Recent advances in skin-interfaced wearable sweat sensors: opportunities for equitable personalized medicine and global health diagnostics

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ABSTRACT: Recent advances in skin-interfaced wearable sweat sensors enable the non-invasive, real-time monitoring of biochemical signals associated with health and wellness. These wearable platforms leverage microfluidic channels, biochemical sensors, and flexible electronics to enable the continuous analysis of sweat-based biomarkers such as electrolytes, metabolites, and hormones. As this field continues to mature, the potential of low-cost, continuous personalized health monitoring enabled by such wearable sensors holds significant promise for addressing some of the formidable obstacles to delivering comprehensive medical care in under-resourced settings. This perspective highlights the transformative potential of wearable sweat sensing for providing equitable access to cutting-edge healthcare diagnostics, especially in remote or geographically isolated areas. It examines the current understanding of sweat composition as well as recent innovations in microfluidic device architectures and sensing strategies by showcasing emerging applications and opportunities for innovation. It concludes with a discussion on expanding the utility of wearable sweat sensors for clinically relevant health applications and opportunities for enabling equitable access to innovation to address existing health disparities.

The previous decades have seen remarkable transformations in medical technology as a consequence of groundbreaking innovations in chemistry, engineering, and materials science. These medical breakthroughs have yielded significant improvements in health outcomes, such as more effective treatments and timely diagnoses.[1–4] Nevertheless, despite this incredible progress, significant disparities in access to state-of-the-art medical technology remain. These disparities lead to marked differences in health and life expectancy between high-, middle-, and low-income countries.[1,5] Notably, healthcare inequalities are not exclusive to low- and middle-income countries (LMIC), as within the United States there are unacceptable disparities in healthcare received by marginalized and vulnerable populations, including those based on race/ethnicity,[6] gender and sexual orientation,[7] and individuals with disabilities.[8] The COVID-19 pandemic has further highlighted these inequalities as evidenced by the disproportionate mortality rate among Black and Latino populations in comparison to white populations.[9] As a consequence, there exists a critical need to develop effective measures that provide all populations access to state-of-the-art medical care.

The gold standard for clinical care involves highly skilled personnel using sophisticated instrumentation to monitor critical biophysical and biochemical indicators of overall health status. Recent advancements in clinical monitoring methods have expanded access to high-quality, small form-factor equipment capable of the real-time monitoring of vital signs (e.g., body temperature, heart rate, respiration rate, pulse oxygenation). For example, the wide adoption of the continuous glucose monitor (CGM) within the management plans for patients with diabetes mellitus highlights the enormous potential real time biochemical sensing holds for improving patient care. Such monitoring devices, when worn continuously, can yield important insights into health status from a limited range of health markers.[10] However, the demands of clinical monitoring present formidable obstacles to delivering comprehensive medical care in under-resourced settings.

Blood-based analysis, the predominant approach to evaluating body chemistry, necessitates invasive sampling techniques, centralized laboratory infrastructure, and prolonged analysis periods. However, recent breakthroughs in wearable sensing technology have facilitated the emergence of biofluids, such as tears,[11,12] saliva,[13,14] urine,[15] and sweat,[16] as viable non-invasive alternatives to conventional blood-based monitoring. Of these, eccrine sweat has attracted significant attention owing to the complex composition of micronutrients, hormones, proteins, metabolites, nucleic acids, and exogenous agents.[17–22] Innovative skin-interfaced wearable platforms, leveraging recent progress in microfluidics, biochemical sensing, and flexible electronics, enable the continuous or intermittent evaluation of sweat composition in a range of conditions and settings.[17,23–26] This resulting time-dynamic insight into metabolic activity offers a promising solution for addressing the challenges of providing equitable access to cutting-edge healthcare diagnostics, especially in remote or geographically isolated areas.[27–31]

This perspective offers a comprehensive overview of the latest advancements in wearable sweat sensing and the wide-ranging implications these devices have for human physiological monitoring. Building on the foundation laid by traditional lab-on-chip microfluidic devices, the field of sweat-based wearable sensors is growing at a rapid, nearly exponential rate. A wide range of recent reviews examine the progress of this emerging field within the scope of skin-interfaced devices,[16,32–34] sensing approaches,[35,36] fabrication methods,[37,38] material systems,[39,40] applications,[41–43] and current challenges.[44] In comparison, this perspective discusses recent innovations in wearable sweat sensing that leverage advanced translational embodiments to highlight the current challenges and future opportunities for the field. The introductory section examines key considerations in underlying principles of these wearable systems including the composition of sweat, innovations in sampling methods, and challenges in sensing biochemical targets of interest. The sections that follow highlight the emerging applications and representative examples of the most advanced integrated sensing platforms to examine new opportunities for the field. The perspective concludes with a discussion of efforts to expand overall utility of wearable sweat sensors for diagnostic applications with a particular emphasis on democratizing access to innovation.

The Current State of Sweat Analysis

Wearable sweat devices have emerged as a powerful non-invasive window into the physiological health state of an individual, offering the potential for continuous, real-time monitoring and personalized health management. Extracting meaningful information from sweat presents a considerable set of challenges, encompassing aspects such as device architecture, sweat collection methods, and application-specific requirements. The time-dynamic biochemical composition of sweat varies in response to numerous physiological conditions and activity levels, further complicating the process of deriving actionable physiological insights. The first section provides context for epidermal microfluidic platform innovations through exploration of the rapidly evolving understanding of sweat composition. The sections that follow highlight the latest developments in wearable microfluidic platforms, examining the advancements in device architecture that facilitate robust fluid handling and sensing strategies employed for sweat analysis.

Sweat Composition. Sweat, a biofluid secreted from eccrine glands dispersed across nearly the entire skin surface, is primarily understood to regulate body temperature through evaporation, although it is also proposed to contribute to skin health and micronutrient homeostasis.[42] Exhibiting slight acidity (pH 5.5–6.5), sweat chiefly consists of water and salt, but also encompasses a diverse array of other biological components.[42,45] Initial investigations (pre-1990s) into sweat centered on the assessment of sweat rate and composition during a range of activities and across various body regions; however, these studies were constrained by the limitations of sweat collection methodologies.[46–51] The emergence of wearable sweat sensors and resultant high-fidelity analytical capabilities has facilitated a more in-depth exploration of sweat composition by contemporary researchers. Despite these advances, recent reviews[42,52,53] attempting to consolidate current sweat composition research reveal ongoing challenges in data availability and consensus, which ultimately hinders a comprehensive understanding of the role of sweat in human health. While additional data is necessary for an exhaustive inventory, commonly identified sweat constituents include electrolytes (e.g., K^+, Na^+, Cl^-),[54] additional common micronutrients (e.g., vitamin C, calcium, iron),[55] metabolites (e.g., lactate, glucose, urea, amino acids),[56] hormones (e.g., cortisol, dehydroepiandrosterone),[57] and other proteins (e.g., cytokines, antibodies).[58]

The detection of numerous biomarkers present both in blood and sweat underscores the need for further correlation studies to corroborate previous findings and broaden our comprehension of the relationship and physiological significance between biomarkers found in both fluids.[59–61] Various analytes, including glucose,[59] alcohol/ethanol,[60,62] and certain therapeutic and illicit drugs,[63] have demonstrated correlations between the concentration found in blood and sweat. However, the clinical utility of some correlations, such as that of lactate, remains the subject of debate among researchers.[64–66] It is important to note that even once correlations are established the concentrations of analytes in sweat may vary across different regions of the body.[54,66] The vast concentration range of bioanalytes of interest, which span from picomolar to millimolar levels,[42,52,58] poses significant sensing challenges, particularly in terms of complex signal interference when detecting low-concentration analytes among highly concentrated constituents.

