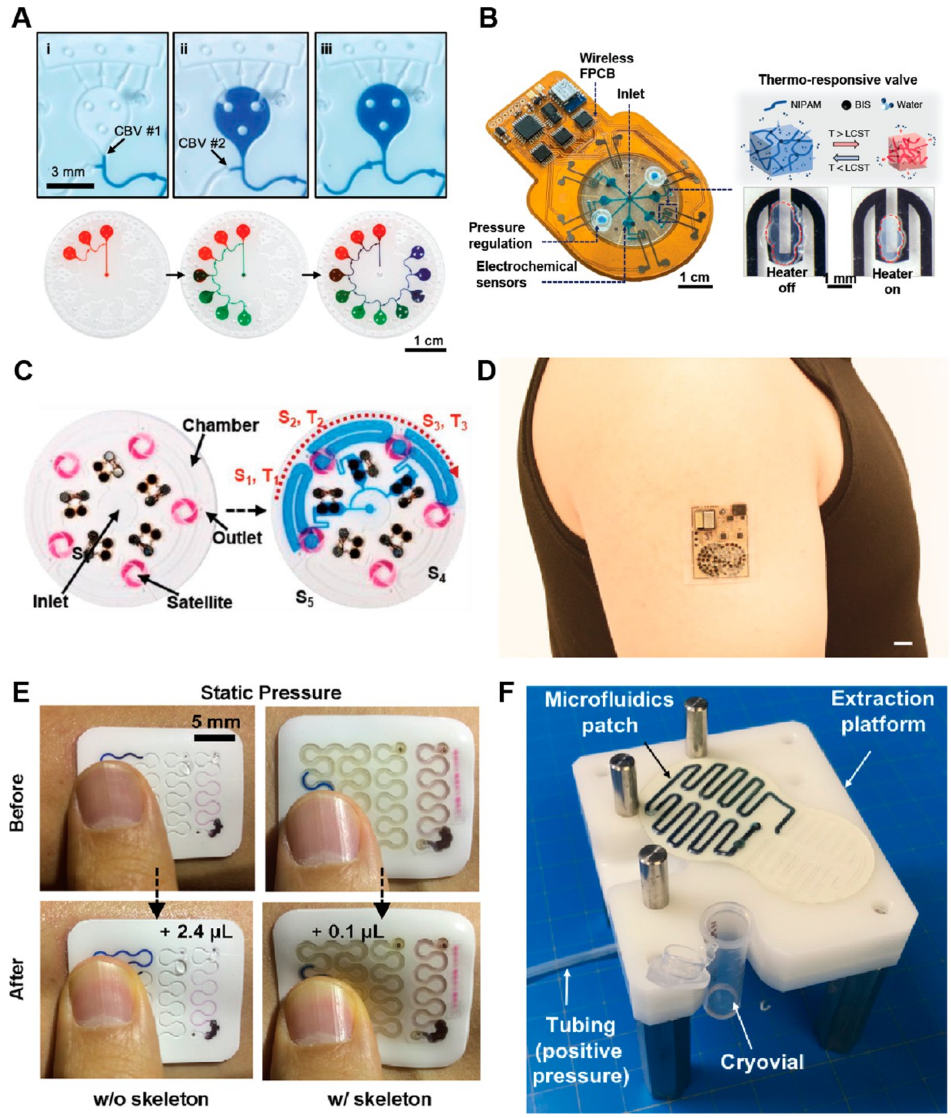

Figure 2. Technology foundations for wearable sweat sensing. Fluid Handling: networks of (A) passive[90] or (B) active valves[91] enable sophisticated routing of harvested sweat in a programmatic manner. Adapted with permission from ref 90, Copyright 2017 John Wiley and Sons, and ref 91, Copyright 2020 Springer Nature, respectively. Timing: nuanced designs integrate sensing features such as sweat-activated galvanic cells shown in (C) to enable temporal analysis of sweat constituents.[92] Adapted with permission from ref 92. Copyright 2019 John Wiley and Sons. In large arrays (D), such biofuel cells support battery-free electrochemical sensing of sweat.[93] Adapted with permission from ref 93. Copyright 2020 American Association for the Advancement of Science. Advanced designs. Optimization of mechanical properties (E) address sensing challenges in high-impact environments.[94] Adapted with permission from ref 94. Copyright 2020 John Wiley and Sons. Utilization of customized extraction hardware (F) assists in reducing sample contamination.[95] Adapted with permission from ref 95. Copyright 2021 Elsevier B.V.

