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Perspective

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The challenges and promise of sweat sensing

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The potential of monitoring biomarkers in sweat for health-related applications has spurred rapid growth in the field of wearable sweat sensors over the past decade. Some of the key challenges have been addressed, including measuring sweat-secretion rate and collecting sufficient sample volumes for real-time, continuous molecular analysis without intense exercise. However, except for assessment of cystic fibrosis and regional nerve function, the ability to accurately measure analytes of interest and their physiological relevance to health metrics remain to be determined. Although sweat is not a crystal ball into every aspect of human health, we expect sweat measurements to continue making inroads into niche applications involving active sweating, such as hydration monitoring for athletes and physical laborers and later for medical and casual health monitoring of relevant drugs and hormones.

Human eccrine sweat is one of the most provocative frontiers in biomedical sensing. Actively produced from blood plasma and interstitial fluid through highly vascularized sweat glands, sweat contains a wide array of biomarkers ranging from electrolytes and metabolites to hormones, neuromarkers and drugs. Furthermore, the accessibility and near-constant production of sweat makes it a prime candidate for wearable, continuous-time monitoring. In addition to the well-established tests of sweat chloride for cystic fibrosis diagnosis and stimulated sweat production for assessment of regional nerve function, some speculative use cases include measurements of sweat volume and electrolyte loss for dehydration monitoring in athletes and in workers in extreme environments; sweat cortisol for stress monitoring; and sweat drug concentrations for medication dosage prescription and monitoring (for example, levodopa for Parkinson's disease)[1]. However, realizing such visions has been difficult in part because gaps remain in scientific understanding of the complex process of sweat production and analyte partitioning and because many new developments begin with a 'tech-first' and 'biology-second' approach, such that technologies that produce exciting in vitro results fail when tested in vivo[2].

In many cases, correlations between sweat characteristics and blood composition or other physiological parameters of interest have not accounted for confounding factors, such as sweat gland secretory rate and the biological generation pathway[3]. In addition, the multitude of proposed collection methodologies, aside from the clinical assay collection method[4], makes it difficult to verify reproducibility for even the most basic but fundamentally important measurements, such as secretory rate, which are influenced by the choice of skin site and the collection procedure[5]. Thus, the compiled results to date on many topics are either conflicting or not comparable.

Certain pilot studies have shown promising evidence for the value of dynamic changes in various analytes in sweat, including glucose, cortisol and neuroimmune biomarkers[6–8]. However, a better understanding of the underlying partitioning mechanisms is needed. These analytes should also be investigated in targeted population studies at scale, with concurrent monitoring of other physiological changes using on-body physical biosensors, external stimuli and any relevant environmental changes. Sensors for these studies must have long-term stability with repeatable, at-scale production, integration of secretory rate and composition sensing, robust leak-free sweat collection and secure packaging with robust interfaces between electrodes and electronics. Furthermore, before such studies are undertaken, researchers should weigh the merits of the investigation. For example, there is clear motivation to study sweat glucose with respect to the basic science of sweat analyte partitioning and possible application for casual health monitoring; however, sweat glucose monitoring will arguably never attain the accuracy of wearable indwelling needle or microneedle sensors in interstitial fluid or blood glucose meter readings for medical purposes.

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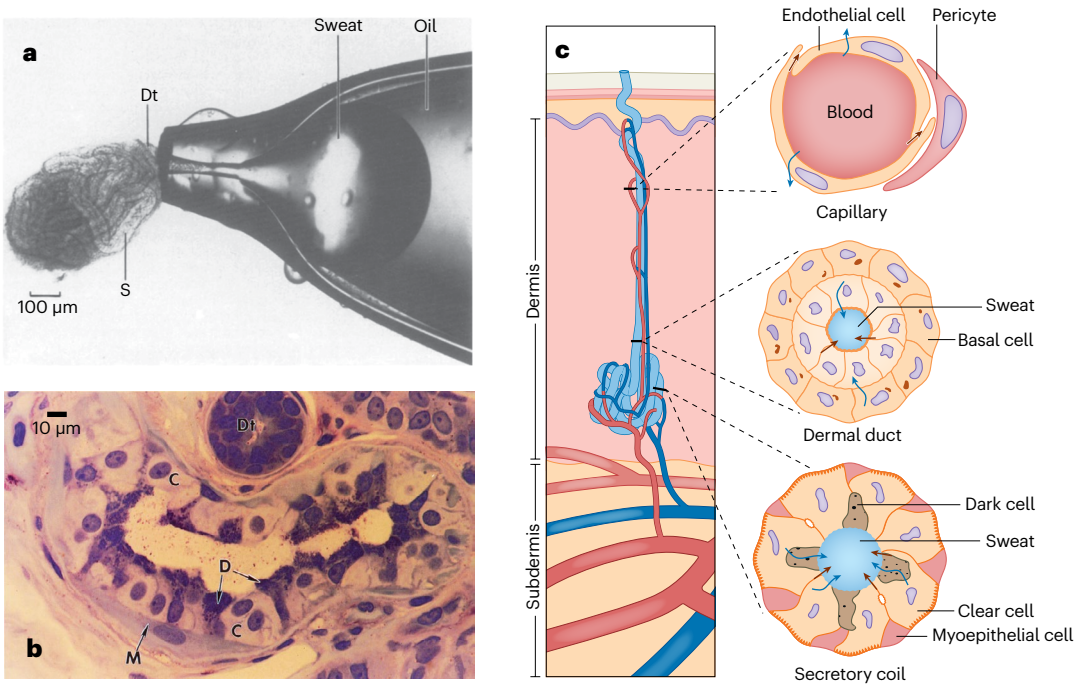

Fig. 1 | Sweat gland structure and physiology. a, Photograph of isolated eccrine sweat gland undergoing in vitro sweat induction, showing a dermal duct (Dt) and a secretory coil (S). **b**, Transverse sections of secretory coil and adjacent dermal duct. Lining the secretory coil are clear (C), dark (D) and myoepithelial (M) cells (2-µm plastic section with optical microscope). **c**, Diagram of the sweat gland showing vascularization, dermal duct and secretory coil. Credits: images reprinted, with permission, from ref. 19, the American Physiological Society (**a**); ref. 106, Springer (**b**); ref. 2, Springer Nature Limited (**c**).

In this Perspective, we review the progress of the young field of sweat sensing from the viewpoints of both engineering and physiology, discuss commercialization challenges and suggest guidelines for future work. In our view, sustained progress will require recognition of the current exploratory state of the field, resolution of various technical challenges and increased collaboration between engineers and physiologists.