Environmental factors, including humidity and dietary habits, can influence both sweat rate and analyte concentrations, though such effects may be biomarker dependent.[67] For example, as sweat rate increases, mass amounts of chloride ions and lactate are excreted at an accelerated rate (in mmol/min); however, chloride concentrations (in mmol/L) remain relatively stable in contrast to the decreasing concentration of lactate.[52] Many existing studies feature relatively small sample sizes, underscoring the necessity for larger-scale investigations to gain a deeper understanding of these variations. Furthermore, variations arising from population diversity merit systematic examination. As a consequence, when compared to other biofluids such as blood, sweat remains a largely unexplored frontier offering rich opportunities for rigorous scientific and medical research to elucidate the nuances of concentration, variation in composition, and overall physiological significance of the biomarkers present.

Device Architecture. Epidermal microfluidic ('epifluidic') devices describe a powerful class of wearable sweat platforms that combine soft elastomeric materials, sophisticated networks of microfluidic channels, and advanced biosensing technologies to establish a conformal, intimate epidermal interface for the real-time collection and analysis of sweat.[68] The transport of sweat within these epifluidic devices relies upon the natural pressure generated by the eccrine glands to generate fluid flow.[69] Considering the minute volumes produced by individual sweat glands (density of 50-400 glands/cm^2,[34] 5-10 nL/min/gland during exercise,[70] >0.1 nL/min/gland during iontophoresis[71]) precise fluid handling and collection are of paramount importance for these devices.

The intricate design of epifluidic devices serves a critical role in overall performance, particularly with respect to sweat collection. In the context of athletics, larger device surface areas offer distinct advantages, such as ensuring secure skin contact during demanding activities, monitoring a broader, representative area of sweat glands, and accommodating long-duration collection at elevated sweat rates.

In contrast, smaller device surface areas provide heightened resolution for observing specific regions of activated sweat glands, enable continuous sweat capture in non-athletic contexts, and support a more comfortable user experience by alleviating body conformity complications that may arise from larger interfacial surface areas. Such design considerations govern the efficient collection and analysis of sweat, as sweat flow rate is a critical determinant of device performance across a broad spectrum of contexts and applications. The need for continuous biochemical monitoring calls for extended duration sweat collection necessitating device architectures that establish a fine balance between capturing adequate sweat volumes to initiate flow while concurrently avoiding saturation of channels or sensors. Advanced wicking materials, such as open-channel nanofluidic hex wick films,[72,73] represent one strategy to enhance the initiation of flow into devices.[74] Alternative methodologies leverage distinct wettability contrasts, utilizing patterned superhydrophilic and superhydrophobic regions to direct sweat towards the inlet of a device, thereby enhancing reliability under varying humidity and hydration conditions.[75–77] One such exemplar employs a polyethylene terephthalate (PET) film coated with superhydrophobic nanodendritic silica alongside superhydrophilic microwells to extract sweat from the epidermis for subsequent analysis.[75] In contrast, another approach integrates sensors on a skin-safe substrate (such as tattoo paper) directly against the epidermis to record sweat biomarker signals in the absence of microfluidic channels.[78–81]

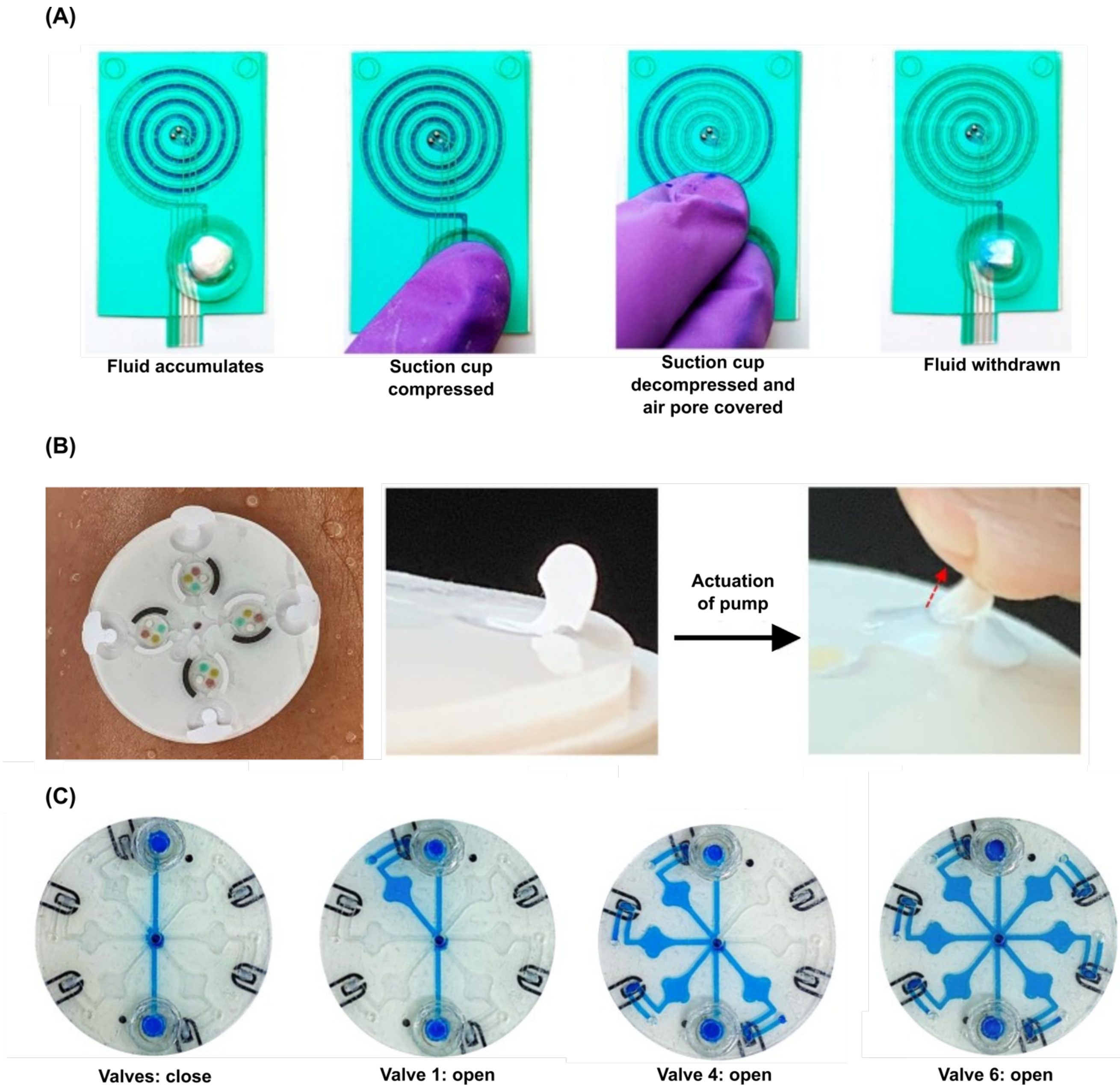
In addition to material selection, both the channel structure and layout can profoundly influence collection performance. A recently reported device draws inspiration from cactus spines, incorporating wedge-shaped superhydrophobic/superhydrophilic channels to generate unidirectional Laplace pressure, which spontaneously wicks sweat towards the sensing region.[82] This design mitigates elongated sweat transport time and sample loss due to retention within the channel. Rapid saturation can impede or decelerate flow, obstructing further measurements as analytes diffuse from the previously collected sweat. One innovative approach to this challenge integrates a manual pressure pump to expel excess sweat thereby enabling continuous measurement over prolonged periods (Figure 1(A)).[83]