Such considerations must occur in tandem to the demands imposed by application-specific requirements.

■ TRANSLATIONAL APPLICATIONS

Wearable platforms for real-time sweat analysis represent a significant advancement for providing personalized and actionable insights across a variety of applications spanning athletic performance to daily health monitoring. Integration of advanced sensors and fluid-sampling designs coupled with soft, flexible substrates establishes a powerful foundation for expanding the suite of biochemical markers and physiological signals accessible to the wearer. The sections that follow highlight emerging epidermal microfluidic devices broadly categorized by use for performance health management and clinical diagnostics.

■ PERFORMANCE HEALTH MANAGEMENT

Many commercial demonstrations of performance driven wearable devices have focused on monitoring physiological and biomechanical signals during physical activity.[131] Initially developed for professional athletes, wide adoption of fitness trackers over the previous decade illustrates the growing consumer interest in understanding the activity-dependent response of the human body to physical stress.[65] Such insight is essential for reducing the risk of injury, monitoring recovery times, and improving overall well-being. Although capable of assessing the core biophysical and kinematic signals for this purpose, these existing wearable platforms lack the sensing capabilities necessary to monitor metabolic health.[126] This section describes the latest representative skin-interfaced microfluidic devices deployed for ambulatory metabolic health assessment.

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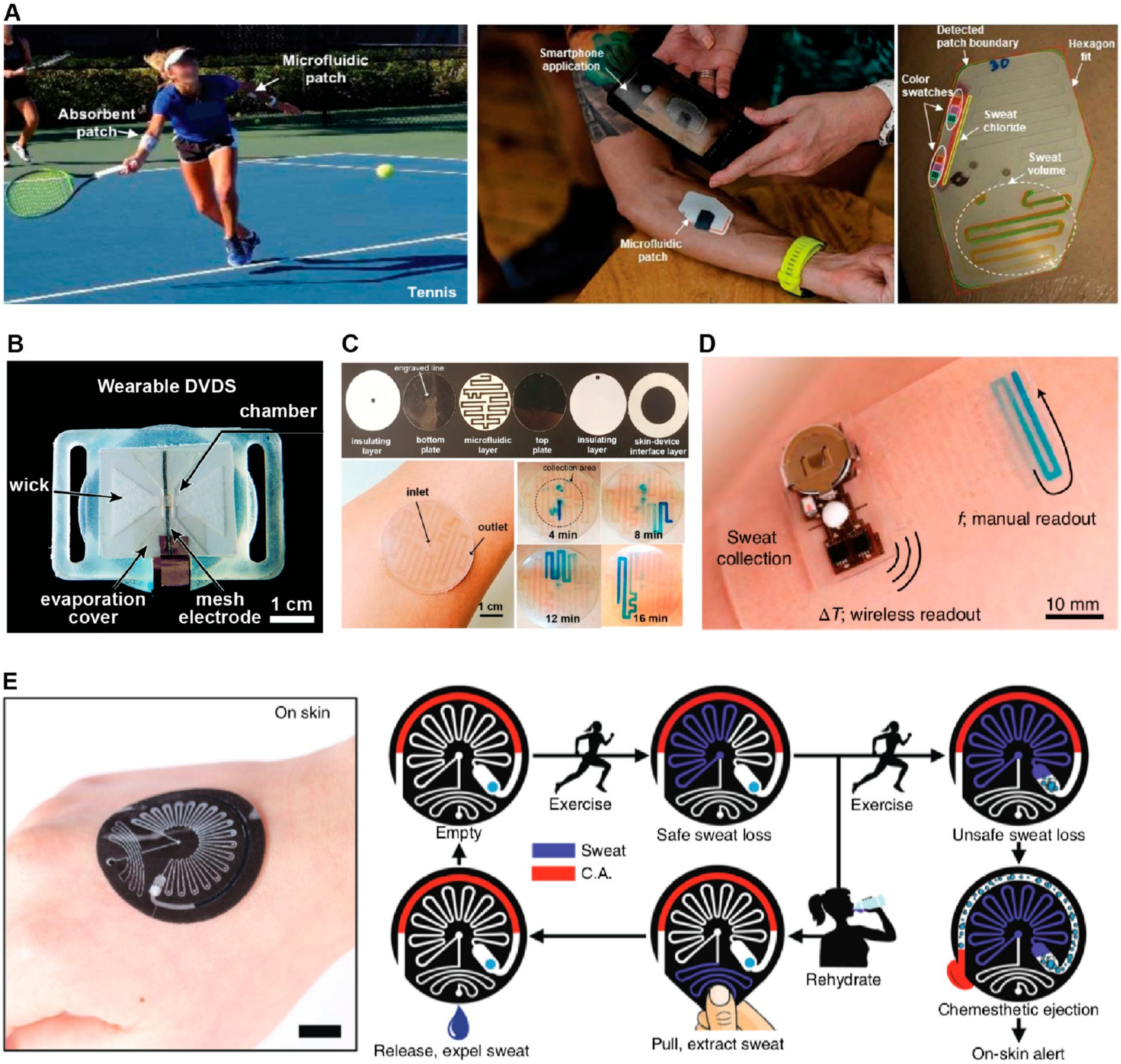

