Perspective

Applied body-fluid analysis by wearable devices

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Wearable sensors are a recent paradigm in healthcare, enabling continuous, decentralized, and non- or minimally invasive monitoring of health and disease. Continuous measurements yield information-rich time series of physiological data that are holistic and clinically meaningful. Although most wearable sensors were initially restricted to biophysical measurements, the next generation of wearable devices is now emerging that enable biochemical monitoring of both small and large molecules in a variety of body fluids, such as sweat, breath, saliva, tears and interstitial fluid. Rapidly evolving data analysis and decision-making technologies through artificial intelligence has accelerated the application of wearables around the world. Although recent pilot trials have demonstrated the clinical applicability of these wearable devices, their widespread adoption will require large-scale validation across various conditions, ethical consideration and sociocultural acceptance. Successful translation of wearable devices from laboratory prototypes into clinical tools will further require a comprehensive transitional environment involving all stakeholders. The wearable device platforms must gain acceptance among different user groups, add clinical value for various medical indications, be eligible for reimbursements and contribute to public health initiatives. In this Perspective, we review state-of-the-art wearable devices for body-fluid analysis and their translation into clinical applications, and provide insight into their clinical purpose.

The current generation of commercially available wearables, such as smartwatches, can readily track mobility and vital signs. But although heart-rhythm analysis using photoplethysmography has revolutionized atrial fibrillation screening[1,2], biophysical devices cannot perform precise biomolecular monitoring. Standard-of-care biomolecular monitoring is today carried out mostly through blood samples in a process that is laborious, invasive, laboratory dependent and generally allows only spot analysis. Emerging wearable devices, however, will be capable of monitoring health at the molecular level[3] through various body fluids, such as sweat, interstitial fluid (ISF) and breath[4], with high time resolution and in real time. Their connectivity with computer tablets, smartphones, software applications and machine-learning algorithms enables automatic data interpretation and outcome prediction[5].

The recent successful application of these wearable devices for body-fluid analysis (such as for non-invasive monitoring of C-reactive protein (CRP) in sweat[6]) in clinical studies has demonstrated their great potential to catalyse the next paradigm shift in remote healthcare monitoring. Furthermore, they could help solve major limitations of traditional clinical laboratory analysis especially in the areas of (1) screening and early diagnostics, (2) measuring longitudinal time-series data to evaluate therapeutic effectiveness and the course of disease, (3) overcoming sampling challenges, for example, in paediatrics, and (4) allowing for simplified access to complex diagnostics in resource-scarce areas. Still, the successful broad clinical implementation of these wearable devices faces several remaining challenges, including (1) assuring sensor accuracy and reliability and a long-lasting power supply,

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(2) the development of software and algorithms addressing clinical needs, (3) the setting up of a regulatory framework, (4) understanding the clinical meaning of derived data, and (5) elaborating clinical-use cases considering patients, public health and resources. The inclusion of all stakeholders from the beginning of the process will be one of the main pillars of a successful translation from bench to bedside, including commercialization[7].

In this Perspective, we provide a holistic, interdisciplinary view of state-of-the-art wearable sensing platforms for body-fluid analysis and their clinically meaningful applications. We further discuss strategies, considerations and challenges pertaining to their successful clinical translation, how to achieve this translation and how it might contribute to solving some major global healthcare challenges.

Wearable devices for body-fluid analysis

Wearable sensors that capture rich dynamic molecular information in real time bring exciting opportunities for monitoring the human body in a broad range of diagnostic applications[3,8,9]. Such devices rely on translating the selective recognition (interaction) of the target biomarker by an immobilized receptor into a measurable electrical or optical signal proportional to the biomarker concentration. A wide range of wearable electrochemical and optical sensors has been developed for the real-time, non-invasive monitoring of diverse chemical markers (electrolytes, metabolites, hormones, drugs and so on) in human body fluids (Fig. 1 and Supplementary Table 1). These sensors rely on different form factors, including epidermal fluidic patches, wristbands, tattoos, bandages, textiles, contact lenses and microneedles (Fig. 2). By continuously and simultaneously monitoring multiple biomarkers, wearable sensor arrays can both provide distinct dynamic chemical signatures contributing to the comprehensive monitoring of an individual's health status and send alerts in the case of abnormal health conditions. The field of wearable devices for body-fluid analysis is expected to grow rapidly over the next decade. To achieve this growth, wearable chemical sensors must offer reliable analytical performance (that is, accurate biomarker detection in complex biofluids) comparable to that of traditional laboratory-based clinical assays. Current efforts aim at expanding the scope of wearable chemical sensors to a wide range of biomarkers and body fluids.

Sweat

Human sweat is non-invasively accessible and contains a range of biomolecular markers, including small electrolytes, metabolites, nutrients, hormones and even proteins. State-of-the-art skin-interfaced wearable sweat sensors employ various mechanisms for marker recognition based on target-specific receptors (such as enzymes, ionophores, antibodies, aptamers and molecularly imprinted polymers) and signal transduction via electrochemical and colorimetric methods. These sensors enable the monitoring of a wide spectrum of analytes in situ in real time, facilitating remote at-home health monitoring and management[3,8,10–14]. Compared with other biofluids, sweat offers advantages such as easier accessibility, lower matrix complexity, reduced risk of sample contamination and a wider range of choices of sensing materials with the desired biocompatibility. To achieve greater accuracy in non-invasive health monitoring, factors such as interpersonal and intrapersonal variations in sweat pH, ionic strength, sweat rate and skin temperature must be considered.