Further innovations in flow control strategies exploit the integration of valves into device architectures to manage fluid flow after the initial ingress of sweat into the device. Early platforms showcased the efficacy of capillary bursting valves (CBVs) that exploit natural pressures generated by sweat glands to facilitate the sequential filling of microfluidic reservoirs during sweat collection. This approach enables high-resolution, temporally distinct sample analysis within a single device, effectively reducing contamination and crosstalk.[69,84] Contemporary epifluidic platforms incorporate finger-actuated pumps, valves, and sensors, where a pull-tab allows sweat to access designated chambers at specific times for targeted, on-demand biomarker analysis (Figure 1(B)).[85] Similarly, electronically controlled valves facilitate the acquisition of measurements from individual sensors at pre-determined intervals or on-demand (Figure 1(C)).[86]

While these advancements in device architecture have established the feasibility of on-body collection, control, and sensing in sweat, challenges remain in monitoring biomarkers in sweat present only in ultra low concentrations. Measuring species such as cytokines and other proteins typically requires complex, multi-stage, environment-sensitive assays performed in centralized laboratory facilities. There is a considerable unexplored potential in establishing similar quantitative monitoring capacities in wearable sweat devices, which is critical for enabling continuous on-body analysis of clinically relevant targets. Emerging concepts draw inspiration from innovations in conventional lab-on-chip devices, such as burst and push valves in adhesive-based capillary devices.[87] The capacity to regulate sweat flow through channel geometry, valves, or other mechanisms enhances the temporal resolution of measurements, permitting the detection of vital biomarker fluctuations and simultaneous multi-analyte monitoring without interference. Off-body demonstrations further underscore the potential for incorporating these innovations into epifluidic device architectures. Additionally, techniques such as electrorepulsion and electro-osmosis provide control over fluid transport without the need for physical valves by directing the flow of charged species within the fluid itself.[78] Such developments are critical to enable wearable epifluidic platforms to perform multi-step assays and the supporting sequential reagent steps on the device.

Sensing Strategies. Wearable sweat sensors must operate under a variety of conditions across a wide array of potential applications. The sensing mechanisms must exhibit precision, sensitivity, and selectivity for a target analyte during operation while withstanding diverse physical exertions (e.g., resting, intense exercise) and environmental conditions (e.g., humidity, temperature).[44] Rapid, accurate, real-time biomarker measurements are critical. Sample evaporation and sensor degradation, which can occur within a timespan as short as 10–20 min, can result in incorrect concentration measurements.[70] For widespread accessibility and equity, these sensing platforms must be affordable, utilize cost-effective materials, and be compatible with scalable manufacturing techniques.

Figure 1. Device Architecture: (A) Manual pressure pump to expel sweat for prolonged continuous measurements. Adapted with permission from Ref. [83]. Copyright 2022 American Chemical Society. (B) Pull-Tab pump for on-demand sensing. Adapted with



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To date, wearable sweat platforms primarily employ colorimetric and electrochemical sensing strategies, with a few instances utilizing alternative methods such as fluorescence (Figure 2(A))[88,89] and surface-enhanced Raman scattering (Figure 2(B)).[90–92] Colorimetric sensors function by producing a color change (either formation or disappearance) upon interaction with the analyte of interest, with the color intensity typically correlating with concentration.[93–97] Results can be discerned visually with the naked eye or by employing a consumer smartphone for more precise quantification, thereby reducing user interpretation errors.[29,94,98] Silver chloranilate, a well-established colorimetric assay for sweat chloride quantification, exemplifies this approach, as a purple color develops in response to chloride (Cl^-) ion concentration.[99] Colorimetric quantification of non-ionic analytes, such as metabolites, often necessitates the use of enzymatic reactions. In these assays, a target biomolecule reacts with an enzyme, yielding a product that induces a color change in a chromogenic agent. For instance, glucose oxidase (GOx) is commonly employed for measuring sweat glucose concentration.[94–96] Enzymatic assays can be adapted for numerous other biomolecules with minimal modifications (e.g., exchanging the enzyme) as chromogenic agents respond proportionally to the products of enzymatic reactions.

Colorimetric assays broadly enable battery-free quantification of key physiological parameters, including sweat rate and pH, as well as the assessment of various biochemical constituents.[95,96,100] Advances in fluid control and storage have facilitated the incorporation of multiplexed colorimetric assays into single epifluidic devices, exemplified by a recent epifluidic platform designed to simultaneously detect glucose, lactate, urea, pH, and sweat loss, along with an electrical skin temperature sensor (Figure 2(C)).[94] While colorimetric sensors yield quantitative measurements, the reliance on non-reversible reactions limits efficacy for continuous measurements.[97]

Electrochemical sweat sensors support continuous, rapid measurements of target analytes, offering a distinct advantage compared to colorimetric sensors, albeit with the trade-off of necessitating the integration of wearable electronics and power sources.[35] These sensors operate by quantifying electroactive species in sweat, such as tyrosine and uric acid, through the optimization of electrochemical measurement parameters.[101] To selectively monitor specific non-electroactive biomolecules, electrochemical sensors must incorporate recognition elements such as ionophores for ions (e.g., electrolytes),[102–105] enzymes for metabolites,[79,106,107] and antibodies for hormones and proteins.[108] Although enzymes and antibodies have been successfully employed for reliable sweat monitoring, performance is contingent on biological manufacturing processes, which can be expensive, unstable, and difficult to immobilize effectively on the sensor surface. The conventional antibody-antigen recognition elements in electrochemical sensors contain intrinsic shortcomings resulting from nonreversible binding for continuous electrochemical sweat monitoring. Upon antigen binding, the site becomes saturated, rendering it unavailable for subsequent measurements. Nonenzymatic sensing approaches based upon metals and metal oxides represent an attractive synthetic alternative to circumvent these issues.[109–111] Additional avenues for continuous electrochemical sensing include electrochemical aptamer-based (EAB) sensors and molecularly imprinted polymers (MIPs). EAB sensors, which can be regenerated and reused, have demonstrated significant progress in real-time in vivo monitoring in blood[112] but have only recently emerged in sweat sensing.[113–115] A notable example is a recent study that achieved continuous on-body cortisol measurements with an EAB sensor, featuring on-body regeneration for extended measurements without necessitating an exchange of the sensing mechanism(Figure 2(D)).[114] MIPs, synthetic receptors that mimic antibody-antigen systems, represent another potential solution for continuous sensing.[116] MIP-based sweat sensors have been developed using polymers[117–120] with one innovative example showcasing simultaneous multiplex detection of cortisol, Mg^{2+}, and pH. This sensor employed three distinct electrochemical detection motifs for real-time sweat measurements of stress indicators, incorporating an MIP cortisol sensor, an ionophore membrane, and a proton-sensitive polyaniline (PANI) film, respectively (Figure 2(E)).[118] Such emerging advancements in EAB and MIP sensors demonstrate the potential to enable continuous, real-time sweat sensing across diverse applications, surmounting traditional antibody-antigen system limitations and promoting accurate, reliable, and cost-effective physiological parameter measurements, with their integration into wearable devices poised to play an increasingly vital role in quantifying parameters relevant to fields such as sports performance and disease diagnosis. A similar work also reported multiplexed analysis of both electrolytes (Na^+, pH) and metabolites (uric acid) using three different detection mechanisms (an ionophore, PANI film, and carbon nanomaterial, respectively). The fully-integrated sensor array could provide real-time detection in sweat and also demonstrated the first example of simultaneous detection of metabolites and electrolytes that could be used in raw sweat, saliva, or urine without separate modification (Figure 2(F)).[121]