Historical sweat study and diagnostics

Human eccrine sweat has been observed for health information as far back as the medieval era, when a European folklore adage warned of a poor prognosis for children with particularly salty sweat. The method of sweat analysis for this condition, at the time considered to be a bewitchment but later termed cystic fibrosis, was the taste of a kiss[9]. Similarly, a 1606 book by the Spanish professor of medicine Juan Alonso y de los Ruyzes de Fonteca records an association held between salty skin on a child's forehead and bewitchment[10,11]. In the 1950s, the observation of elevated sweat chloride accompanying cystic fibrosis was quantitatively verified[12], and the diagnostic method was overhauled by pediatricians, who used sweat-collection techniques involving absorbent pads of gauze and filter paper and collection vessels made of plastic bags and sheets. To generate sufficient volumes of sweat, heat stimulation was performed using hot water bottles, blankets, heat lamps and humidifying incubators as well as chemical stimulation by injection of the drug pilocarpine, a cholinergic agonist. Sweat analysis of sodium and/or chloride was performed with flame spectrometry or a polarograph[13,14]. Around that time, Gibson and Cooke introduced the sweat-induction method still used today for clinical cystic fibrosis diagnosis: regional sweat gland stimulation with pilocarpine applied via iontophoresis, an electrical technique for drug transport through the epidermis. Absorbent material then collected the stimulated sweat over a fixed period of time[14]. Several commercial devices were developed to implement this test, including the still-popular Macroduct Sweat Collection System by Wescor, introduced in 1982 (ref. 15). This system includes a standardized pilocarpine iontophoresis system with a reliable collection device in the form of a coiled capillary tube inside a wristwatch-style sealed receptacle.

In the 1970s, sweat was becoming a topic of interest for other applications as well, such as monitoring electrolyte balance for those working in intense environmental conditions or participating in intense physical activities. Foundational studies on the physiology of the sweat gland, both in vivo and in isolation, were conducted by the dermatologist Kenzo Sato[16] (Fig. 1a). These impressively detailed studies covered a range of topics including sweat gland anatomy, pharmacologic response, energy metabolism and secretion of ions and organic molecules[16–19]. Sato pinned nervous system control of sweating to the hypothalamus as the body's 'thermostat', but the effects of individual stimuli (core temperature, skin temperature, subdermal temperature, muscle temperature, neuromuscular drive and psychological stress) were poorly understood at the time.

Physiology of sweat secretion and stimulation

Sweat glands are widely distributed throughout the body surface, with their highest density in the palms and soles at 600–700 cm^{-2}, and most other areas having moderate densities near 100 cm^{-2}. From an anatomical perspective, the sweat gland is a fairly simple structure: a single long tube with a coiled end that sits in the lower dermis and an elongated straight segment that traverses the dermis and epidermis and opens in the skin surface (Fig. 1). Two types of glands are present: eccrine glands, which are smaller and widely distributed throughout the body, and apocrine glands, which are larger and confined to the underarm and groin. Eccrine glands are primarily involved in thermoregulation and produce a clear fluid with high water content. The less-abundant apocrine glands produce a milky fluid that contains proteins, lipids and sterols and are primarily activated in response to stress or sexual stimulation. Most of the secretory activity is carried by eccrine glands, predominantly through cholinergic stimulation that involves both muscarinic and nicotinic receptors. Although eccrine glands also have

the receptors and a small secretory response for adrenergic stimulation, the role of this is unclear[11,20].

The coil in sweat glands serves primarily a secretory function, with dark cells lining most of the lumen, clear cells lying sometimes between and sometimes behind them and myoepithelial cells interspersed in a basal position (Fig. 1b). The clear cells are the main secretory type and express high levels of ion channels and Na^+–K^+ ATPase, also known as the sodium–potassium pump. Most small solutes that easily enter into sweat do so by transcellular diffusion if they are small and hydrophobic (for example, steroid hormones and many drugs), whereas a more challenging and diluted paracellular entry path occurs for small hydrophilic solutes (for example, metabolites). The entry of larger solutes such as proteins is still not fully understood and could be a mix of paracellular transport or transcytosis[2]. Evidence for dark cells releasing glycoproteins of varying sizes from granular contents was provided by a combination of histochemical staining and antibody binding[21].

Sweat is naturally produced in pulses at a frequency of 12–21 cycles per second[22]. This may be in part due to contraction of myoepithelial cells but is mostly driven by sympathetic sudomotor discharge and resulting activation of cholinergic receptors[20,23]. Sweat secretion follows the Thaysen–Schwartz two-step model: primary sweat is produced in the coil and is modified as it moves up the duct[16,24,25] (Fig. 1c). The duct is composed of roughly two layers of cells, basal and luminal ductal cells, and it serves primarily an active electrolyte-reabsorptive function, which at low sweat rates brings the concentrations of sodium and chloride six to eight times lower than those present in plasma to render the secreted sweat hypotonic[26]. Through this highly evolved mechanism, cooling can be effectively produced in the skin surface by water evaporation without severe electrolyte losses.

From an engineering perspective, there are two categories of methods for sweat generation: pharmacological stimulation and natural or physiologic stimulation, the latter including thermal stimulation, exercise stimulation, psychological stimulation, some combination of these or even none at all, here referred to as non-stimulation. Thermal sweat stimulation occurs with an elevation in body temperature, detected by internal and skin-based thermoreceptors, which is then translated to sympathetic nervous control by the hypothalamus[27–29]. Exercise stimulation involves this same thermal pathway owing to the heat generated by muscular contraction. Additionally, there is strong evidence for non-thermal mechanisms related to muscular activity involving central command, which describes the radiation of neural impulses from the motor cortex, muscle metaboreceptors, which detect metabolic products of muscle contraction, and input from baroreceptors (blood volume) and osmoreceptors (hydration)[29,30]. One last distinct class of natural sweating, primarily seen in apocrine sweat glands and uniquely mediated by adrenergic receptors, is triggered by stress or other strong emotions[31]. Further, even during rest, the body still generates a measurable quantity of sweat, presumably via baseline stimulation of the aforementioned pathways, which we refer to as non-stimulated sweat. Finally, there is pharmacological stimulation, which typically involves the administration of cholinergic agents via epidermal application, iontophoresis or injection; this directly stimulates the muscarinic receptors on sweat glands and triggers sweat production[29]. Some of the more powerful and slowly metabolized sweat stimulants, such as carbachol, have been demonstrated to generate local sweating for a remarkably long duration of 2–3 d, with multiple low-dose or single higher-dose treatments[32].