Sweat can be conveniently collected through vigorous physical exercise or heat stress. Analysing sweat induced by these physical stimuli using wearable sweat patches holds promise for monitoring hydration status and human performance[14,15]. There is growing interest in monitoring naturally secreted sweat at rest, especially at fingertip areas with high sweat-gland density, via point-of-care sweat analysis[16]. Iontophoresis is often employed for accessing sweat reliably in various biomedical applications; it delivers positively charged cholinergic agonists (for example, pilocarpine, acetylcholine or carbachol) to stimulate sweat glands and induce continuous localized sweating across activities[17,18] and is of advantage for many applications as it does not require vigorous exercise. Utilizing wearable sensor patches to collect and analyse Cl^- in iontophoretic sweat enables the rapid diagnosis of conditions such as cystic fibrosis[17,19]. Many analytes in iontophoresis-induced sweat show high correlations with their blood counterparts, making them ideal for remote and personalized health assessment[6,20].

Through a combination of miniaturized iontophoresis modules, microfluidics and electrochemical nano-biosensors, trace-level (micromolar to picomolar) circulating nutrients[18], hormones[20] and proteins[6] can be monitored in situ using disposable wearable sensor patches. This enables the monitoring of nutritional status, inflammatory proteins and female hormones.

Interstitial fluid

ISF, the biofluid surrounding cells in tissues inside the body, contains chemical markers that are exchanged with blood capillaries[21]. The temporal profiles of most ISF analytes (except very large molecules, for example, lipids) closely follow blood concentration profiles. ISF thus holds considerable promise for monitoring health status. However, ISF has been relatively unexplored for in vitro diagnostic assays owing to the challenges of collecting it. Wearable devices for monitoring ISF constituents rely on either non-invasive ISF extraction protocols or minimally invasive microneedle sensor protocols along with various electrochemical transducers. The most successful example of ISF sensors is the continuous glucose monitoring (CGM) needle device, which displays temporal ISF glucose trends and is widely used in the management of diabetes. The success of commercial ISF-based CGM has led to major efforts in developing wearable ISF sensors for the continuous monitoring of other key biomarkers, particularly small molecules (<3 kDa) that partition rapidly to ISF from blood with minimal dilution.

Non-invasive ISF monitoring of chemical markers commonly relies on conformal epidermal platforms that combine ISF extraction and sensing functions into a single device. Through repeated extraction and detection cycles, such devices can perform several non-invasive ISF measurements per hour. The most common ISF sampling technique is reverse iontophoresis, which involves the application of a localized electric field (mild current) across the skin to induce an electroosmotic flow transporting charged molecules. Its first use dates back to 2000[22].

Microneedle electrochemical sensors, which rely on painless skin penetration, enable the continuous monitoring of different metabolites, electrolytes and drugs[23]. They can capture rich molecular data in real time during diverse daily activities. Such devices are fabricated by assembling electrochemical sensors on the tips of microneedles with micrometric dimensions. Arrays of several spatially resolved individually addressable needle electrodes on a single patch can offer continuous simultaneous multiplexed detection of key chemical markers[23]. Although early efforts have focused on microneedle enzyme electrodes for monitoring metabolites and ion-selective electrodes for monitoring electrolytes, the scope of microneedle sensors is currently being expanded to include additional biomarkers by using aptamer-modified microneedle electrodes.

Exhaled breath

Breath analysis, which offers simple and convenient sampling, holds great potential for the diagnostics and treatment monitoring of various diseases. Exhaled breath contains more than 3,500 substances, including volatile organic compounds, metabolites and proteins, present in concentrations 1,000–10,000 times lower than in blood. Nevertheless, owing to high blood circulation through the lungs, there is a rapid exchange of these (bio)molecules between blood and respiratory fluid, resulting in a reliable and simultaneous correlation between blood