Emerging Applications

Numerous commercial demonstrations of performance driven wearable devices monitor the physiological and biomechanical signals that arise during physical activity.[122] Initially developed for professional athletes, wide adoption of fitness trackers over the past decade illustrates the growing consumer interest in understanding the activity-dependent response of the human body to physical stress.[123] Such insight is essential for reducing risk of injury, monitoring recovery times, and improving overall well-being. While these existing wearable platforms are capable of evaluating the essential biophysical and kinematic signals for such purposes, they fall short in the necessary sensing capabilities to track metabolic health.[124] However, the advent and rapid development of wearable sweat sensors create new opportunities for ambulatory metabolic health assessment.

Until recently, commercially available wearable technology, such as the Apple Watch or Fitbit, monitor heartrate and movement to indicate general health and fitness,[125] but did not provide insight into biochemical health. Although wearable microfluidic platforms offer powerful capabilities for health monitoring applications,[65,126,127] the commercial availability and viability of such devices remains limited. The most prominent example of a commerical wearable sweat sensor on the market is the Gatorade Gx Sweat Patch from Epicore Biosystems. Launched in 2021 for sports performance applications, the Gx Sweat Patch enables athletes to monitor sweat rate and sweat chloride concentration (Figure 3(A)) to guide rehydration.[128] Other commerical platforms that address hydration and fitness are also emerging including Nix Hydration Biosensor,[129] hDrop,[130] and Onalabs Onasport.[131]

Although not yet commerically viable, investigational efforts seek to establish broader assessments of health related sweat biomarkers for expanded insight into nutritional status. Promising steps towards precision nutrition have been shown through dynamic monitoring amino acids,[56] vitamins,[79] and other nutrients in sweat.[132] Such platforms could identify and prompt correction of nutritional deficiencies before medical intervention is necessary by providing noninvasive assessment of nutrient uptake. Nutrient delivery can also be incorporated into monitoring devices to provide necessary supplements (Figure 3(B)).[132]

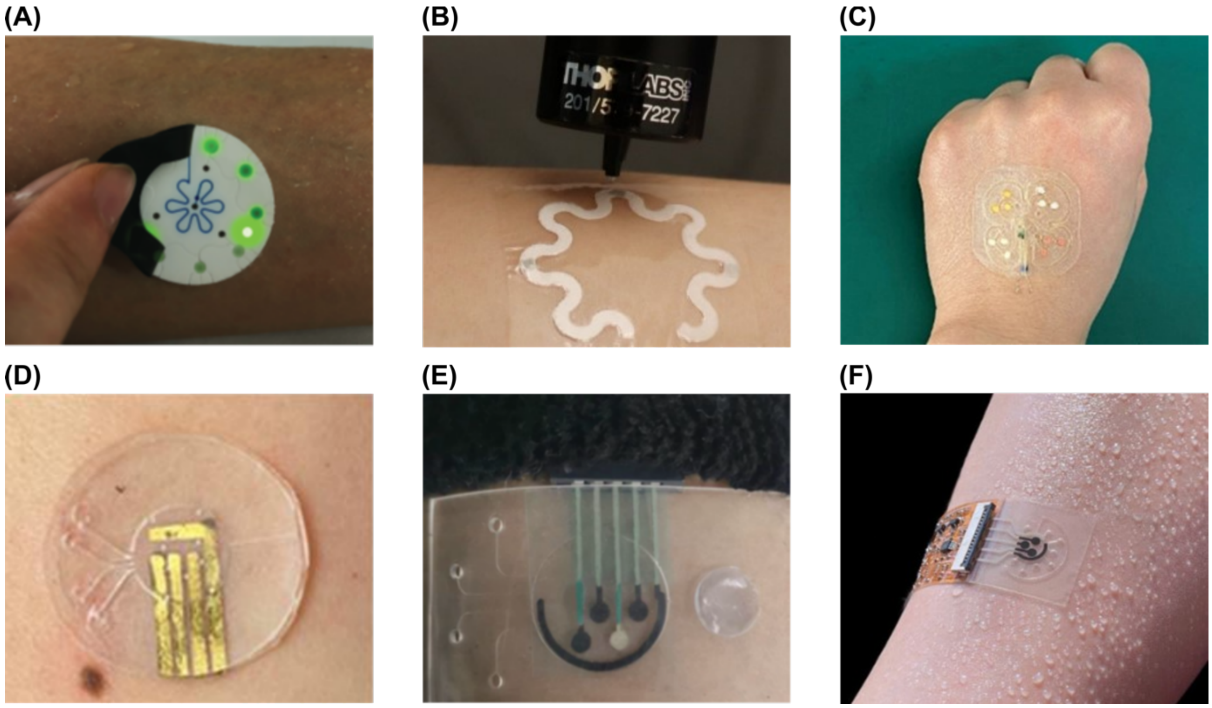

Figure 2. Sensing: (A) Fluorometric sweat sensor for *in situ* measurements of chloride, sodium, and zinc. Adapted with permission from Ref. [88]. Copyright 2018 Royal Society of Chemistry. (B) Plasmonic paper–based microfluidic system with label-free surface-enhanced Raman spectroscopy (SERS) sensing for quantification of uric acid in sweat. Adapted with permission from Ref. [92]. Copyright 2022 American Association for the Advancement of Science. (C) Colorimetric sweat sensor for glucose, lactate, urea, and pH with only 2.5 µL of sweat required. Adapted with permission from Ref. [94]. Copyright 2022 American Chemical Society. (D) Electrochemical sensor functionalized with a regenerable pseudoknot-assisted aptamer and a flexible microfluidic sweat sampling system to continuously monitor cortisol level fluctuations in sweat. Adapted with permission from Ref. [114]. Copyright 2023 Elsevier. (E) Multiplexed electrochemical sensing patch for cortisol, Mg^{2+}, and pH detection in sweat employing MIPs, ionophores, and proton-sensitive films as sensing mechanisms. Adapted with permission from Ref. [118]. Copyright 2023 Wiley. (F) Fully integrated wearable sensor array for Na^{+}, pH, and uric acid detection using an ionophore, PANI film, and carbon nanomaterial. Adapted with permission from Ref. [121]. Copyright 2023 American Chemical Society.