Some differences are known to exist between sweat samples obtained by different stimulation methods, due to their varying generation pathways and typical secretion rates. Pharmacological sweat is known to be secreted in a steady stream, unlike naturally stimulated sweat, which is pulsatile owing to its origin in bursts of activity in dermal sympathetic nerves[20]. It has been observed that, at matching flow rates, pharmacological sweat contains significantly higher concentrations of potassium and sometimes sodium than thermal sweat but similar concentrations of lactate and several other metabolites[17,33]. Some trends distinguish sweat samples on the basis of secretion rate, adding a layer of distinction between low-secretion-rate classes like non-stimulated sweat and high-secretion-rate classes like pharmacological sweat. One well-studied effect is the increase of sodium and chloride with increase in sweat rate due to saturation of reabsorption in the sweat duct[34,35]. There is also limited evidence for the secretory rate influencing the protein content of sweat, with an observation of a higher content of proteins sized about 68 kDa at high secretory rates[34,36]. The reasons for this are unclear, although potential mechanisms include varying proteolytic degradation during outflow, contribution from different cellular compartments and differing protein synthesis[34]. Overall, the current corpus offers conflicting evidence on the trends of various analytes and does not present the full picture of sweat rate alongside concentration[3]. There is more basic science to be conducted in this area; until a consensus has been established, the various biological pathways of sweat generation should not be considered completely interchangeable. In particular, more data are needed to understand relationships between sweat rate and sweat-generation method across all analytes.

Devices for sweat analysis

Several sweat-sensing modalities have been established clinically or commercially (see Fig. 2 for notable examples). Many of these are designed to analyze a single analyte in a single sample (for example, chloride levels for cystic fibrosis and drug tests). So far, no commercial devices have been shown in peer-reviewed studies to provide continuous and accurate on-body measurements of either sweat composition or secretory rate. Rather, several commercial devices exist for robust sweat collection in various applications but leave the chemical analysis to be performed off-body. Others make real-time, quantitative measurements of indices of sweat rate, such as skin conductivity or skin capsule humidity, but cannot provide a volumetric flow rate and often involve bulky instrumentation.

The Macroduct Sweat Collection System, perhaps the most well-known product in the sweat-sensing field, was introduced in 1982 for the diagnosis of cystic fibrosis and has since become the most popular device for the clinical gold-standard quantitative pilocarpine iontophoresis test (Fig. 2a). The Macroduct system, in two steps, chemically induces and then collects sweat from a designated skin site for off-body measurement of the sweat with an accompanying chloridometer, conductivity analyzer or osmometer as a proxy for electrolyte concentrations[37]. Another sweat-sensing product cleared by the US Food and Drug Administration (FDA) is the PharmChek Sweat Patch, developed in 1990, which is a sweat-collection device providing court-admissible evidence intended for drug-abuse detection (Fig. 2b). The simple yet tamper-proof device accumulates sweat in a long-term-wear absorbent patch[38]. Used patches are sent to a laboratory for chemical analysis. These products laid the groundwork for reproducible sweat-collection technology, with many academic studies using and building on the Macroduct to this day[39–41].

Several commercial devices and clinically established tests observe sweat production by quantitative but non-volumetric methods for detection of diabetic neuropathy and some other autonomic neurological disorders. The most widely available test for sudomotor function is the quantitative sudomotor axon reflex test, a humidity-based sweat measurement from pharmacologically stimulated skin sites circumscribed by sealed capsules. This device was commercialized as the Q-Sweat Quantitative Sweat Measurement System[1] (Fig. 2e). Another clinically established test is the thermoregulatory sweat test, which uses a colorimetric powder for qualitative whole-body sweat monitoring[1]. Designed to replace the quantitative sudomotor axon reflex test with a simpler and quicker process for clinicians, the SUDOSCAN device assesses sudomotor function via electrochemical skin conductance,

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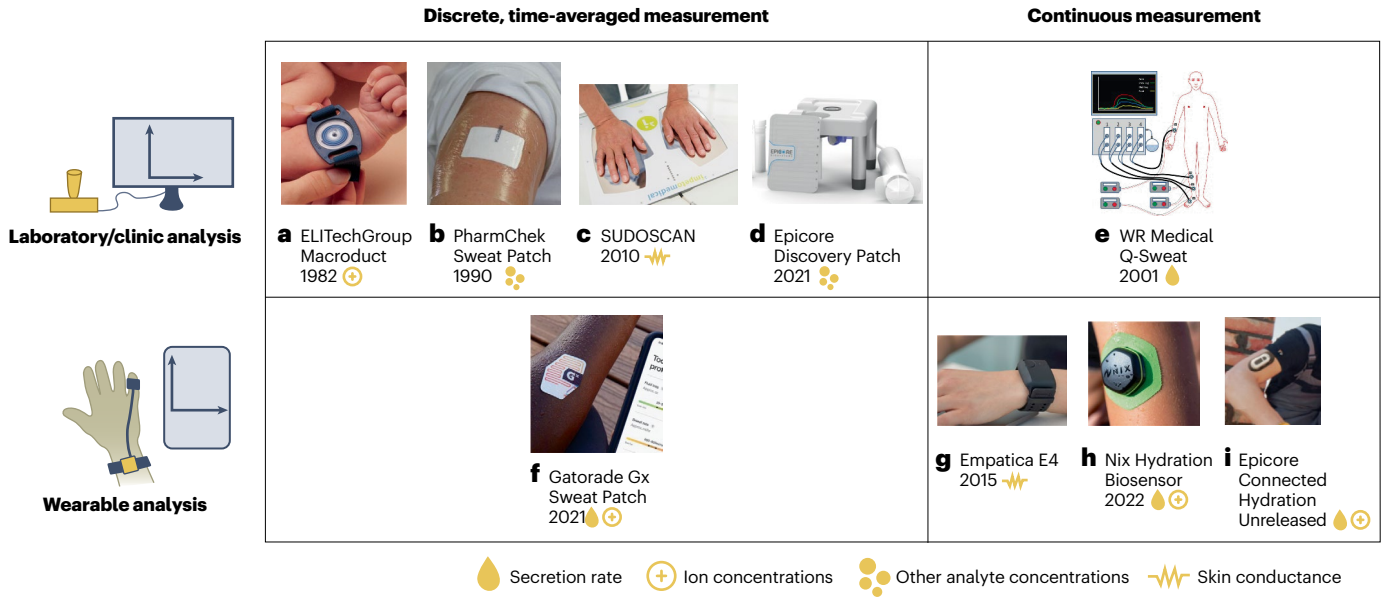