Figure 3. Performance health management. (A) A recent large-scale study validates the performance of a wearable microfluidic patch for estimating whole-body sweat parameters from regional sweat analysis.[126] Many sweat biomarkers exhibit a concentration dependence on rate of sweat loss. Adapted with permission from ref 126, Copyright 2020 American Association for the Advancement of Science. Recent embodiments utilize (B) conductivity,[127] (C) capacitive,[128] or (D) thermal[129] sensing strategies to continuously measure real-time sweat rate. Adapted with permission from ref 127, Copyright 2019 The Royal Society of Chemistry; ref 128, Copyright 2020 American Chemical Society; and ref 129, Copyright 2021 Springer Nature, respectively. (E) Emerging device architectures integrate chemesthetic sensors and user-activated valves to alert wearers to anomalous physiological conditions during exercise.[130] Adapted with permission from ref 130, Copyright 2019 Springer Nature.

Thermoregulatory sweat response is essential for maintaining homeostasis and gives rise to the loss of water, electrolytes, and other sweat constituents during physical activity.[102] Excessive total sweat fluid and electrolyte losses could impair cognitive and athletic performance or result in severe conditions such as heat stroke or death.[101] These effects manifest as changes in sweat parameters (rate, composition) and tend to vary widely across individuals.[100] Differences in physiology, training, activity type, physical intensity, and the surrounding environment necessitate personalized hydration strategies based on individual sweat profiles to ensure adequate fluid replenishment.[101,132] Practitioners and athletes typically estimate whole-body sweat loss by recording changes in body mass after physical activity.[103] This approach requires high-fidelity measurements through careful adherence to testing protocols and precise accounting of fluid intake and urine loss during the exercise period to obtain meaningful, albeit retrospective, insight. By contrast, regional sweat sampling estimates whole-body sweat loss by collecting sweat from a localized anatomical site via absorbent pads, filter paper, or plastic coils and specialized, wired equipment.[133] Although more practical, the absence of a standardized assessment