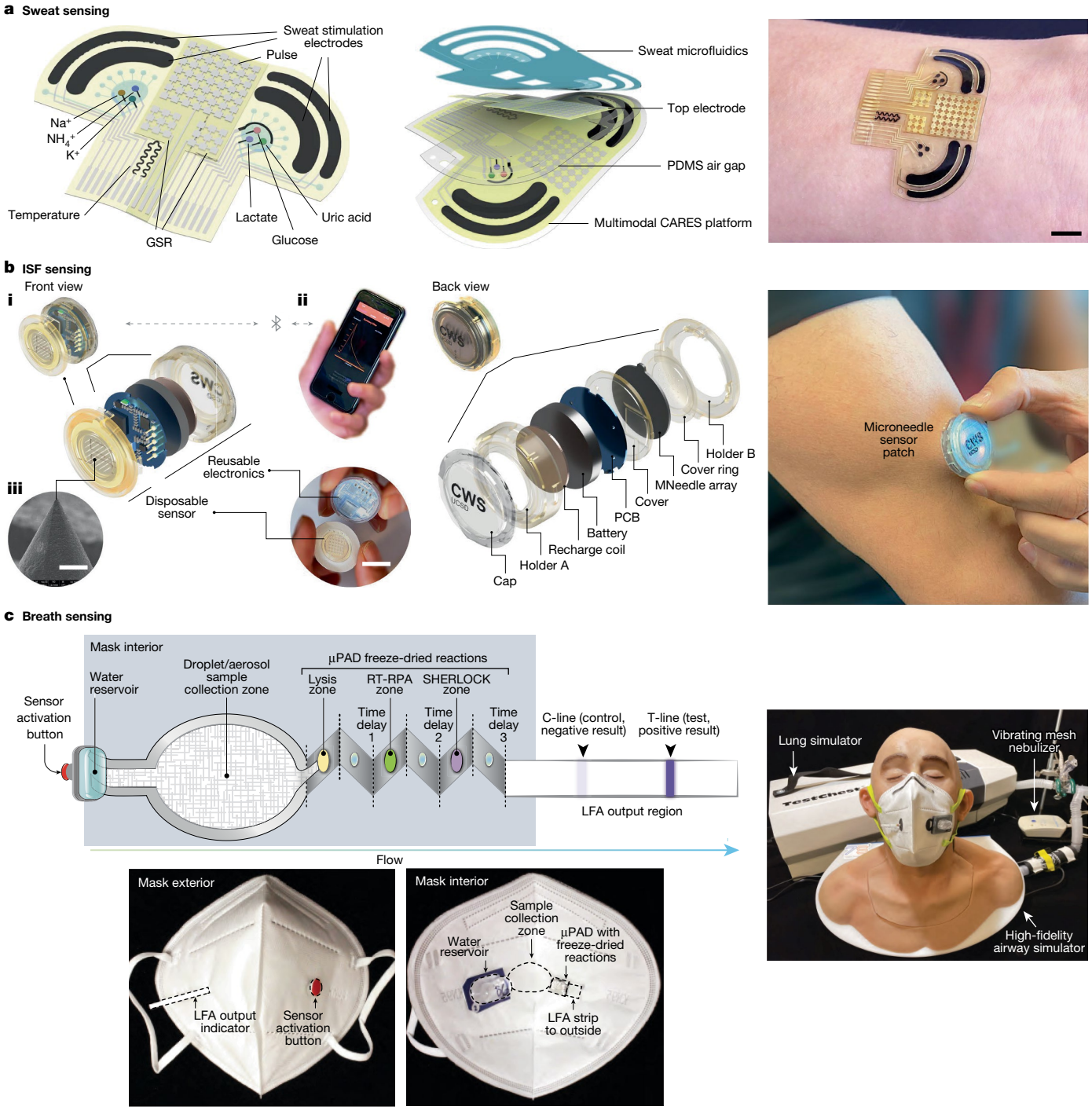

Fig. 1 | The anatomy of wearable sensing platforms for body-fluid analysis. **a**, For sweat sensing, an electronic skin is shown that enables multimodal sensing including biochemical sweat analysis (such as Na^+, NH_4^+, K^+, lactate, glucose and uric acid) combined with biophysical measures (such as temperature, pulse and galvanic skin response (GSR))[67]. Scale bar, 1 cm. CARES, consolidated artificial-intelligence-reinforced electronic skin; PDMS, polydimethylsiloxane. **b**, For ISF sensing, a microneedle-based device with a disposable sensor and reusable electronics is shown that allows monitoring of glucose, lactate and alcohol[23]. A microneedle sensor patch with a disposable sensor array and reusable electronics visualized from the front (**i**). Scale bar, 1.5 cm. Sensing results are displayed on the smartphone of the user (**ii**). The tip of an individual microneedle electrode visualized by scanning electron microscopy (**iii**). Scale bar, 75 µm. MNeedle array, microneedle array; PCB, printed circuit board. **c**, For breath sensing, a CRISPR-based lateral flow assay (LFA) platform along with an origami sample preparation unit is shown that is embedded into a facemask, enabling straightforward detection of SARS-CoV-2 genes[26]. RT-RPA, reverse transcription-recombinase polymerase amplification; SHERLOCK, a CRISPR-based molecular diagnostic tool; µPAD, microfluidic paper-based analytical device. Panels reproduced with permission from: **a**, ref. 67, Springer Nature Ltd; **b**, ref. 23, Springer Nature Ltd; **c**, ref. 26, Springer Nature Ltd.

and breath levels of different analytes[24]. State-of-the-art systems for breath analysis require the condensation of exhaled breath, however, which involves either separate or bulky devices for the collection and analysis of exhaled breath condensate (EBC).

In recent years, various facemask-based sensing platforms for wearable exhaled breath analysis have been introduced, which overcome the necessity of EBC collection while offering direct detection of a number of molecules: (1) hydrogen peroxide, a biomarker associated