Fig. 2 | Commercial sweat-monitoring devices. a, The Macroduct Model 3600 from ELITechGroup takes a single-point, off-body measurement of sweat chloride after chemical sweat stimulation for the diagnosis of cystic fibrosis. **b**, The PharmChek Sweat Patch collects sweat for a single-time point, off-body measurement for drug-abuse monitoring. **c**, The SUDOSCAN performs a conductance-based measurement of sweating function for neuropathy assessment. **d**, The Epicore Discovery Patch is a nonspecific collection patch for a single-time point, off-body sweat measurement. **e**, The Q-Sweat measures regional sweating with humidity capsules for clinical assessment of various neuropathies involving loss of sweat function. **f**, The Gatorade Gx Sweat Patch collects sweat during exercise for an on-body, single-point measurement of average sweat rate and sodium concentration. **g**, The Empatica E4 measures skin conductance, an index of sweat rate, on the ventral forearm. **h**,**i**, The Nix Hydration Biosensor and the Epicore Connected Hydration device both continuously stream sweat rate and electrolyte concentration. Credits: images reprinted, with permission, from ELITechGroup; Nemours KidsHealth; WR Medical Electronics; ref. 107, Elsevier; PharmChek; Epicore Biosystems; Sudoscan (Impeto Medical); Empatica; Gatorade; Nix Biosensors.

a measure of the conductance at the hands and feet during electrical stimulation across an array of direct-current voltages[42] (Fig. 2c).

None of these devices for clinical tests perform wearable, ambulatory, on-body analysis. However, integrated wearable devices do exist for obtaining an index related to sweat rate: the conductance of skin, also known as galvanic skin response, or electrodermal activity. Galvanic skin response is a simple concept in which increased sweat-secretion rate and corresponding saltier sweat raise electrical conductivity through the normally insulating stratum corneum of the skin. One modern iteration of measurement devices is the continuous-monitoring Empatica E4 wristwatch, which includes several common wearable physiological sensors as well as a sensor for ventral forearm galvanic skin response (Fig. 2g). This response may serve as a proxy for sweat-secretion rate, with perhaps its most well-known use in 'lie-detector' testing to monitor the sweat response accompanying psychological stress. However, it is limited by signal saturation, sensitivity to sweat ionic content and residual contamination.

Next, the Gatorade Gx Sweat Patch, released in 2021, is a wearable microfluidic patch for athletic applications that uses colorimetry for measurement of regional sweat loss and chloride[43] (Fig. 2f). Owing to the inconvenience of obtaining measurement images during physical activity, the system performs a single-point reading. Its measurements of regional sweat loss on the forearm have been shown to correlate with whole-body sweat loss and can help assess hydration status[43,44]. A similar but pared-down device, the Epicore Discovery Patch, only collects a volume of sweat, leaving the analysis off-body and open ended and is FDA cleared (Fig. 2d).

Lastly, two of the first continuous-monitoring electrolyte and sweat-rate products were recently launched. The Nix Hydration Biosensor system includes a rechargeable electronic pod that clips onto a single-use adhesive sensor patch worn on the bicep to report estimated whole-body fluid loss and net electrolyte mass loss, enabling hydration-guidance features such as an Apple Watch alert upon the loss of 16 oz of sweat, for example (Fig. 2h). Along with the Epicore Connected Hydration device, another two-component wearable for sodium and fluid loss, success remains to be seen after public reception and external scientific validation (Fig. 2i). Other than these two recent products, no commercially available device has harnessed the power of accurate continuous sensing for either sweat composition or volumetric sweat rate. Furthermore, much of the physiological information that sweat may carry (metabolic, hormonal and pharmacological, aside from average sweat rate and sodium and chloride concentrations) remains to be verified by the scientific community.

The challenge of continuous sweat monitoring

The rise of wearable technology in this century with the promise to 'measure everything' for precision medicine together with real-time, personal health and fitness analytics has drawn a burgeoning academic interest to sweat as a potential sensing target. Fig. 3 illustrates this growth and surveys notable devices over the years.

Early on, most reported devices focused on single components, introducing a new analyte sensor or a new sweat-rate-measurement method without full system integration. Although some devices measured signals on-skin, often lacking was investigation of any correlations with blood analyte concentrations or other deeper physiology. Several initial studies pioneered flexible, electrochemical sensors on tattoo-like patches for analytes like lactate, ammonium and sodium, advancing the design of solid-state electrodes and the temporary transfer tattoo platform[45–47] (Fig. 3a). One study integrated a portable measurement system and a wireless transceiver with the sensor[47]. Others developed colorimetric sensors, such as a microporous patch with capacitive electrodes for volumetric sweat measurement and optical sensing of ions and pH[48].

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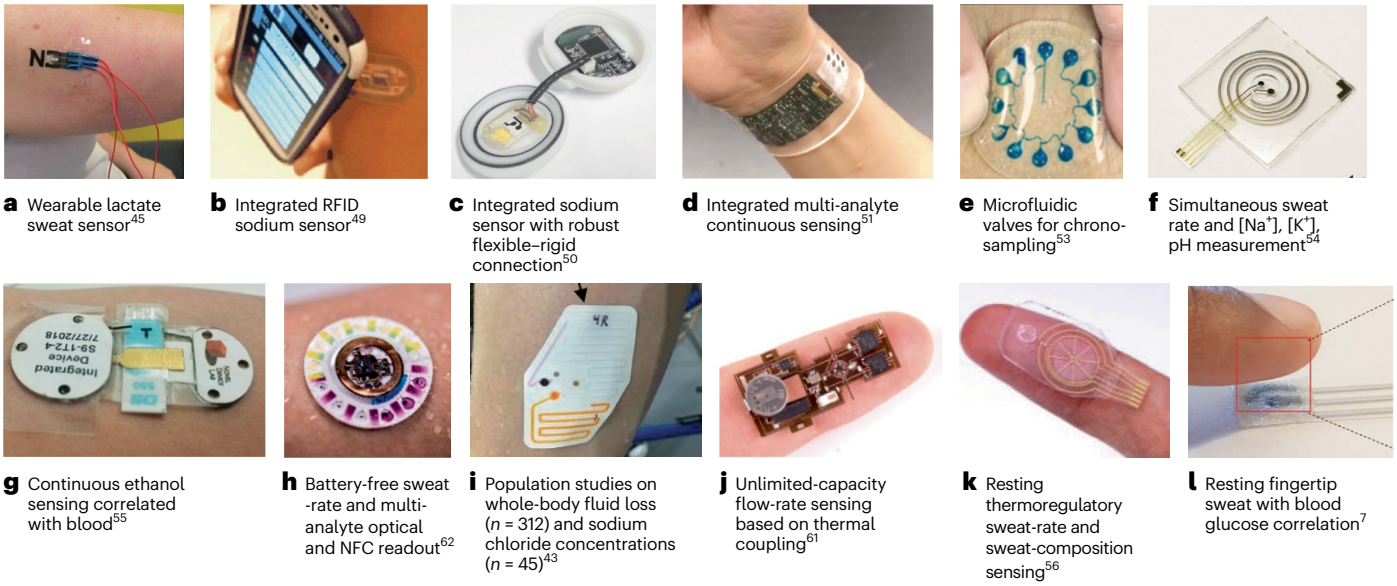