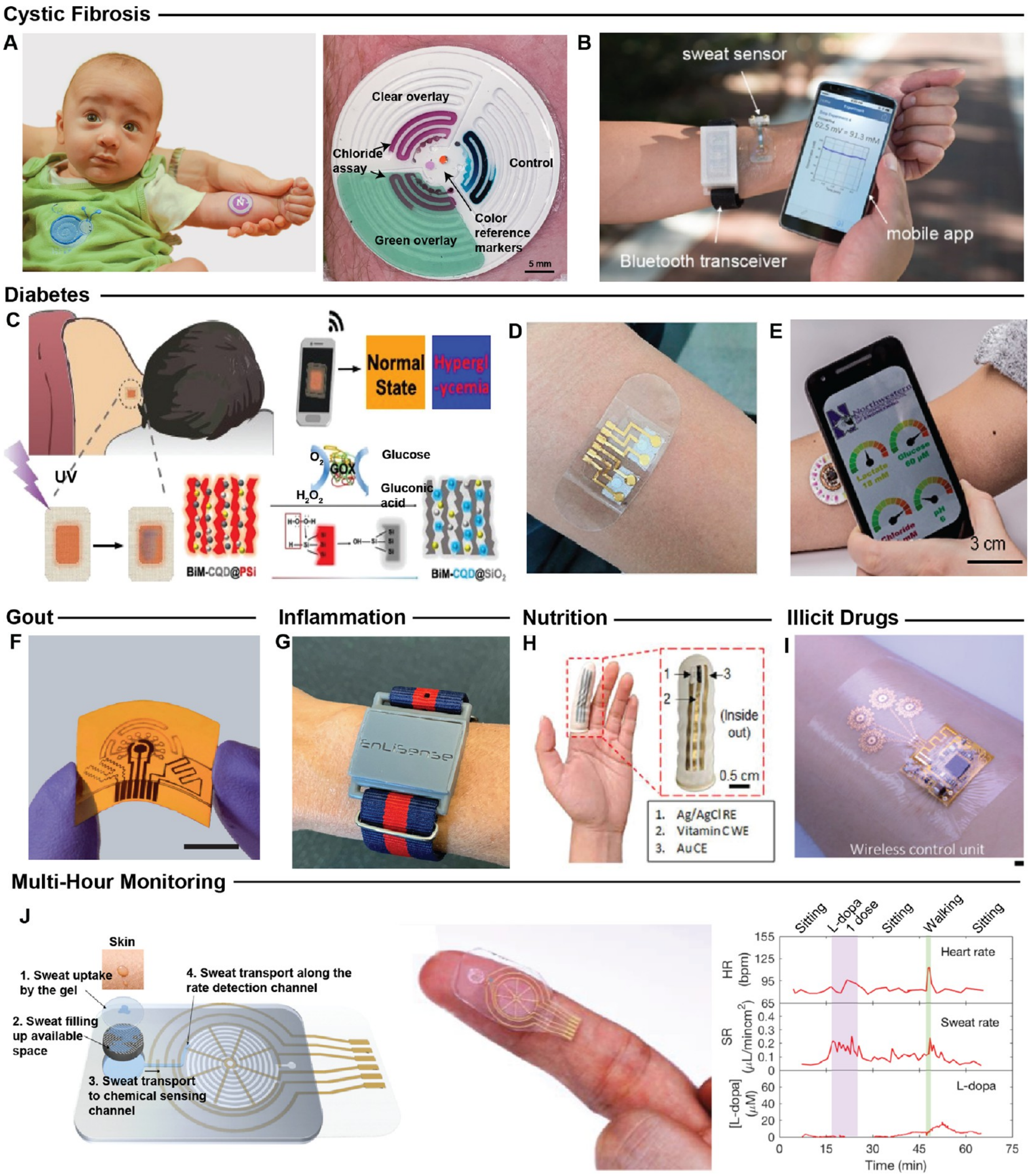

Figure 4. Clinical diagnostics. Sweat chloride: Sweat chloride is a longstanding clinically validated diagnostic biomarker used for confirmatory diagnosis of cystic fibrosis (CF). Recent reports demonstrate (A) the first large-scale study of a soft, flexible epidermal platform ("sweat sticker")[140] for clinical diagnosis and (B) the use of wearable sweat sensors for monitoring sweat chloride levels outside of clinical settings.[141] Adapted with permission from ref 140, Copyright 2021 American Association for the Advancement of Science, and ref 141, Copyright 2020 Springer Nature, respectively. Emerging sweat biomarkers: Use of sweat glucose as a noninvasive replacement for blood glucose monitoring in diabetes management is of academic and commercial interest with recent efforts demonstrating sensors for monitoring sweat glucose levels (C) at rest[83] and (D) during exercise.[111] Adapted with permission from ref 83, Copyright 2020 American Chemical Society, and ref 111, Copyright 2020 American Chemical Society, respectively. (E) One embodiment demonstrates glucose monitoring during exercise in a wireless, battery-free form factor.[116] Adapted with permission from ref 116. Copyright 2019 American Association for the Advancement of Science. Other targets of interest include the concentration of (F) uric acid in sweat[142] (for gout), (G) various cytokines[143] (inflammation, fever), (H) vitamins[144] (nutrition monitoring), and (I) illicit drugs.[145] Adapted with permission from ref 142, Copyright 2020 Springer Nature; ref 143, Copyright 2021 John Wiley and Sons; ref 144, Copyright 2020 American Association for the Advancement of Science; ref 145, Copyright 2021 American Association for the Advancement of Science, respectively. (J) Device designs exploiting wicking materials enable passive (i.e., absence of active sweating) multiparameter monitoring of disease biomarkers or the concentration of drug therapeutics.[146] Adapted with permission from ref 146. Copyright 2021 Springer Nature.

method has historically restricted the utility of regional sampling resulting in the generation of only limited physiological insight.