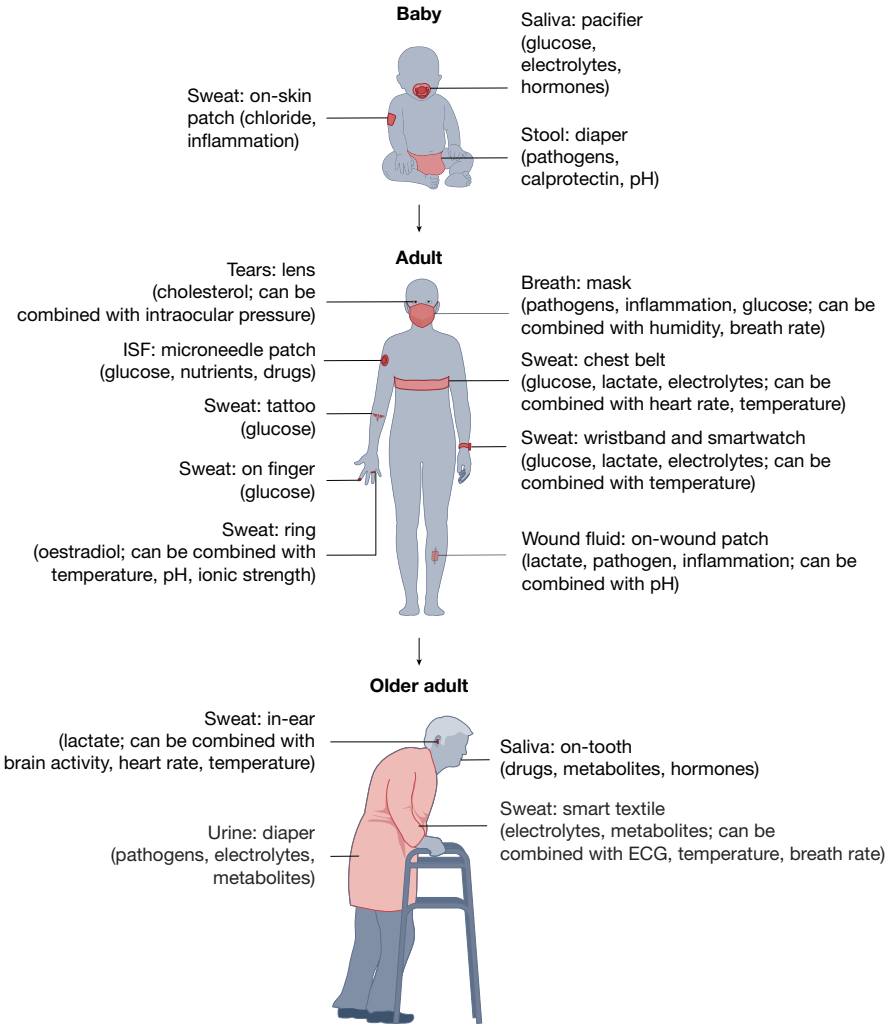

Fig. 2 | Current wearable sensing devices for various body fluids in context of the human life cycle. Each life cycle comes with differing challenges and needs. It is crucial to understand the relation between age and disease as well as to integrate these with the usability. Thus wearable sensors might be developed as pacifiers for toddlers, rings for adults and hearing aids for people of advanced age. ECG, electrocardiogram.

with respiratory illnesses, detected by electrochemical paper-based sensors[25]; (2) nucleic acids of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), detected by an origami-based sample preparation and CRISPR-based signal amplification, and subsequent lateral flow assays[26]—a low-cost, highly scalable and comparatively accurate alternative to PCR tests that can easily be performed by patients; (3) glucose, detected non-invasively by a self-powered wearable device using printed electrodes[27], a compelling alternative to microneedle-based patches for CGM; and (4) nitrite, measured by an electrochemical sensing platform that utilizes a tandem cooling strategy combined with automated microfluidics to enable continuous EBC condensation, sampling and analysis, for airway inflammation monitoring in patients with asthma and chronic obstructive pulmonary disease (COPD)[28]. Wearable breath analysis is likely to be delivered by various platforms in the near future, including in/under-nose patches, respiratory tract implants and vaping devices, all of which can be combined with closed-loop drug delivery for theranostic applications[4].

Alternative body fluids

Wound fluid. Chronic wounds, often complicated by factors such as diabetes, pose a substantial challenge for existing wound dressings. Smart wearables promote the healing process through electrical and mechanical stimulation[29,30] and the on-site monitoring of relevant biomarkers[31–35] to track healing progress and inflammation. They encompass features such as drug delivery, electrical stimulation and photodynamic therapy, actively adjusting drug release to adapt to the changing wound environment[36]. An ideal smart bandage platform should: (1) integrate sensing and stimulation, (2) be flexible and wireless, and (3) provide on-demand skin adhesion for reliable signal transmission and energy delivery and allow easy detachment to prevent secondary skin damage. Obtaining an adequate quantity of wound fluid to ensure the optimal performance of sensing units—preventing fluctuating sample concentrations and inconsistent analytical outcomes—poses a considerable challenge.

Tear fluid. A wide range of substances—among them ions, molecules, proteins, lipids, hormones and glucose—can traverse the blood–tear barrier, linking the composition of tears to that of the bloodstream[5,37]. Microfluidic eyeglasses for electrochemical alcohol detection[38] and flexible electrochemical sensors for glucose monitoring[39] are currently under development for use in tear analysis. Powering smart contact lenses presents a unique challenge.

Saliva. The strong correlation between glucose levels in saliva and blood provides motivation for developing saliva-based diagnostics into a wearable format. Saliva-based diagnostics have been utilized to assess hormone levels[13,40–43]. Wearable devices for saliva analysis face challenges owing to the viscous nature of saliva, which complicates

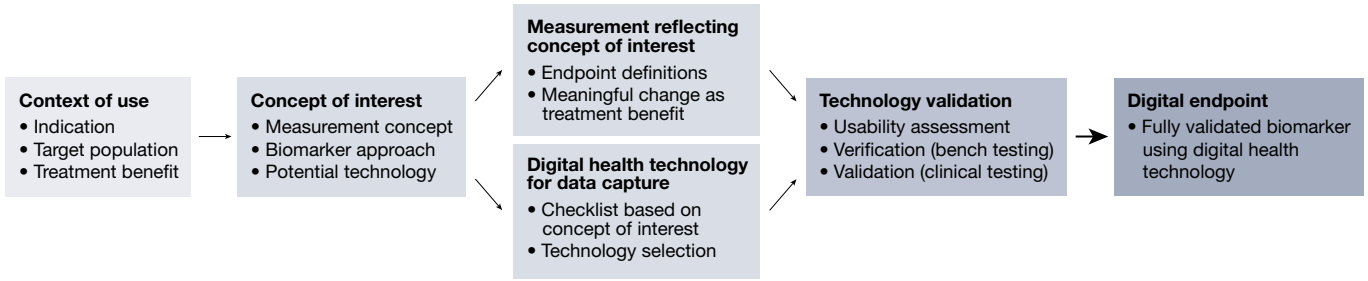

Fig. 3 | The development of digital endpoints. The development of digital endpoints begins with understanding the context of use and defining the concept of interest, including the measurements and the digital technology. Only after thorough validation, a digital endpoint is ready to serve in clinical trials. Workflow based on recommendations of the CTTI (ctti-clinicaltrials.org).

the design of microfluidic-based sampling systems. Moreover, the rate at which various substances equilibrate between saliva and blood can vary, leading to delays in detecting biomarkers, and common oral activities can induce variations and contamination[13,44].