a Wearable lactate sweat sensor[45]
b Integrated RFID sodium sensor[49]
c Integrated sodium sensor with robust flexible–rigid connection[50]
d Integrated multi-analyte continuous sensing[51]
e Microfluidic valves for chrono-sampling[53]
f Simultaneous sweat rate and [Na^+], [K^+], pH measurement[54]
g Continuous ethanol sensing correlated with blood[55]
h Battery-free sweat -rate and multi-analyte optical and NFC readout[62]
i Population studies on whole-body fluid loss (n = 312) and sodium chloride concentrations (n = 45)[43]
j Unlimited-capacity flow-rate sensing based on thermal coupling[61]
k Resting thermoregulatory sweat-rate and sweat-composition sensing[56]
l Resting fingertip sweat with blood glucose correlation[7]

Fig. 3 | Growth of the sweat-sensing field over the last few decades. **a**–**l**, Devices representing important advances in sensing and integration. RFID, radio frequency identification. NFC, near-field communication. Credits: images reprinted, with permission, from (top row, left to right) ref. 45, the American Chemical Society; ref. 49, Institute of Electrical and Electronics Engineers; ref. 50, Wiley; ref. 51, Springer Nature; ref. 53, Wiley; ref. 54, the American Chemical Society; (bottom row, left to right) ref. 55, the Royal Society of Chemistry; ref. 62; ref. 43; ref. 61, Springer Nature; ref. 56, Springer Nature; ref. 7, the American Chemical Society.

Publication of these initial devices accelerated sweat-sensing research, including the refinement of sensing techniques and the introduction of several fully integrated, wireless systems, along with a proliferation of startups. Interest in sweat remained high even while other wearables in the consumer market stagnated because they reused the same standard set of optical and physical measurements, namely pedometry, pulse and perhaps blood oxygen saturation, whereas sweat promised access to new, deep physiological information.

Concurrently, physiological understanding of sweat was enriched by the development of a practical model of eccrine sweat microfluidics and biomarker partitioning[35]. New, fully integrated devices included a compact, inductively powered, radio frequency identification platform in Band-Aid form factor for discrete ion measurements[49] (Fig. 3b). A highly engineered arm band sodium sensor brought together robust mechanical and electrical design[50] (Fig. 3c). A fully integrated, battery-powered Bluetooth system using a flexible, multiplexed sensor array tracked concentrations of several analytes along with temperature[51] (Fig. 3d). Additional technological advancement was made for simpler optical measurement as well, such as a wearable microfluidic patch with an array of colorimetric sensors for monitoring regional sweat composition and sweat loss[52]. Time-resolved chemical measurements were later implemented using capillary-bursting valves in soft, conformal microfluidics[53] (Fig. 3e,h). Furthermore, simultaneous measurement of continuous sweat rate alongside chemical composition was achieved with electrodes stretching along the channel of a microfluidic patch[54] (Fig. 3f). Then, for the first time, strong, continuous correlations between analyte concentrations in sweat and blood were observed with a fully integrated, wearable ethanol sensor that used a sweat stimulant capable of sustaining local sweating for several days[55] (Fig. 3g). Further focus on small hydrophobic molecules, the class of analytes with the highest likelihood for blood–sweat correlation, led to promising successes in sweat-based continuous measurements of drug levels[56–58]. Broad analyses of therapeutic drugs found that hydrophobicity and charge state seem to determine the level of correlation between sweat and plasma[59]. In another vein, proteomic and metabolomic analyses began to lay the groundwork for broader biocomposition studies[60].

More recent academic-driven advances have included large-scale athlete-population studies with prediction of whole-body sweat loss from multifactor models and chloride concentration from regional levels[43] (Fig. 3i), unlimited-capacity measurement of sweat-secretion rate[61] (Fig. 3j), investigation of the secretion rate and composition of resting thermoregulatory sweat[56] (Fig. 3k) and strong correlations with blood glucose of non-stimulated fingertip sweat[7] (Fig. 3l), among others[62]. However, clinical and commercial progress appears to be stalling.

Rocky history of sweat startups

It is no surprise that, after a confident start, sweat sensing fell into a well-worn technology plotline, the Gartner Hype Cycle, in which an innovative technology experiences phases of inflated expectations and disillusionment and in rare cases transitions to a successful future (Table 1). For example, the startup Eccrine Systems, of which one of us (J.H.) was a cofounder, aimed to measure electrolytes in sweat but later found electrolytes to have limited utility beyond simply reflecting the sweat-secretion rate[2,63]. Eccrine Systems next pursued a sweat volume-loss wearable for dehydration prevention but found it infeasible to balance product complexity and cost. This spurred a third pivot to applications in therapeutic drug monitoring. This final pivot was too late to survive downward investment forces as the coronavirus disease 2019 pandemic crashed markets worldwide in 2020, and the company closed operations in 2021. Just before the founding of Eccrine Systems, the startup Electrozyme was spun out of an academic laboratory with the aim of measuring various sweat electrolytes and metabolites, including lactate, which to this day has no established correlation with blood levels[45,46]. Electrozyme later rebranded as Biolinq and switched its focus to microneedles for access to interstitial fluid, which it continues to pursue for glucose sensing. Another startup, Kenzen, initially focused on wearables for continuous measurement of sweat volume and electrolyte loss but pivoted to measurement of body temperature[64]. GraphWear similarly began with sweat and later moved to measurement of interstitial fluid with electro-osmosis devices.

Not all startup paths have been so tumultuous. For example, Epicore Biosystems, more recently spun out of an academic laboratory[52,53], also initially explored metabolite sensing but, with the advantage

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Table 1 | Startup history in the sweat-sensing field

Startup, operation headquarters	Timeline	Status	Funding ($US)	Patents	Launched products
Biolinq (previously Electrozyme), San Diego, US	Founded 2012, pivoted 2015	Pivoted to microneedle interstitial fluid sensing as Biolinq	$1.25 million before pivot to microneedles	2 issued, 4 pending (excluding microneedle patents)	–
Eccrine Systems, Cincinnati, US	Founded 2013, closed 2021	Closed (IP assets acquired by Epicore Biosystems)	$27.9 million	11 issued, 39 pending (IP assets acquired by Epicore Biosystems)	–
Kenzen, Kansas City, US	Founded 2014, pivoted 2018	Pivoted to existing measures for heat-stress sensing	$5 million for initial product, $4 million after pivot	5 pending	KENZEN
Xsensio, Lausanne, Switzerland	Founded 2014	Active	$7.3 million	1 issued, 3 pending	–
Nix Biosensors, Medford, US	Founded 2015	Active	$7 million	1 issued, 1 pending	Nix Hydration Biosensor
Epicore Biosystems, Cambridge, US	Founded 2017	Active	$9.9 million	5 issued, 1 pending	Gx Sweat Patch Discovery Patch Connected Hydration
FLOWBIO, London, UK	Founded 2020	Active	$1.1 million	–	–