Epidermal microfluidic devices offer powerful capabilities for accurately monitoring sweat dynamics by virtue of the conformal, fluid-tight interface. These devices harvest sweat directly from sweat glands in a manner that isolates the sample from environmental contaminants thereby enabling precise, real-time characterization of sweat biomarkers. Although the performance of these sensing platforms has been extensively validated for a variety of biomolecular targets and sensor architectures,[23,43] there is an absence of studies correlating regional measurements from such wearable sensors and the whole-body sweat response. A recent report[126] (Figure 3A) represents the first large-scale systematic study ($N = 312$) correlating regional and whole-body sweat rate and sweat chloride measurements using a soft, flexible microfluidic patch. The device comprises two discrete networks of microfluidic channels which contain either an integrated colorimetric assay for quantifying sweat chloride concentration or a highly visible dye to facilitate the assessment of sweat volume. Use of a smartphone and companion app enables digital image capture and automated measurement of instantaneous sweat rate, sweat chloride, and total sweat loss. Contralateral comparisons of these epidermal microfluidic devices to absorbent patches in combination with whole-body sweat measurements in a controlled laboratory environment demonstrate good agreement between the predicted (from regional measurements) and measured whole-body sweat rate and sweat chloride concentrations (mean absolute error of 14% and 13%, respectively), which serves as the basis for actionable hydration feedback.

Establishing a strong correlation between regional and whole-body sweat-based measurements represents a key step for developing new insights into the physiological relevance of sweat biochemical signals. In addition to fluid and chloride loss, the concentration of glucose,[125,134] lactate,[135,136] ammonia,[137] and cortisol[138] in sweat has value for monitoring athletic training and conditioning. Varying dynamically with physiological status (diet, stress, overall health) and activity,[20] biomarker concentrations also correspond to dynamic variations in instantaneous sweat rate.[125,139] Recent efforts (Figure 3B–D) offer the requisite temporal resolution of instantaneous sweat rate to deconvolve this variability with real-time continuous sensing strategies. Representative devices integrate electrical conductivity[127] (Figure 3B), capacitive[128] (Figure 3C), or temperature[129] (Figure 3D) sensors with wireless data transfer and ultrathin batteries to support continuous monitoring of physiologically relevant sweat rates (0 to 5 μL min^{-1}). Conductive[127] or capacitive methods utilize electrode pairs embedded in microfluidic channels to measure the change in conductivity or capacitance across the channel as sweat fills. The conductive method comprises direct contact to sweat and electrodes, whereas the capacitive method relies on noncontact measurement of sweat fill into the device. An alternative noncontact approach measures real-time sweat flow rate using a localized heater embedded between two thermistors. This design architecture can quantify flow rates with high sensitivity and without direct contact within the microfluidic device. Sensing platforms that leverage real-time sweat rate measurements with highly sensitive and selective multiparameter sensors for monitoring low-concentration sweat constituents (e.g., cytokines) may yield further insights for assessing the health status of athletes during activity, recovery, and rest.

A logical progression for performance assessment is the development of bidirectional communication between the device and user upon detection of an anomalous physiological event (e.g., dehydration). Figure 3E shows a skin-interfaced platform[130] that circumvents the need for user engagement during wear with the automated delivery of sensory warnings via sweat-triggered chemesthetic agents. The device deploys an effervescent pump to eject menthol (or capsaicin) onto the epidermis when a dehydration condition is detected due to excessive sweat loss.

The device geometry and reversible visual sweat indicators permit the sensor to be manually reset after rehydration. In the aggregate, these representative platforms constitute key advances in establishing the compatibility of regional sweat analysis at prescribed anatomical locations with development of holistic personalized hydration strategies or for athletic performance monitoring.