Sweat-based monitoring is well established for athletic performance assessment and, to a lesser extent, nutrition adherence; however, limited understanding of the correlation between sweat biomarkers and blood-based equivalents currently restricts broad clinical utility. At present, the only clinical sweat-based diagnostic is for cystic fibrosis (CF).[132] In patients with CF a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene results in the inability to properly transport chloride ions resulting in an elevated concentration of chloride in sweat.[49,133] First established in 1959, the quantitative assessment of the concentration of sweat chloride (i.e. sweat test) serves as the gold standard method for CF diagnosis. Conventional sweat tests must be performed in a centralized, certified testing facility by trained personnel; however, the recent development of a low-cost wearable "sweat stickers" that support both collection and in situ chloride analysis holds promise for expanding access to CF diagnostic testing in a variety of settings (Figure 3(C)).[134] Another recent work reports the continuous detection of C-reactive protein in sweat to monitor chronic inflammation in chronic obstructive pulmonary disease patients.[135] Similar concepts are in earlier stages of development for providing clinically-relevant diagnostic information for other diseases including diabetes,[136] bacterial infections,[137,138] inflammatory bowel disease,[139] and cancer.[140] Continued advances in sensing capabilities will enable an expanded understanding of the clinical relevance of the time-dynamic and activity dependent variations of various sweat biomarker concentrations. For example, recent work reveals that tracking fluctuations in sweat cortisol concentration provides insight into the stress response of the body and the resulting impact on body functions/diseases (Figure 3(D)[115]).[114,115,141,142]

The potential implications of devices capable of continuously monitoring clinically relevant sweat biomarkers for evaluating the progression or treatment of a variety of diseases are substantial. The need for such technologies is notably exemplified for diabetes. Although the past decade has seen meaningful strides in the management of diabetes, notably through advances in real-time continuous glucose monitoring (CGM), all existing monitoring modalities necessitate invasive sampling (blood, interstitial fluid). Moreover, the financial burden associated with access to CGM devices is substantial for many patients.[143] As a consequence, the prospect of using sweat as a non-invasive means for glucose monitoring attracts considerable commerical and academic attention.[111,136,141,144] Sweat glucose sensing was first attempted commercially in the early 2000s with the launch of the GlucoWatch (Cygnus); however, the device was withdrawn shortly after introduction due to a issues related to inaccurate measurements, complicated user instructions, lengthy sensor initiation time, patients receiving burns, and other malfunctions.[143,145] While a handful of non-invasive sweat-based glucose sensors are either in clinical trials or have recently received either FDA approval and/or CE certification, none have yet been made widely available to the consumer market.[146]

A fundamental challenge to using sweat as a replacement for blood glucose measurements remains the time lag between blood and sweat glucose levels.[132] Initial research efforts established a correlation, yet questions remain regarding the efficiency and consistency of sweat glucose measurements. A powerful opportunity afforded by the unique measurement capabilities of wearable sweat platforms exists for developing a platform for a comprehensive approach to diabetes management rather than simply replacing CGMs. Through the incorporation of multiparameter monitoring of additional analytes (e.g., lactate, chloride, pH, cortisol) wearable sweat sensors can assess the status of co-morbidities associated with diabetes in combination with sweat glucose monitoring.[69,141] Examples include a platform for diabetic wound monitoring (Figure 3(E))[147] or ketoacidosis.[144] Although the latter is a touch-based rather than wearable platform, this work demonstrates the dual detection in fingertip sweat of glucose and β-hydroxybutyrate (HB), which is one of the primary physiological ketone bodies serving as an indicator of diabetes ketoacidosis. Ketone detection in a wearable sweat platform, alongside detection of several other analytes mentioned, is of significant interest for improving diabetes management.

Recent papers also demonstrate the powerful utility of multiparameter monitoring for other diseases. One study[101] reports a promising solution for monitoring gout, a painful form of inflammatory arthritis, through a platform that combines sweat sampling, vital-sign monitoring, and sensing of associated biomarkers. The platform employs microfluidic channels to direct sweat to electrochemical sensors for monitoring tyrosine and uric acid and incorporates resistance-based sensors for monitoring temperature and respiration rate. Another work[148] highlights the use of wearable sensors for managing the theraputic treatment of Parkinson's disease. The work presents real-time drug monitoring of levodopa in sweat, sweat rate, and heart rate to detect fluctuations in levodopa dosage and the resulting side effects to allow for earlier intervention (Figure 3(F)). In addition to therapeutic drug monitoring, wearable sweat devices have been used for monitoring illicit and psychoactive drug use.[113] Several commercial platforms for similar applications are available including the PharmChek Sweat Patch[149] for drug abuse testing off-body and the SCRAM CAM ankle bracelet[150] for continuous on-body sweat alcohol monitoring.

The advancements discussed in this section show great promise for more personalized and precise disease management. However, realization of this potental requires continued progress to establish the clinical utility of sweat-based biomarkers and correlation to existing health indicators. Combining such insights with wearable sweat platforms could not only provide a non-invasive window into health-related biological mechanisms but also broaden access to high-quality health monitoring across geographic and demographic boundaries. Not only will this bring significant impact to those who currently require invasive and/or in-laboratory tests, but also increases utilization as healthcare services are statistically utilized to a higher degree by individuals with chronic diseases.[151]

Opportunities for Innovation

The continued development of wearable platforms for sweat analysis depends on addressing key challenges in sweat sampling methodologies and biomarker sensing strategies. Fundamental research for understanding the clinical relevance of sweat emerges as another crucial element for enabling platforms to enable sweat sensors to positively impact health monitoring. Innovations in scalable manufacturing techniques offer new possibilities for facilitating place-based device development. In this context, recent developments offer strategic routes to address long-standing challenges for commercialization including manufacturing, power management, and environmental sustainability.

Sweat Sampling. In comparison to other non-invasively sampled biofluids (e.g. urine, saliva), sweat-based analysis requires relatively small sample volumes ranging from nanoliters to microliters.[152] Traditional methods for sweat stimulation incorporate physical activity, exposure to elevated temperatures (e.g. sauna), or drug-facilitated stimulation by a cholinergic agonist.[153] Pilocarpine iontophoresis serves as the clinically-established method for stimulating a sweat response, particularly in the context of cystic fibrosis diagnosis.[154] This method prompts a localized, time-limited sweat response of approximately 30 min through the use of a low intensity electrical current (iontophoresis) to introduce a topically-applied cholinergic agonist (pilocarpine) into the body.[155–157]

Ongoing research efforts seek to establish sweat stimulation methods compatible with wearable form factors that are safe, effective, and non-demanding in order to enable reproducible sweat generation without compromising biochemical composition. More conventional active sweat generation methods (e.g., exercise, temperature) present additional challenges for continuous measurements owing to inconsistent sweat rates.[34] Several recent examples demonstrate the use of iontophoresis-based sweat induction for extended and continuous sampling and analysis, during physical exercise and at rest (Figure 4(A)).[56,158,159] These efforts illustrate the potential of other cholinergic agonists to modify the duration and physical area of the sweat response for wearable sweat analysis platforms.[34] An alternative approach[160] for achieving long-term sweat collection utilizes a combination of hydrogels with paper microfluidic channels to facilitate passive (i.e. battery-free) osmotic sweat extraction at rest.