Most early startups in the field have struggled to find their footing and have either pivoted away from sweat sensing or closed altogether. However, some recent startups are acquiring funding, patents and promise. Source for funding data: Crunchbase, MedCity News. For international currencies, conversion rates at the time of funding were used. Patent counts were compiled for US utility patents that have been issued as well as those that are pending with published applications. The list does not include provisional patent applications or patents licensed from universities, as this information is not all publicly available. IP, intellectual property.

of hindsight, refocused product development on the single-point measurement Gatorade Gx patch for sweat sodium and volume loss. In February 2022, the company announced their acquisition of the intellectual property assets of Eccrine Systems, which focused on integrated sweat stimulation and the ability to measure small-molecule drug concentrations. Epicore's early product success enabled the company to develop a continuous-monitoring sodium and sweat-rate system (Connected Hydration), which has yet to launch. Another company that found some success by limiting their scope to ion and sweat-rate sensing is Nix, which recently released their first product. Several nascent startups, such as FLOWBIO and SM24.ai, are also developing products in this field. Numerous other startups, past and present, perhaps lacking the venture investment traction of the others, are not covered here.

These well-financed but thus far largely unsuccessful commercial ventures highlight the nuanced profile of the information in sweat and current challenges in the field. Many target measures were pursued for commercialization only to reach a bottleneck, not of technology but of biology. Prolonged, continuous and population-scale studies will be important to ascertain the relevance of specific analytes for successful products in the future. Careful consideration of widespread technical challenges related to the stimulus, collection, storage and finally compositional and secretion-rate analysis of sweat, during device and experiment design, will enable execution of these studies and underlie future progress in the field.

Foundations for future success

On the basis of current understanding, we believe that the short-term commercial applications of sweat sensing, beyond established use cases in cystic fibrosis and neuropathy, are likely to be limited to electrolyte and fluid loss for hydration, with notably stable ionophore sensors, drug abuse and medication adherence and high–low level determination of steroids or other membrane-permeable hormones. Other visions are exciting but lack biological or technological foundation at present. Successful commercialization will hinge on good characterization of differences in baseline levels, sensitivity and sweat rate between individuals, and identifying factors of influence such as age, sex, ethnicity, and health and medical conditions.

Taking a step back, there is a clear need to advance the fundamental understanding of sweat composition via basic physiology research. To this day, the field lacks a thorough understanding of sweat composition and the extent to which it correlates with blood serum, even for the metabolites in sweat that are the most explored and easily accessed. Such broad fundamental research is needed for wise investment of resources and acknowledgement of the limitations of commercial products to make full use of the informative value in sweat (Supplementary Fig. 1 and Supplementary Table 1).

Sweat generation

Most sweat-sensing work to date has centered on event-driven sweating during limited periods of exercise or thermal stimulation. However, recent work has focused on enabling sweat access during everyday activity so as to increase the diversity of users and use cases and, in particular, to monitor dynamic changes over long time periods[32,56]. Two approaches that have been demonstrated are capture of low-volume, non-stimulated, thermoregulatory fingertip sweat and integrated stimulation and collection of pharmacological sweat. The former presents unobtrusive analyses of endogenous biomarker concentrations but with the possible challenge of greater variability in sweat rate[65]. Hydrogel-based interfaces have been designed to sample the nanoliter-to-microliter-per-cm^2-per-min sweat rates of the fingertip. These interfacing films are designed with a few key characteristics: hydrophilicity and, in some cases, porosity for sweat uptake from the skin by wetting properties and capillary forces as well as minimal thickness for a quick sensor response time[7,56,66]. A second method, pharmacological sweat generation, has the advantage of a reliably high sweating rate available on demand. Pilocarpine, an FDA-approved sweat stimulant, has been integrated into numerous wearable-device demonstrations, and emerging stimulants show promise for continuous, multi-day sweat measurement[32,55,67,68]. Prolonging the power and capacity lifetimes of these systems for 24-h use (or more) is a key step toward fundamental correlation studies of stimulus-driven and circadian biomarker shifts to support commercial products in continuous, non-invasive physiological monitoring.

Sweat collection and transport

After secretion, sweat must be collected for analysis while avoiding four key pitfalls that often undermine continuous-sensing, on-body devices. First, for precise, regional sweat-rate measurements, the device should sample from a defined collection area while preventing

leakage, evaporation and confluence of surrounding sweat that may run across the skin during heavy sweating. In other words, it should collect all the sweat and only the sweat from the specified area. In either gland-pressure-driven or wicking-mode sweat collection, this may be done using a robust seal around the skin collection area. Second, the device should also keep the sample free from contamination, whether from the epidermis, in particular, when cells are sloughed off of the skin[69], or from the environment, for example, during aquatic activities[70]. Third, preventing evaporation until the sweat has been sampled by the sensing element(s) is critical for accurate measurements of analyte concentrations. Finally, consideration should be given to blockage or suppression of sweat glands. Hydromeiosis is an effect seen across the whole body but in particular on the palms and areas with thicker skin, where exposure to water or dilute salty sweat leads to swelling of the epidermis and blockage of sweat ducts[71]. Use of a microfluidic device or wicking material to pull sweat away from the collection site can mitigate many of these complications[44,52,55,72].

During transport and storage of the sweat sample to the sensing element for continuous or prolonged measurement, there are additional considerations. First, old sweat must be flushed past the sensing element before new sweat may be analyzed. Second, diffusive mixing of sweat from different points in time will inevitably occur in any collection area, channel or wick, with increased solute diffusivity during shear flow via Taylor dispersion. Minimizing the dead volume of the device (the open space spanning the path from the collection site to the sensing element) will keep measurement time resolution high and lag time low.

Sweat rate

Sweat-secretion rate is a measure that may seem simple to obtain, but implementation in a low-cost wearable has proved unexpectedly difficult. The gold standards in the field for measuring local sweat rate are hygrometry and gravimetry, although these both require trained technicians for device use[73]. Several promising academic devices have been developed[54,61,74,75], such as the first continuous-monitoring commercial product, Epicore's Connected Hydration patch.