Urine and faeces. Wearable urine-/faeces-based biosensors are being integrated into diapers, primarily for diabetes monitoring and the detection of urinary tract infections. Although urine and faeces provide non-invasive and abundant sample volumes, their use in wearables is generally limited to infants, the elderly and long-term care patients[45–48]. Furthermore, these sensors are typically limited to a single use.

Translation and healthcare implementation

The successful translation of wearable body-fluid biosensing platforms is crucial to realizing their clinical application. For this translation, a variety of structures and procedures are needed. In this section, we first discuss the involvement of patients as stakeholders with equal rights to healthcare professionals and the development of a meaningful research environment. Furthermore, we explore the general clinical environment needed for body-fluid analysis by wearable devices and its chances of improving healthcare (1) for patients, (2) for societies, by addressing public health challenges, and (3) by reducing health disparities in resource-scarce areas.

Patient-centred innovation process

It is important that biomarker research projects involve patients and research participants from the beginning. Patients offer perspectives and lived experience that can greatly improve the design of technological interventions. Frameworks developed elsewhere for the involvement of patients can easily be adapted for this type of research[49]. Patients and healthy research participants can contribute during various phases, from project ideation to actual implementation, including in the design of consent documents and other information materials. Patients can have significant roles in the co-design of digital devices, research endpoints and patient-reported outcomes. Distinct considerations for wearable technologies to which patients and research participants can contribute include specific challenges in the remote and autonomous use of the technology, privacy and end-user compliance, which is essential for collecting reliable and accurate data. Body-fluid analysis by wearable devices represents a recently developed approach, so it is especially important to understand the needs of patients from the very beginning. Although wearable devices for biophysical monitoring have up to now mostly been integrated in everyday objects such as wristbands and rings, next-generation wearables will come in the form of patches and masks that are either stuck to the skin or cover the mouth, and once fully validated will trigger clinical consequences such as the adjustment of drug doses even at home. Patients will thus be involved more obviously and directly than they might be used to. It is also important, however, to integrate other stakeholders, such as clinicians, in the early development phase. Forward-thinking, competent, creative and collaborative clinicians, as medical experts, can significantly contribute to clinical innovation[50].

Clinical trials for digital biomarkers

Although digital biomarkers offer great potential for remote and/or decentralized trials, strict regulation is necessary when using them in clinical trials (Fig. 3). Although the biomarker validation process has been clearly described, the digital component adds complexity[51]. The Clinical Trials Transformation Initiative (CTTI) provides guidance on how to utilize digital health technology to improve clinical trial quality[52]. It includes advice on selecting and testing digital health technology, managing digital data flow, supporting sites, interacting with health authorities and developing endpoints. Owing to recent advances, technology is no longer a limiting factor in planning and conducting clinical trials. Questions about not only necessary accuracy (fit for purpose) and sampling frequency[53] but also technical factors such as battery life and patient comfort need special attention. The early involvement of health authorities[54] is also encouraged to obtain early buy-in to trial designs and endpoints; for this, clinical relevance needs to be established. Furthermore, the application of the technology in early-phase clinical trials is recommended to demonstrate fit-for-purpose design. One of the main challenges of body-fluid analysis by wearable devices is the need to set biochemical markers into their physiological and environmental context to understand what exactly is being measured. Therefore, sensing platforms will integrate the biophysical monitoring of molecules with the use of powerful data analytics. This combination is challenging from a health regulatory perspective, but essential for allowing the derivation of clinically meaningful knowledge.

Healthcare

Once the body-fluid analysis by wearable devices has been successfully translated, it enables precise on-demand molecular analysis for use in healthcare. Precise molecular analysis in healthcare has up to now been largely restricted to occasional in-hospital visits detached from everyday life with, for the most part, invasive and painful sampling procedures that depend on specialized laboratories and trained healthcare workers. The recent successful application of body-fluid analysis by wearable devices in clinical studies has made it available for broader clinical investigation[6]. It will make health monitoring more convenient and accessible at the hospital, in outpatient settings and at home, and will also foster longitudinal outcome assessments of health interventions and provide (patho-)physiological insights through newly or better accessible diagnostic matrices at successive time points. Wearable body-fluid analysis has the potential to improve care in general medicine and brings exciting opportunities for optimizing care for underserved patients, allowing for body-fluid sample access in children and straightforward health assessments for patients living in resource-scarce areas. Thus, body-fluid analysis by wearable devices has significant potential for increasing health equity[55].