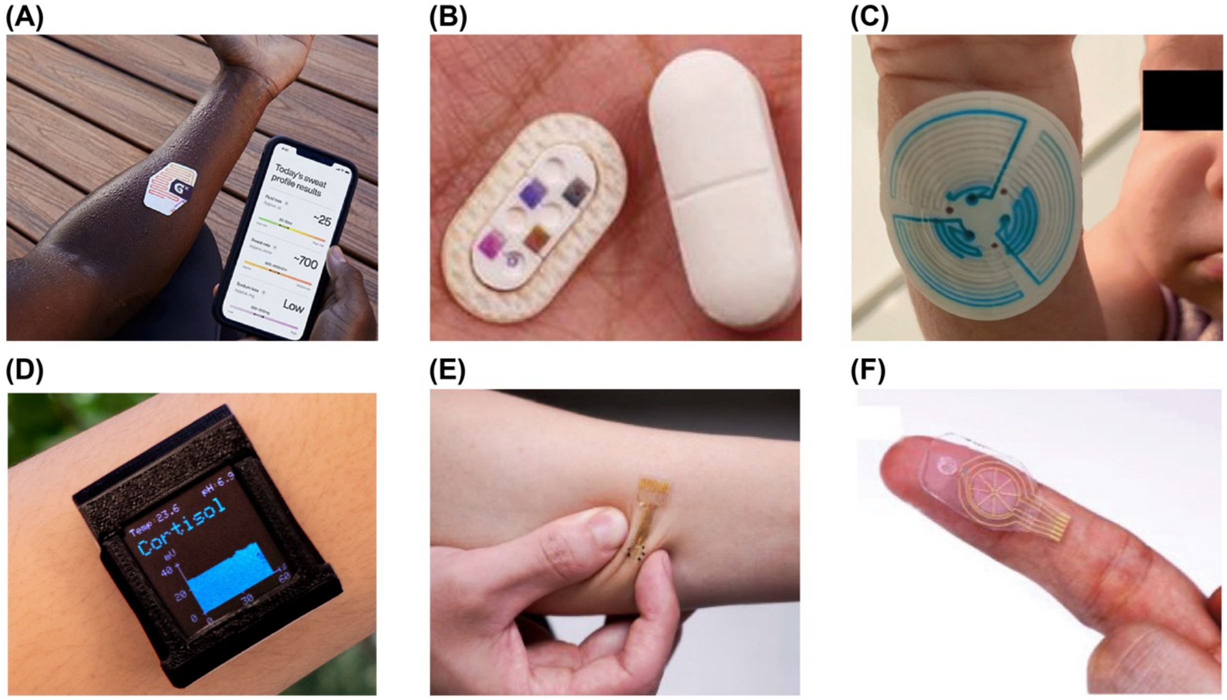

Figure 3. Emerging Applications: (A) Gx Sweat Patch soft, wearable, microfluidic patch for monitoring sweat rate, sweat loss, and NaCl composition for hydration management. Adapted with permission from Ref. [161]. Copyright 2023 Epicore Biosystems. (B) Miniaturized wearable microfluidic system for quantitative analysis of vitamin C, calcium, zinc, and iron in sweat with integrated transdermal nutrient delivery. Adapted with permission from Ref. [132]. Copyright 2021 Wiley. (C) Soft, epidermal microfluidic device ("sweat sticker") for rapid collection and on-body colorimetric analysis of sweat chloride for cystic fibrosis diagnosis. Adapted with permission from Ref. [134]. Copyright 2021 American Association for the Advancement of Science. (D) Freestanding smart watch with a flexible field-effect transistor (FET) biosensor array using aptamers for cortisol monitoring. Adapted with permission from Ref. [115]. Copyright 2022 American Association for the Advancement of Science. (E) Electrochemical biosensor array for multiplexed monitoring of wound biomarkers with controlled drug release for non-healing chronic wounds common in diabetic patients. Adapted with permission from Ref. [147]. Copyright 2023 American Association for the Advancement of Science. (F) Wearable device for rapid uptake of thermoregulatory sweat at rest and monitoring levodopa for assist medication management of Parkinson's disease patients. Adapted with permission from Ref. [148]. Copyright 2021 Nature Portfolio.

Considerations on the methodology of sweat collection sweat are equally important for a wearable platform. Within the nascent field of wearable sweat analysis, there currently exists an absence of standardized collection methodologies. Conventional sweat collection methods, including whole body-washdown, arm bags, Macroduct collection tubes, and other strap-based devices, often prove cumbersome, uncomfortable, and inconvenient.[162] These approaches necessitate collecting and storing sweat samples at centralized laboratories to enable subsequent biomarker analysis. In contrast, wearable sweat platforms leverage breakthroughs in flexible electronics, microfluidics, and materials science to demonstrate the potential of patch or sticker-like collection form factors to overcome these diagnostic and interfacing limitations. Such devices employ soft materials and integrate absorbent materials[163–165] or superhydrophobic/superhydrophilic surfaces, along with intricate microfluidic networks, to enable the precise collection and routing of sweat without the need of high-pressure, strap-based interfaces.[162,95,134,166]

Despite the intimate skin interface such epifluidic devices afford, challenges persist in sample contamination from the skin surface.[59,167,168] Innovative solutions are required to minimize contamination while preserving the key sweat components of interest. Current research primarily focuses on the collection and analysis of liquid sweat, although "insensible" sweat–sweat that constantly evaporates from the body as vapor–serves a vital role in thermoregulation. The collection and analysis of this form of sweat is challenging[67]; however, recent efforts report a superhydrophobic sweat sensor that harvests insensible sweat for continuous sweat rate monitoring (i.e. sweat loss) (Figure 4(B)).[169] With proper correlations, the insensible sweat rate measurements can be used to evaluate skin health, disease conditions, and psychological stress, anxiety, or pain. The capability to monitor both sensible and insensible sweat is of particular interest owing to the diverse and variable composition of sweat from different body areas and among participants.[52,170]

As this field rapidly evolves, it is crucial to assess the various sweat stimulation techniques and document variations in sampling and analytical measurements to address reproducibility concerns[171] and enable data comparison. The use of validation platforms, such as commercial assay kits or traditional analytical techniques, benchmarked against a time-dynamic sweat response is essential for data comparison, especially when considering the necessity for adequate representation of varied populations during the development and deployment of new technologies.

Clinical Utility of Sweat. Promising significant advancements to our understanding of human health, wearable sweat sensing platforms demonstrate an ever-increasing capacity for accurately and reliably measuring physiologically relevant signals. However, the physiological and clinical implications of sweat-based biomarkers remain relatively underexplored. Deployed in tandem or in combination, chemical analysis techniques such as mass spectrometry (MS), nuclear magnetic resonance (NMR), various forms of chromatography (e.g., high-performance liquid chromatography (HPLC), gas chromatography (GC), liquid chromatography (LC), ion chromatography (IC)), and enzyme-linked immunosorbent assays (ELISAs) offer powerful capabilities for elucidating the complex biomolecular relationships of sweat constitutients. Equally crucial to the realization of personalized health monitoring is a thorough understanding of the relative quantities of sweat-based analytes and their correlations to gold standard body fluids such as blood and urine, or correlations to specific health states. While the clinical relevance of sweat has been established for a limited number of conditions (e.g., cystic fibrosis), much remains to be discovered about the correlation between the dynamic responses of various sweat constituents to other biochemical and biophysical signals produced by the body over varying timescales. A recent study[172], for example, reports the use of a multifunctional wearable device to wirelessly measure local sweat loss, sweat chloride concentration, and skin temperature. The deployment of a network of 20 devices across the body enables the mapping of body temperature under varying conditions and over time (Figure 4(C)). This type of research[99,173] represents a pivotal step toward generating comprehensive datasets, which are essential for extracting meaningful insights from sweat-based information. Similiarly, future research should focus on incorporating a broad range of participants, spanning different sexes, races, ethnicities, ages, socio-economic statuses, and abilities. This would help decipher the variations in sweat composition and rates among diverse populations. Ultimately, such comprehensive studies will be key to establishing universal baselines for sweat biomarkers, enabling the detection of significant deviations that might indicate a disease state.