Local sweat-secretion rate carries well-known standalone information on hydration status, health conditions and psychological stress, and it also has value as a calibration factor for continuous sweat-composition measurements. For hydration, while self-assessment may be sufficient in most cases, during exercise in the heat, the sensation of thirst is known to be an unreliable indicator, in many cases leading to incomplete rehydration[76,77]. Whole-body fluid loss can be predicted from local sweating rates[43,78], making key information accessible for managing both hydration and electrolyte balance, as electrolyte losses can generally be recovered by simply replacing fluid losses with a standard sports drink[79].

The medical–diagnostic applications of sweat rate include some widespread and others rare but grave, including hyperhidrosis in an estimated 5% of the US population[80], diabetic neuropathy, regional paralysis in patients suffering from stroke[81], defects of the central nervous system in infants[82] and other autonomic dysfunctions[83]. Additionally, dynamic changes in sweat rate can provide insight into psychological stress, anxiety or pain, with applications in healthcare, education and human–computer interaction that have not yet been fully explored[56,83,84]. Finally, sweat rate is an important measure for the rigorous study of sweat analytes. The secretion rate from the glands provides a dilution factor and must be known to determine the flux of analytes lost in sweat. Additionally, the flow rate through a device's dead volume sets the lag time of sensor measurements. In low-volume sweat stimulation, it may also be important to correct for confounding effects of transepidermal water loss in parallel to active sweating.

With the high dynamic range of sweat-secretion rates across individuals, skin sites, activities and environments, it may be important to monitor additional variables such as heart rate, core body temperature, ambient temperature and humidity to elucidate the control mechanisms for this bodily function[5,85].

Sweat composition

Three modalities currently predominate in wearable, continuous chemical sensors: ion-selective electrodes, enzymatic sensors and aptamer sensors.

Ion-selective electrodes are the most stable and reliable class but have limited value for sweat sensing. Recently, much work has been done toward calibration-free readout of ion concentrations from their Nernstian signal voltages; recommendations for reproducibility include the use of a redox buffer to define the redox potential with its two states in close concentrations and, for long-term stability, the incorporation of a highly hydrophobic conducting polymer such as PEDOT[86]. The ions present at highest concentrations in sweat (sodium and chloride) are known not to correlate directly with blood plasma levels, and potassium, while tightly regulated in blood, does not have a well-established correlation[2,25].

Enzymatic sensors span many analytes but in practice have been limited to those with micromolar-to-millimolar concentrations. The enzymatically accessible analytes in sweat are often diluted by one or two orders of magnitude from blood plasma, meaning that not all sensor technologies that work for blood have the precision to properly analyze sweat composition[2,25]. Furthermore, as the sensor response current is fundamentally set by the flux of analyte to the sensing element, it may require simultaneous monitoring of flow rate to determine an accurate concentration. Correlation is disproven for some analytes (for example, lactate), not certain for some (for example, glucose) and significant for others (for example, ethanol)[55,87]. Importantly, ethanol and other exogenous compounds also have zero baseline concentration in sweat and therefore can be detected with high certainty for applications such as drug dosing and drug-abuse monitoring[57,58].

Finally, aptamer sensors are often required to address the analytes of highest interest, in particular, proteins, hormones and drugs[75,88,89]. In general, strong sweat–plasma correlations can be found for small hydrophobic molecules including cortisol and other steroid hormones because they diffuse easily through hydrophobic cell membranes[2]. For proteins, however, an emerging understanding accounts for the heavy presence of some by active secretion (for example, dermicidin). For others that are too large for unfiltered passive transport (for example, cytokines and anti-viral antibodies), two proposed pathways are tight-junction remodeling in paracellular transport and vesicular transcellular transport[2]. Drug sensing is another important avenue for aptamers and has been the analyte assayed in most of the in vivo rodent demonstrations. Potential targets include small hydrophobic drugs (for example, codeine and fentanyl) and larger or hydrophilic drugs (for example, penicillin and ibuprofen). Sensitivity requirements are high because many hormones and drugs bind at high proportions to large proteins in circulation, and these complexes cannot easily partition into sweat by either passive transcellular or paracellular permeation, including some half of common drugs at a 90–100% binding rate[2,90].

Aptamer measurements can be strongly confounded by variable pH and salinity. However, solutions are beginning to emerge, and, in addition, sweat's filtered composition naturally alleviates some biofouling issues[91]. In the past, although their target binding is reversible, aptamers have not been capable of prolonged continuous sensing due to biofouling and progressive sensor degradation with repeated electrochemical interrogation[92]. However, new strategies are being developed to improve sensor selectivity and longevity, with a recent report of week-long sensor operation in serum at bodily temperature[91–93]. Further advances in this area will broaden the scope of sweat sensing from ions and metabolites to hormones, drugs and other biomarkers, even more so as emerging sensor modalities with receptors such as molecularly imprinted polymers, antibodies and nanobodies become more developed alongside their various transduction techniques.

As detailed in previous reviews, universally desired sensor characteristics include high sensitivity, good selectivity, long-term stability and fabrication reproducibility. Often, the limit of detection needs to be orders of magnitude lower for an analyte in sweat than in blood plasma. Selectivity and protection from biofouling are also key; sensors may face interference from changes in pH, temperature and other analytes, as well as blockage by accumulated macromolecules or microorganisms. However, for the small molecules that are the most promising analytes in sweat, fouling may not be a serious issue, as robust size exclusion membrane protection can be used against albumin and the other large and most problematic foulants, as is done in commercial subcutaneous continuous glucose monitors (CGMs)[93,94]. The reproducibility of sensor responses within and across batches is also important because subject studies at scale will require large numbers of sensors to (dis)prove any physiological correlations. Before on-body use, sensors should be calibrated to stock concentrations of their target biomarker to yield measurements in units of absolute concentration rather than just relative change. Depending on its linearity, a sensor typically requires two or more calibration points. Low sensor variance within a fabrication batch can reduce this to a single-point calibration for each sensor or even eliminate individual calibration entirely, greatly facilitating population studies[86]. Ratiometric measurement has also been demonstrated for calibration-free operation of electrochemical aptamer-based biosensors[95]. Another consideration is drift, the instability in the sensor response over time. This is always present to some degree and may necessitate repeated recalibration depending on its magnitude and consistency across fabrication batches. Optimized strategies for enzyme immobilization such as those used in commercial CGMs may also be used to reduce drift[96]. Note that many of the above characteristics are important not only for sensing electrodes but also for reference electrodes[97]. In the academic laboratory or in collaboration with manufacturing facilities, researchers may achieve repeatable results using methods such as roll-to-roll screen printing of electrode designs[78] and use of pipetting robots[98]. With consistent manufacturing processes and batch analyses, even a polynomial drift can be handled. For example, the Dexcom G6 commercial CGM uses a nonlinear, time-dependent sensitivity function calibrated to each production batch to reliably translate sensor signal to glucose concentration for 10 d with no user calibration[99].