■ CLINICAL DIAGNOSTICS

Prior to the advent of epidermal microfluidic sensors, few applications have existed for clinical utilization of biochemical sweat analysis. Chloride is a critical sweat biomarker used in clinical diagnostics of cystic fibrosis (CF). Diagnosis of CF is perhaps the oldest sweat-based diagnostic based upon recorded instances from the Middle Ages.[147] Established clinically in 1959,[148] quantitative evaluation of sweat chloride in neonates remains the only widely available method for confirmatory diagnosis of cystic fibrosis. Conventional clinical diagnostic methods are cumbersome; they utilize wrist-strapped devices to collect sweat from infants that often produce insufficient sweat for analysis. Recent work[140] (Figure 4A) highlights the immense promise of wearable sweat sensors in mitigating such diagnostic and interfacing challenges. This demonstration utilizes a soft elastomeric microfluidic platform and a skin-safe adhesive to maintain conformal integration with the skin to facilitate near-perfect efficiency in collecting sufficient sweat volumes for analysis ($N = 51$, infants to adults). Integration of colorimetric chloride sensors with advanced image processing techniques enables smartphone-based image analysis to quantify sweat chloride levels with an accuracy similar to the established clinical method (coulometric titration) in a limited study ($N = 5$, adults). Another device platform[149] integrates a salt-bridge based potentiometric sensor with wireless Bluetooth communications to monitor sweat chloride concentration from a smartphone in real-time during exercise. A small field study highlights performance for adult patients with ($N = 10$) and without ($N = 10$) cystic fibrosis. Although these platforms and others[150,151] demonstrate immense potential to improve cystic fibrosis diagnostics, substantial expansion of clinical study populations is a requisite for establishing operational performance equivalence to current clinical methods.[152]

Resulting from recent interest in utilizing sweat as a noninvasive target for metabolic health monitoring, considerable research efforts seek to expand the utility of diagnostic sweat testing from CF and atopic dermatitis to diabetes. Self-testing and frequent assessments of blood glucose concentration are vital components to diabetic health management strategies.[153] Conventional sensing approaches for daily assessment rely on invasive, painful, skin-piercing microneedle sampling (finger prick). Although continuous glucose monitoring systems[154,155] may mitigate the need for frequent self-testing, development of a noninvasive, pain-free glucose monitoring device remains of intense academic and commercial interest. Sweat represents an attractive biofluid in this context, as recent studies demonstrate a linear correlation between sweat and blood glucose levels.[156−160] One recent demonstrator device[83] (Figure 4C) employs a ratiometric fluorescence sensing strategy to detect the onset of hyperglycemia during sleep. A simple wearable pad containing coimmobilized functionalized dual-fluorescence nanohybrid substrates (luminescent porous silicon nanoparticle/carbon quantum dot structure with bimetallic nanoparticles) and glucose oxidase measures sweat glucose concentration by monitoring a proportional color shift (red to blue) under UV illumination using a smartphone camera.

A recent paper[111] (Figure 4D) reports the utilization of a Janus-wettability (hydrophobic/hydrophilic) textile band to self-pump microdroplets of sweat from the epidermis to functionalized chronoamperometric sensing electrodes to monitoring concentrations of glucose, lactate, Na^+, and K^+ in sweat. Another approach[116] (Figure 4E) achieves wireless, battery-free sweat glucose monitoring during physical exercise from biofuel cell glucose sensors, near-field communication (NFC) technology for data retrieval, and a smartphone. The biofuel cell-based glucose sensor generates electrical signals in proportion to the concentration of glucose, which circumvents the need for a potentiostat (as required for amperometric sensors) thereby minimizing overall device size. The integration of colorimetric sensors for sweat chloride and pH in addition to biofuel cell lactate sensors permits simultaneous multiparameter analysis of metabolic activity and overall physiological state.

Other wearable sensor designs seek to harness blood-correlated biomarkers beyond chloride and glucose (e.g., lactate,[161−165] ethanol,[156] and cortisol[166,167]) to address diagnostic challenges related to diabetes and other diseases. Recent examples of wearable electrochemical sensing platforms demonstrate the promise of sweat analytics for monitoring biomolecular changes relevant to diseases such as gout[142] (uric acid, Figure 4F) or general conditions such as fever[143] (cytokines, Figure 4G). A nitrile glove-based system, with integrated electrode sensors[144] (Figure 4H), provides in situ monitoring of sweat biomarkers including ethanol, Zn, pH, chloride, and vitamin C. The glove creates a local environment that is conducive to passive sweat induction and analysis across multiple biomarkers. To achieve a broad target specificity, a recent study[145] (Figure 4I) uses flexible plasmonic metasurface designs with surface-enhanced Raman scattering (SERS), whereby the intensities of the biomarkers are measured via Raman spectrometer equipped microscope. Because the SERS spectrum is different across different biomarkers, the sensor showed robust target specificity compared with wearable electrochemical sensors. Another recent demonstration device[146] (Figure 4J) circumvents the need for aggregate sweat collection or physical activity with a design that integrates hydrophilic wicking materials, an optimized microfluidic channel network, and electrochemical sensors to collect and analyze thermoregulatory sweat at a resting state. Supported by small pilot studies, this platform is capable of monitoring the onset of disease conditions (hypoglycemia) and variations in psychological factors (stress) through changes in sweat rate as well as the time-dynamic variations in concentration of drug therapeutics (Parkinson's disease) through electrochemical analysis. These and other recent examples[93,138,143,145,168−173] highlight the powerful capabilities that wearable sensors offer for noninvasive clinical diagnostics and disease management.