Biomarker Sensing Strategies. Sophisticated sensing strategies are critical for addressing the challenges of sweat stimulation, fluid-handling, and contamination to enable the extraction of meaningful physiological insights from sweat. Decoupling target signals from interfering species, co-dependent biomarkers, and other sources of noise is non-trivial. The meticulous selection of chemicals, reagents, and substrates is crucial for sensor development, as even slight variations from different suppliers can significantly alter chemical behavior. Simultaneously, devising technology to normalize factors in real-time that may vary in real-life settings is essential to maintain accurate device measurements. For example, differences in sample volumes and flow rates often result in divergent sensor measurements due to analyte mass transport to the sensor.[70,94,174] Considering the common observation of varying sweat rates among individuals and body locations, fluidic control strategies, such as meandering microchannels, could be employed to normalize the flow rate in applications where instantaneous sweat rate variations are not of clinical interest.[96]

Interferents, skin contaminants, and sensor fouling, frequently addressed in the literature, can be mitigated with selective membranes and modifications.[175,176] Less discussed, yet crucial, is the impact of electrolyte concentration on electrochemical sensors. As electrolytes are indispensable for electron transfer, fluctuations in chloride and other electrolyte levels can erroneously skew sensor responses. To successfully commercialize electrochemical sweat sensors, incorporating algorithms or mechanisms to control electrolyte concentrations is essential. Furthermore, environmental factors in real-world settings, such as temperature variations or physical impacts, can affect sensor performance. Colorimetric sensors face challenges from uncontrolled lighting and warping due to body integration, which can be addressed with sophisticated strategies like incorporating color reference markers[96,128] or machine learning algorithms.[127] In aggregate, these challenges underscore the critical need for comprehensive device testing across all possible conditions and usage scenarios for a given application in order to facilitate the translation of such wearable platforms from the benchtop to less controlled environments.

Pathway to Commercialization. Translating promising research prototypes into commercially viable devices presents a formidable challenge as it demands strategic consideration of scalable manufacturing, clinical validation, regulatory approval, and environmental impact. Prior to commercialization, wearable sweat sensors necessitate comprehensive on-body system integration, demanding continuous, long-term operation within a compact, comfortable platform. Although these factors were once outside the scope of academic research, they now serve as critical design considerations during prototyping, as decisions made at the development stage can lead to costly revisions during mass production. Moreover, to effectively introduce sweat sensing devices effectively in healthcare for resource-limited regions, innovations are required to develop cost-effective and scalable manufacturing approaches suitable for such application spaces.

A considerable number of powerful research demonstrations rely on epifluidic devices formed from biocompatible, low-modulus elastomeric substrates such as poly(dimethylsiloxane) (PDMS).[134,177,178] While the process facilitates rapid innovation, soft lithographic fabrication can be costly, poorly suited for translation to traditional large-scale manufacturing processes, and often impractical in resource-limited or remote locations, limiting opportunities for reproducible research and placed-base innovation. Recent efforts have sought to overcome these limitations by employing processes that complement traditional mass manufacturing without necessitating specialized equipment, such as screen-printing[36] and laser etching/cutting.[101,104,142] Alternative approaches to epifluidic channel fabrication involve laser-cut double-sided adhesive and polymer films, like polyethylene terephthalate (PET).[101,141,179] However, these methods offer limited feature resolution compared to conventional cleanroom-based prototyping approaches. Additive manufacturing (AM) techniques, commonly referred to as three-dimensional (3D) printing, hold immense potential for addressing some of these fabrication challenges through an expanded design space. By constructing structurally complex objects from a digital computer-aided design (CAD) file, 3D printing enables rapid, cost-effective fabrication of microfluidic devices either directly or through production of soft lithographic templates, albeit at the expense of printer resolution (>200 μm). A recent report[180] details the first 3D-printed epifluidic device with true microfluidic dimensions (~ 50 μm) using a standard, commercial resin-based 3D printer, highlighting the feasibility of leveraging AM for rapid prototyping and localized production. This novel 3D-printed epifluidic platform ('sweatainer') allows for a new mode of sweat collection that facilitates the acquisition of multiple, independent sweat samples via a channel architecture uniquely achievable through AM (Figure 4(D)). Such examples highlight the potential of future research endeavors focused on optimizing existing manufacturing technologies for epifluidics or exploring innovative fabrication approaches (such as AM) in unlocking pathways for successful production of affordable, real-time sweat sensors.

Alongside scalable manufacturing, integrating adept power management for long-term operation can impede progress towards commercialization. A recent work[181] addressed power management by developing fully-integrated microgrid sweat lactate biofuel cells with a rechargeable Zn–AgCl battery. These bioenergy modules used lactate oxidase (LOx)–bilirubin oxidase (BOx) biofuel cell groups to harvest biochemical energy from the user sweat lactate for sustainable bioenergy harvesting combined with with Zn–AgCl batteries for extended energy storage (Figure 4(E)). Although still an improvement compared to traditional health monitoring methods, the requirement for fully integrated systems to have power management, data acquisition, wireless communication, among other components can increase the bulkiness of wearable sweat sensing platforms. Electronic, sensor, and device feature miniaturization must be a key focus to enable more discreet wearable sweat sensors, enhancing user comfort and acceptance. [132,182–184] Advancements in self-sustaining power systems[181,185] and miniaturized devices [132,182–184] aid the realization of fully integrated systems. As devices approach regulatory approval, safety features need to be incorporated for safe operation by the end user. For instance, the incorporation of thin, flexible bladders into wearable sweat devices has been demonstrated as a safety measure, automatically detaching the device from the user if the electronics overheat.[186] As highlighted in several recent reviews,[187,188] additional considerations spanning data security[189] and user privacy[190] to accessibility[191] and platform interoperability[192] are essential for ensuring end user safety, which is imperative for commercialization. Consideration of such precautions ensure the end user safety which is imperative for commercialization.