Device packaging and integration

For long-term on-body monitoring, it is important to design for wearability, especially the comfort of the skin–device interface. Rigid, flexible, adhesive and smooth materials each offer different advantages[43,100]. While robust against leakage or contamination, devices should not be painful or harmful to the wearer.

For integrated devices, there is also a tradeoff between device simplicity and sophistication. One device may choose a single-point discrete sensor measurement with an external readout device to be fully flexible, unpowered and disposable[43]. On the other end of the spectrum, a device may incorporate minimal, low-power electronics and a high-energy-density battery and make use of a wireless protocol to offer a continuous stream of measurements[61].

Careful consideration of device fabrication, integration and packaging will enable valuable population-level studies moving forward. Findings of either absent correlations or strong correlations between sweat and blood serum should be viewed as equally impactful: one will help the field to avoid pursuing a non-existent channel of information, the other to focus on one with value.

Case study: glucose sensing in sweat

As an example of the nuanced profile of sweat, sweat glucose has attracted widespread and contentious interest as a potential replacement or supplement for invasive blood measurements in diabetes management. Some studies show correspondence between glucose in sweat and blood, with similar changes from before to after glucose intake for iontophoretic sweat[101] and strong correlations for resting non-stimulated sweat[7,87]. Other studies report a lack of a correlation in time-averaged glucose levels for iontophoretic sweat across fasting populations of healthy and diabetic individuals[78] and for exercise-stimulated sweat in healthy individuals at 60% and 80% of maximal heart rate[102]. This conflicting evidence does not preclude the possibility of finding a reliable correlation after correcting sensor readings for fluctuations in temperature and pH[103], involving a relationship with sweat-secretion rate, accounting for an absorptive–metabolic

BOX 1

Guide to sweat-sensing research

How should a research direction in sweat sensing be evaluated? We recommend that investigators should aim to target applications in which sweat has known or probable physiological relevance while navigating areas of uncertainty in the field and should continue to fill knowledge gaps with rigorous studies of basic science, according to the following criteria.

Is there an unmet need that could be filled by sweat sensing?

1. Yes, there is a need for more accessible and non-invasive sample collection for single-point measurement applications, and sweat offers sufficient precision. Potential applications include off-body, at-home tests, mail-in tests sent to a laboratory and non-invasive tests in the clinic. Note that not every application benefits from continuous, on-body monitoring.
2. Yes, there is a need for continuous measurements that are non-invasive and wearable, and sweat offers sufficient precision and reliability. Potential applications include continuous personal health tracking, athletics and worker safety, especially in event detection.
3. Yes, it has implications for the basic science of sweat, improving our understanding of analyte partitioning and blood correlation, regional gland recruitment, efficient thermoregulation, etc.
4. None of these? Reassess the motivation before embarking on this project.

Is it informative to make this measurement in sweat?

1. Yes, the analyte levels are known to be correlated with those in blood plasma. This is more common for small hydrophobic molecules.
2. Yes, the measurement is informative of its own accord, containing information found uniquely or more accurately in sweat. Examples include cystic fibrosis diagnostics, fluid-loss monitoring and basic science research.
3. Neither of these? If device measurements do not reflect any deeper physiological information, it may not be worthwhile to study.

Is it feasible to make this measurement in sweat?

1. Yes, sensors exist with sufficient sensitivity, selectivity, stability and reproducibility for the analyte and application. Furthermore, sensor readings can be properly compensated for sweat-rate effects, if any, via integration of sweat-rate sensors or use of analyte ratios (for example, with a control protein such as albumin).
2. No? Before proceeding, the sensor platform must be developed and/or sweat rate integrated with the measurement.

lag time, doing individual-specific calibration or selecting only particular modes of sweat stimulation. The current controversy highlights the need for continuous studies capturing dynamic changes in sweat glucose to examine the lag time and possible relationship with secretion rate. Supposing that a strong correlation can be confirmed between sweat glucose and blood, the question remains of which use cases are best suited for the precision and price point that can be achieved for sweat sensing, especially in the wake of emerging microneedle platforms that are expected to have superior accuracy. Measurements of interstitial fluid with these highly reliable, minimally invasive, commercial CGMs (for example, Abbott FreeStyle Libre and Dexcom G6) may be better suited for preventing dangerous deviations in blood glucose. Nevertheless, a less-precise but completely non-invasive method of glucose monitoring may still be valuable for casual personal health monitoring, dietetics and athletics, especially with the increasing prevalence of prediabetes. Box 1 generalizes this thought process for assessing the value of other studies in sweat.

Reasons for optimism

In its short history, the field of sweat sensing has seen many demonstrations of innovation that are aligned with commercial, clinical and consumer markets and with physiological reality. Sweat patches can help inform about hydration needs, as demonstrated by Epicore and Hydrolabs and academic groups for monitoring of sweat rate and electrolyte concentrations[54,78]. There has also been innovation in sweat collection, including non-stimulated sweat, as well as long-lasting chemical sweat stimulation[7,32,56]. Demonstrations have also been made of theoretically unlimited continuous sweat-rate tracking[61,104]. Toward biomedical applications, there have been several advances in monitoring pharmacokinetic profiles of drugs in sweat. For example, the profile of levodopa was continuously tracked through its metabolism with possible relevance for the management of Parkinson's disease[58,105], and the profile of caffeine, a methylxanthine drug, was monitored after consumption of espresso[57]. Wearable medication sensors could be used for monitoring compliance (was the drug taken responsibly or in a timely fashion?) or for optimal dosing (did the dose and timing meet the drug's often-narrow therapeutic range?). Recently, the field has also begun to expand into aptamer sensors for the study of perhaps the most physiologically interesting analytes. Development of continuous-sensing platforms for days-long periods would be a big step toward fundamental correlation studies of these analytes. Lastly, as a diagnostic fluid, sweat has several advantages over blood, saliva and urine.

Moving forward, several lessons can be learned from previous mistakes. Specific recommendations are provided in Box 1. More generally, we suggest that investigators focus on physiologically meaningful analytes using the knowledge compiled by the field and refine and advance emerging aptamer sensor technologies. It is advisable to use long-lasting sweat stimulation and resting thermoregulatory sweat capture for continuous biomarker study. In addition, emphasize detailed population studies to understand the biology so that investments are not wasted on irrelevant technology. Finally, innovate to fill societal needs and technological gaps, exploring the wealth of possible applications of this rich, non-invasive sensing modality. Just know that it might require breaking a sweat.

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Competing interests

J.H. has multiple patents that have been licensed to entities pursuing commercialization of sweat biosensing devices.

Additional information

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