■ FUTURE OPPORTUNITIES AND COMMERCIALIZATION

Rapid manufacturing and process development of wearable sweat sensors has gained significant traction recently, due in part to the convergence of key advances in flexible electronics, biochemical sensors, and materials science. The initial cohort of epidermal microfluidic sensors established an analytical pathway for obtaining personalized, real-time, continuous assessment of physiological parameters relevant tracking and managing hydration and human health. The wearable sweat sensing platforms highlighted here represent key technological developments for realizing this significant potential. While these milestones suggest rapid maturation of this class of technology, a few key challenges remain before widespread adoption could be achieved.

Continued progress requires technological innovations with particular emphasis on scale-up manufacturing and robustness. An important frontier of this research is in the integration of multimodal sensing platforms for monitoring biochemical and biophysical parameters in a continuous, long-term mode of operation. This necessitates consideration of sensor performance within a broad context of power management, wireless communication, and data acquisition of fully integrated biochemical sensing systems. The recent emergence[93,169,174−177] of biofuel cell-based self-powered wearable sensors represents a successful pathway to realizing such a fully integrated platform.

The complex composition of sweat poses some of the most interesting challenges for wearable sweat sensors. In contrast to conventional laboratory-based analytical methods, these sensing platforms must operate in a robust, stable manner under dynamic conditions and without the oversight of skilled technicians. Demonstrations of selective and multimodal sensors offer routes toward rapid, repeatable on-body measurements; however, certain constructs exhibit susceptibility to measurement errors caused by biofouling, varying ambient conditions (e.g., temperature or pH fluctuations), and motion artifacts. Although highly multiplexed sensors and nuanced device designs can mitigate such influences, the development of new encapsulation materials and packaging strategies that protect against noise factors such as moisture and corrosion could eliminate deterioration and sources of noise from nonspecific binding or cross-talk, particularly for ultralow concentration species (e.g., DNA, RNA), which is of critical importance.

Key to the widespread adoption of wearable sweat-sensors is the comprehensive validation of the systems. Although sweat offers enormous potential for noninvasive physiological monitoring, it has remained relatively unexplored in comparison to traditional biofluids such as blood. The emergence of novel physiologically relevant sweat constituents, such as cortisol, lactate, and ethanol, is the direct result of the interest in noninvasive monitoring and rapid advances in the development of wearable sensing platforms. Continued progress requires extensive, large-scale, multicenter validation studies and formalized clinical trials. Such efforts could yield critical insights into the correlations with blood and urine analytes (and associated time-scales) requisite for establishing