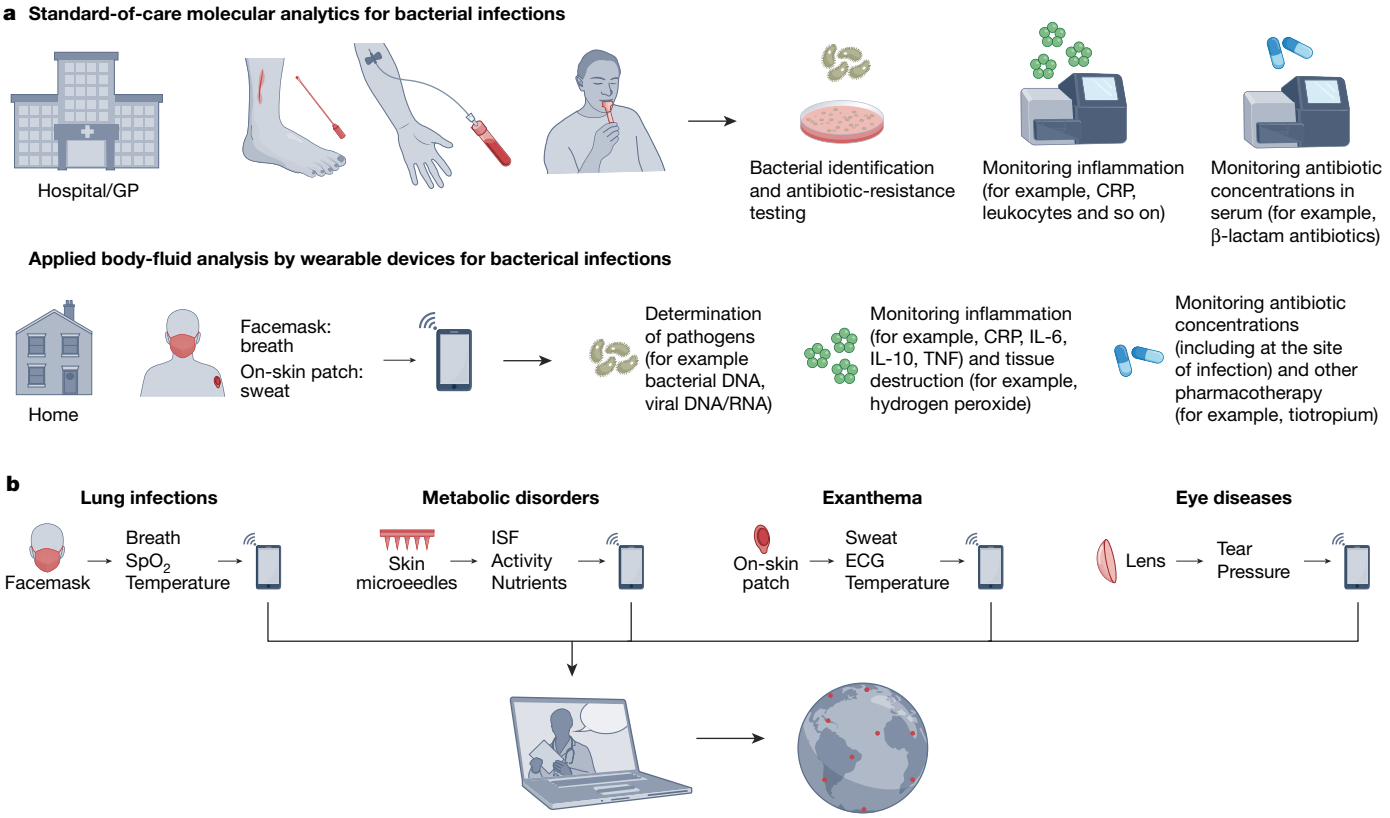

Fig. 4 | Applied body-fluid analysis by wearable devices in clinical medicine. Schematic overviews are provided of how wearable devices can improve the current standard of care in molecular body-fluid analysis by facilitating access to continuous and lab-independent monitoring and adding information from various body fluids collected in different locations. **a**, One example application is for monitoring antibiotic treatments to manage bacterial infections. So far, assessing bacterial infections to identify the underlining pathogen, assess the state of inflammation and monitor drug concentrations have been mainly feasible in specialized laboratories using time-consuming and costly procedures. The integration of these tests into connectable, smartphone-based analytics enables a seamless and patient-centred health monitoring at the hospital and in the outpatient setting. GP, general practitioner; IL-6, interleukin-6; IL-10, interleukin-10; TNF, tumour necrosis factor. **b**, Another example application is for facilitating healthcare access to complex diagnostics in resource-scarce areas of the world. Body-fluid analysis by wearable devices can allow to identify and monitor lower respiratory infections, diseases leading to exanthema, eye diseases, and metabolic disorders at sea and on land by choosing the respective biosensor and body fluid by medical indication. SpO_2, peripheral arterial oxygen saturation.

General medicine

The inflammation markers CRP and cytokines provide important health information in general medicine and have been reliably measured in human sweat using wearables[6,56]. This underscores the clinical potential of body-fluid analysis by wearable devices in general medicine and beyond. CRP might be a non-specific clinical inflammation marker, but it can be used to set therapeutic indications, monitor treatment success and disease progression in communicable (such as coronavirus disease 2019 (COVID-19)) and non-communicable (such as rheumatoid arthritis) diseases. Combining measurements of cytokines in sweat with measurements of the stress hormone cortisol will allow for the continuous assessment of psychoneuroimmunological status, which will provide diagnostic opportunities in the field of mental health. In the management of chronic diseases such as diabetes, sensing devices have already demonstrated their utility, adding tremendous clinical value by optimizing glycaemic control[57,58]. In cardiovascular diseases, breath analysis could be potentially used for assessing expiratory air humidity to detect pulmonary oedema and sweat analysis to monitor intensified diuretic therapy in patients with acute decompensated heart failure[59]. These wearable devices can also be used for the parallel monitoring of haemodynamic parameters, such as blood pressure, and metabolic parameters, such as glucose, to detect and manage cardiovascular risk factors such as metabolic syndrome[60,61]. Potential applications in patients with cancer include therapeutic drug monitoring at the site of cancer based on a concept monitoring drug tissue penetration through a three-level model[62]. The three-level model allows to monitor drug concentrations in blood (upstream of the site of cancer) and in excreted body fluids (downstream of the site of cancer) to derive the concentration at the site of cancer. In addition, patient's nutritional status through sweat analysis can be assessed, which is important because malnutrition in patients with cancer has a negative impact on treatment tolerance, leading to increased side effects, treatment interruptions and higher hospital re-admission rates[63].