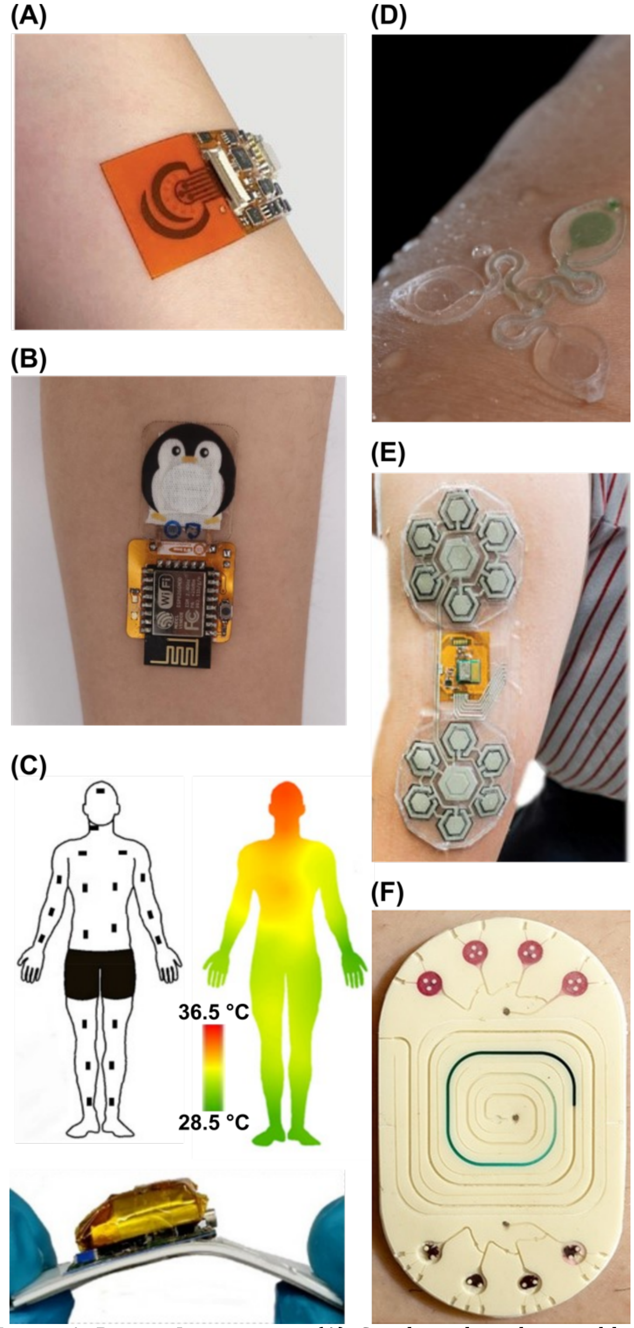

Figure 4. Recent Innovations: (A) Graphene-based wearable device, with material optimized by an automated computational framework, that can perform autonomous sweat induction, sampling, and sensing. Adapted with permission from Ref. [158]. Copyright 2023 Wiley. (B) Superhydrophobic sweat sensor to measure sweat vapor with flexible wireless communication and powering module for a standalone sensing system to continuously monitor insensible sweat rates. Adapted with permission from Ref. [169]. Copyright 2023 American Chemical Society. (C) A multifunctional wearable platform that can wirelessly measure local sweat loss, sweat chloride concentration, and skin temperature for mapping throughout the body. Adapted with permission from Ref. [172]. Copyright 2023 American Chemical Society. (D) 3D printed epifluidic platform, called a "sweatainer," that enables collection of multiple, independent sweat samples. Adapted with permission from Ref. [180]. Copyright 2023 American Association for the Advancement of Science. (E) A fully integrated wearable electronic skin patch, powered by two microgrid bioenergy modules with extended

energy harvesting and storage ability. Adapted with permission from Ref. [181]. Copyright 2022 Wiley. (F) Wearable microfluidic device with key components fully degradable in natural soil environments or industrial compost facilities. Adapted with permission from Ref. [193] with permission. Copyright 2022 Wiley.

With any manufacturing and commercialization effort, innovators are responsible for acknowledging and if possible minimizing ecological harm. The widespread adoption of single-use medical devices for at-home use has significantly enhanced the quality of life for countless individuals, yet it has concurrently spawned adverse environmental consequences.[194] For instance, the utilization of disposable masks and single-use rapid diagnostic tests have been instrumental in individual protection and management of COVID-19 transmission. However, such broad usage has been concomitant with a significant increase in the daily production of medical waste, the environmental repercussions of which are only now just beginning to emerge.[195–197] To avoid a similar impact the emerging generation of wearable biomedical devices, particularly plastic-based sweat sensors, must conscientiously address the associated environmental ramifications across the device lifecycle spanning manufacture, use, and disposal. Implementing strategies that use biodegradable polymers and transient electronic systems may ameliorate such waste dilemmas.[198] One recent example[193] highlights such an approach by demonstrating the materials, fabrication approaches, and assembly techniques necessary for fabricating an epifluidic device that can undergo complete natural biodegradation (Figure 4(F)). Future sweat sensor development must prioritize the integration of degradable, compostable, or recyclable materials and sensing technologies to foster environmentally sustainable healthcare systems.

Considerations for the Next Generation of Platforms

Wearable sweat platforms represent a promising pathway for augmenting existing health and disease monitoring strategies. To facilitate broad adoption, such devices must seamlessly integrate within an individual's existing device ecosystem by offering physiological monitoring capabilities inaccessible to conventional wearable platforms (e.g. watches, bands, and rings).[179] Concurrently, harnessing the rapid advances in artificial intelligence and machine learning will enable the next generation of wearable platforms to deliver clinically-relevant health insights drawn from previously undiscovered signals in sweat-based biomarkers.[199]

As the field of sweat sensing technology advances, it is vital to prioritize equity in research and commercialization to avoid perpetuating existing healthcare disparities. Recognizing and overcoming the barriers to equitable innovation is paramount. Historically, the development of medical technologies often occurs without sufficient attention to the needs of diverse populations, resulting in pronounced healthcare disparities. Consider the example of pulse oximeters. Universally deployed in clinical settings, pulse oximeters are known to exhibit decreased accuracy for patients with dark skin tones, potentially leading to severe clinical implications.[200] While wearable sweat sensors offer an opportunity to expand participation in innovation, there remains a critical need for researchers to intentionally include community members of marginalized and vulnerable groups as partners throughout the development process, from initial device design and function research to clinical evaluations. This proactive stance stems from the understanding that one cause of existing healthcare disparities is the historic and ongoing limited representation in scientific research, which results in nonrepresentative studies of the overall population.[6] Moreover, even when included in research, certain groups, such as the Native Hawaiian and Pacific Islander (NHPI) population, are often aggregated with other diverse populations, which further biases research data and compounds representation issues.[201]

The generation of representative physiological data sets underscores the critical need to enhance research reproducibility and data sharing. Drawing from existing research, the creation of a comprehensive, accessible database detailing the relative quantities of proteins, small molecules, and other biomarkers excreted in sweat with potential correlations to other biofluids and clinical conditions would accelerate the establishment of the clinical utility of sweat-based analysis in a manner similar to the IEEE*DataPort* Wearable Sensors database. The medical community has started recognizing the substantial benefits of such openness, with data sharing facilitating scientific progress, expediting the translation of discoveries from bench to bedside, and ultimately, improving patient outcomes.[202] Large institutional efforts such as NSF Open data,[203] NIH's biomedical data repositories,[204] and Chan Zuckerberg Initiative Open Science[205] have created resources for biomedical data sharing to become more widespread. As the scientific community continues the shift towards open science, the ongoing enhancement of information accessibility and supportive infrastructure remains a pressing need.

Through these efforts to establish a comprehensive understanding of sweat composition and resulting correlations to blood and other biomarkers, sweat sensors can provide valuable insights into human health and quality of life, particularly for those individuals in resource-limited settings. Geographic and resource barriers, as exemplified in the context of Hawaiʻi and US-Affiliated Pacific Islands, often result in limited access to high-quality, reliable medical care and technology, particularly in rural regions.[206] This restricted access has been associated with higher maternal mortality rates, suboptimal disease management, and deteriorating mental health compared to many regions of the continental United States.[207–211] Telemedicine has emerged as a strategy to address these issues,[211–213] but most devices proposed for use in this context fail to provide performance sufficient to meet clinical needs. If developed in a thoughtful manner, wearable sweat sensors hold the potential to bring cutting-edge, comprehensive medical monitoring to those who currently lack access, particularly in resource-limited settings.

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Notes

The authors declare the following competing financial interest(s): T.R.R. is an inventor on patents and patent applications related to epidermal microfluidics and has a consulting and advisory relationship with Epicore Biosystems.

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