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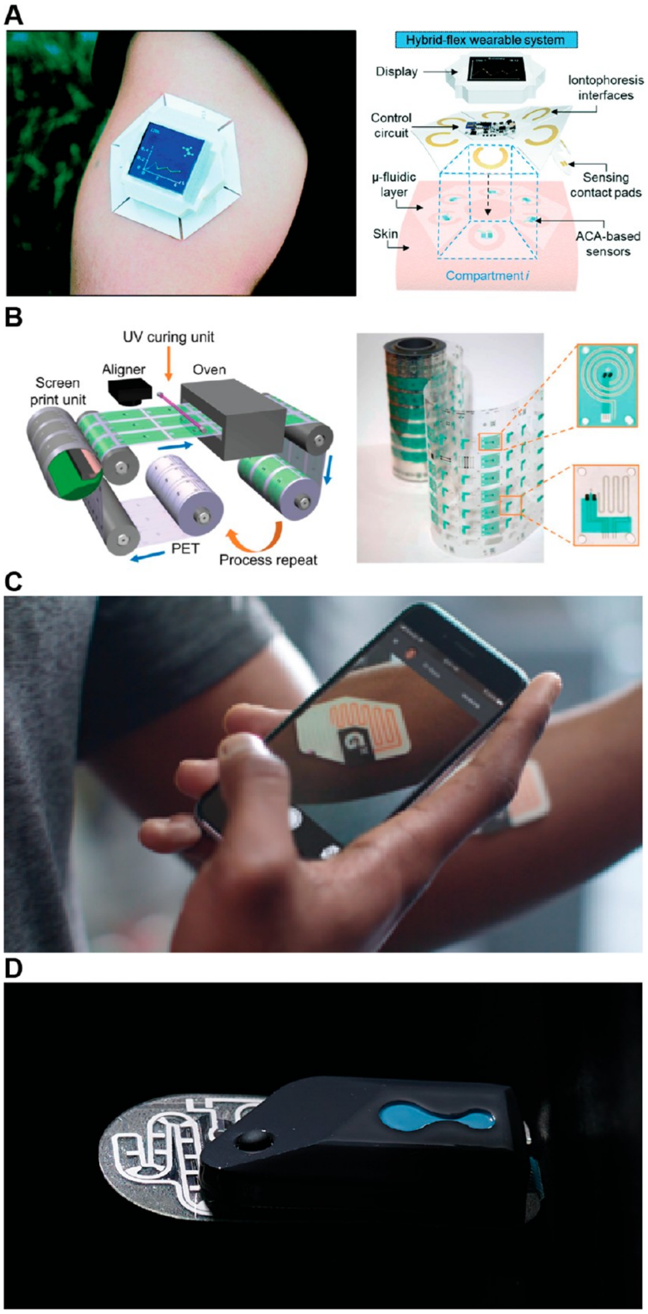

Figure 5. Integrated devices and commercially available systems. (A) Integrated device strategy for long-term sweat analysis via on-demand sweat stimulation.[178] Adapted with permission from ref 178. Copyright 2020 The Royal Society of Chemistry. (B) Recent effort details a strategy to utilize roll-to-roll manufacturing to produce epidermal microfluidic sensors in a scalable manner suitable for mass manufacture.[180] Implementation of such fabrication strategies enables further maturation of wearable sweat sensing platforms and offers opportunities for broad consumer adoption. Adapted with permission from ref 180. Copyright 2019 American Association for the Advancement of Science. (C) Gx Sweat Patch and (D) Connected Hydration System, both developed by Epicore Biosystems,[181] represent the emerging commercial sensing platforms being manufactured at scale. Reprinted with permission from ref 181. Copyright 2021 Epicore Biosystems.

a comprehensive profile of sweat-based biochemical markers with physiological relevance. Moreover, such testing could, in turn, validate device performance beyond the research prototype stage of development.

Another important factor driving the demand for wearable sweat-sensor technologies is the development of multi-parameter, long-duration biochemical and biophysical sensing capabilities. One recent demonstration[178] achieves long-term sensing via on-demand iontophoretic stimulation at defined intervals (Figure 5A) to monitor sweat biomarkers with integrated electrochemical sensors. Another recent example[179] integrates a suite of sensor constructs within a single wearable platform to obtain multiparameter measurements of hemodynamic and metabolic biomarkers simultaneously throughout daily activities. Commercialization efforts around these multi-modal systems tend to be costly,[70] requiring novel manufacturing tooling and test strategies for large-scale production at high yield[180] (Figure 5B). It is only within the past few years that the first commercial consumer-wearable sweat sensors became widely available to consumers. Developed by Epicore Biosystems and The Gatorade Company and clinically validated in blinded studies[181] (the G^x Sweat Patch, Figure 5C), these microfluidic devices measure regional and whole-body sweat loss, sweat rate, and electrolyte parameters, which are relevant to athletic performance and hydration. The G^x Sweat Patch employs colorimetric dyes and assays, along with real-time image processing via a smartphone application to compute results and actionable feedback in real time. Integration of this class of microfluidic technology with electronic modules enables continuous biochemical sensing and real-time alerts. These electronics-enabled epifluidic solutions rely on advances in energy storage, wireless communication, and memory storage as part of the fully integrated system. Large-scale clinical validations studies in sports and industrial safety are underway for the Connected Hydration System (Figure 5D) and other representative examples of this technology.

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Notes

The authors declare the following competing financial interest(s): R.G., J.A.R., and T.R.R. are inventors on patents and pa-tent applications related to epidermal microfluidics. R.G., J.B.M., and J.A.R. are cofounders of Epicore Biosystems, a company that develops epidermal microfluidic devices. J.A.W. and D.E.W. are employees of Epicore Biosystems. T.R.R. has a consulting and advisory relationship with Epicore Biosystems.

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