At present, diagnostic concepts based on body-fluid analysis by wearables aim at addressing major health challenges of our time. First is the use of sweat analysis by wearable devices to monitor the expression of, for example, heat shock proteins during heat stress to determine an individual's biological age[64] and subsequently draw conclusions about their resilience according to their age. Second is a way of implementing body-fluid analysis by wearable devices to determine antibiotic concentrations at the site of infection for extended therapeutic drug monitoring during the treatment of bacterial infections[62] (Fig. 4a). This approach may be further expanded to immunosuppressive treatment. The third diagnostic concept addresses substance-use disorders, which are of great concern to global public health. Withdrawal from substances is associated with a high risk of relapse. Here, wearable sweat analysis enables the monitoring of changes in vegetative arousal through sweat-rate measurements[65] as well as the continuous and non-invasive monitoring of a variety of substances in sweat[66].

Last but not least, monitoring stress (for example, physiological stress in a climate-changed environment and psychological stress in mental health) is feasible using a multimodal sweat analysis approach including biophysical and biochemical analysis[67].

Paediatrics

Wearable devices for body-fluid analysis in paediatrics need special mentioning, as devices aimed at this age group need to accommodate children's smaller sizes, more sensitive skin and higher activity levels, while ensuring comfort and accuracy of measurement. In paediatrics, invasive procedures such as blood sampling are challenging owing to both physiological and psychological factors. For example, blood sampling from veins in infants and children is difficult owing to children's small and fragile veins, the smaller blood volume available, and a lack of understanding and cooperation on the part of the patients. Failed venipuncture is frequent in paediatrics, estimated to occur in 30–50% of all attempts. It can lead to delays in diagnosis, repeated blood sampling and iatrogenic anaemia. In addition, the psychological impact of repeated invasive procedures in childhood may lead to a considerable and lifelong fear of medical procedures. Capillary blood sampling is a potentially less invasive intervention and therefore frequently performed. However, it is of limited use owing to the small blood volume and an increase in preanalytical errors[68]. Wearable devices for body-fluid analysis in paediatrics are particularly attractive to overcome these shortcomings.

Most available wearable devices in paediatrics are single- or multiparameter devices for vital signs[69]. The only exceptions are wearable CGM devices, which have increasingly been used in the past few years. Still, CGM continues to be insufficiently accurate, burdensome for patients and their families, and costly, and there is a lack of evidence for its ability to reduce hypoglycaemia when provided to families without support[70]. Straightforward biochemical diagnostics using alternative body fluids, such as sweat, ISF and breath have the potential to (1) shorten the time to diagnosis, which can be lifesaving, for example, in cases of sepsis, (2) reduce the trauma of blood drawing, and (3) provide first-of-its-kind therapeutic drug monitoring to better understand pharmacokinetics and pharmacodynamics in children of all ages, from newborns to teenagers.

Importantly, wearable devices designed primarily for adults often perform less well for children. One study has found substantial data gaps and an underestimation of body temperature by more than 1.5 °C when a wearable device for vital sign assessments in adults was worn by children[71]. Meanwhile, several studies have assessed the tolerability of wearable devices in children, and especially children under 5 years of age have shown lower levels of compliance[72]. Discomfort and potential health hazards caused by wearable devices are more likely to appear and are more difficult to detect in infants and children. For example, one study found that gel-based electrodes are abrasive for infants' skin over the long term[73]. In addition, the positions of sensors can render them uncomfortable and therefore need to be carefully thought out. Wearable devices on teenagers require a high degree of involvement on the part of the patient. Moreover, when developing wearable body-fluid analysis platforms, parents must be involved in the process, both as care provider and as users. Despite these challenges, applied body-fluid analysis by wearable devices has great potential for overcoming current limitations in paediatric health assessments.

Resource-scarce areas

Access to healthcare in resource-scarce and remote areas remains challenged by (1) scarce availability of advanced diagnostic and therapeutic services, (2) low levels of insurance coverage, and (3) long distances to health facilities and associated expenses for patients. The result is underdiagnosis, late presentation of disease and poor disease control, with an associated increase in mortality and underestimation of disease prevalence—despite improvements in the digitization of health data[74]. Body-fluid analysis by wearable devices might allow remote, detailed and complex diagnostics and facilitate chronic-disease management in various environments (Fig. 4b). Ideally, this could also lead to reduced health expenditures[75]. Telemedicine and artificial-intelligence-based technologies have the potential to provide treatment advice to support community workers with little or no medical training in the interpretation of data[76].

So far, research on wearable devices in low-income settings has focused on, for example, the geolocation of the transmission of diseases such as schistosomiasis[77], the characterization of social contact patterns[78], the monitoring of atrial fibrillation[79] and of movement for the early detection of stroke[80]. Adaptation and research on the performance of complex biosensor technologies to conditions in resource-limited and climatically different areas will be needed to foster their implementation[81,82]. The feasibility and acceptance of wearables have been demonstrated in studies in Kenya and Burkina Faso with a focus on climate-change-associated health issues[83]. To successfully exploit the significant potential of digital health technologies, including microfluidic analysis, strong local policy support and functioning infrastructure (for example, stable electricity and network coverage) are needed[82,84]. In addition, acceptance of wearables is influenced by socioeconomic and cultural factors and depends on linkage to a trustworthy healthcare system offering adequate services[85] (Box 1). Most importantly, diagnostics through wearable devices must be coupled with therapeutic advice and treatment options (Box 2).

The environment required for mainstream adoption

The development, validation, enrolment and commercialization of body-fluid analysis by wearable devices depends on reliable, scalable and cost-effective manufacturing processes. Here we discuss these needs as they pertain to (1) the combinational use of multimodal biophysical sensors to generate clinically meaningful measures, (2) data usage in terms of automatized digitalization and analysis, (3) bioethical prerequisites for developing a socioculturally sustainable solution, (4) regulatory prerequisites, and (5) device commercialization, which is essential to make reimbursement possible.

Multimodal sensing

Physical sensors, for example, for heart-rate and temperature measurements, represent sensing modules that can complement body-fluid analysis by wearables and are broadly available. The addition of such physical sensors to wearable body-fluid devices would eliminate the need for using multiple gadgets (finger-pricking blood meters, blood pressure cuffs, heart-rate watches and so on) and reduce time, cost and hassle for patients. Most importantly, the integration of multisensing modalities into a wearable biofluid device would increase the level of reliability in the analysis by adding a new variable to the system. For instance, a potential infection could be identified by monitoring the relevant molecule levels and confirmed—and its dynamics understood—by simultaneously monitoring changes in the body's and environment's temperature[86]. The implementation of a multiplexed and multimodal platform would also make possible biophysiological signature monitoring, which allows for more precise diagnostics[87,88]. Moreover, multiplexed and multimodal systems can calibrate readings in real time. For example, temperature sensors can compensate for fluctuations of external or skin temperature that can alter enzyme activity, and measurements of sweat pH, Na^+ and NH_4^+ can be used to normalize analyte concentrations and thereby improve overall accuracy[9,89]. Processing the data generated by these sensors, artificial intelligence, assisted by machine learning, can infer correlations between measurements and, with sufficient information, the system would be able to make real-time predictions and send alerts[9] (Box 2). Recently, a multiplexed and multimodal system was reported that could monitor metabolites and electrolytes (glucose, lactate, sodium and so on) in sweat and ISF

Box 1

Sociocultural considerations pertaining to developing and applying innovative health assessments

The underuse or rejection of diagnostics technology presents an ethical dilemma and can be a critical issue for families, medicine, technology and research development. In the past, various technologies have been accompanied by societal controversies that have resulted in public rejection of their use[112]. Up to now, there has been limited embracing of the complexity of innovative diagnostics, and the cultural and psychosocial contexts of technological devices have remained underexplored compared with the design and operational aspects of such devices[113,114]. Consumers' perceptions of the technology are impacted by cultural meanings attached to being a device user, and this can result in a very different perspective from that of healthcare professionals who employ the technology[114]. Conflicting social messages may arise that increase patients' reluctance to make use of recommended equipment[114]. Sociocultural elements, including shared beliefs, values, norms, expectations, feelings and sentiments that are internalized during the socialization of individuals, may determine how people interpret or ascribe meaning to devices and diagnostic technological innovation. To promote the application of wearable devices for body-fluid analysis on a global scale, therefore, it is necessary to study the underlying sociocultural paradigms associated with them. Focusing on only the basic operation of the technological device ignores the critical challenge of user acceptance. For example, in Tanzania, opinions vary regarding the acceptance and use of diagnostic tools. One study found strong acceptance among mothers of a rapid malaria diagnostic[115]. However, another study investigating the digital adherence tool found that although patients were positively disposed to the digital adherence tool, they had concerns about (1) carrying the device, (2) the device's comfort, and (3) ethical issues regarding the content of the messages it delivered. Some participants were also reported to have experienced challenges associated with connectivity and networks[116].

concurrently with blood pressure and heart rate[61]. The device was used to investigate how changes in metabolites affect blood pressure and heart-rate functions.

Digitalization

The data generated by wearable sensors, whether electrical or optical, are typically converted to digital data and shared with the user and other stakeholders such as healthcare professionals. Users can read the output of colorimetric sensors with the naked eye; to understand long-term trends, however, digitization via cameras or electro-optical transducers is required.

Chemical transducers almost always produce an analogue signal; the intensity of the output signal depends on the concentration of the analyte in the sample. Computers, however, cannot store analogue signals; the signals must therefore be quantized (or digitized) before storage. Transduction, conditioning and digitization can all be performed on the same platform, often the wearable device itself or nearby digital systems, including smartphones and personal computers.

In the current paradigm, digital wireless communications including Bluetooth[90], Wi-Fi[91] and near-field communication (NFC)[92] dominate short-distance communication with sensors. Whereas Bluetooth and Wi-Fi require batteries to operate, NFC can be operated passively without batteries. Bluetooth and Wi-Fi have much larger ranges of operation (>10 m) than NFC (<10 cm). Because of this, NFC is considered to be a more secure communication protocol and, along with similar battery-less communication technologies, will probably dominate the future of wearable devices for the analysis of body fluids[93].

Digitized data are typically stored on-device in the short term to prevent collisions owing to excessive wireless data transfer. However, the computational constraints of miniaturized electronics make on-device processing beyond simple signal conditioning (for example, filtering) difficult. Once the data are transferred to a computing system, sufficient processing power and connectivity are available to perform more sophisticated analysis (Box 2) and to store data on the cloud or on on-premises servers. Centralized data storage provides clinicians with remote access so they can easily monitor patients; it also ensures patient data protection through the implementation of robust encryption protocols and access controls.

Bioethical framework

Continuous collection of body fluids through wearable technology brings risks for both privacy and autonomy that need special consideration. One major issue pertaining to these devices concerns data security and access. Although these privacy issues are not unique to biomarkers, they certainly apply to them, given what biomarkers can reveal about a person and how such information could be misused. Who has access to what data about individuals must be clearly and transparently articulated with privacy considerations in mind. Furthermore, the opportunity that wearables offer for easily collecting more data than necessary can conflict with the principle of data minimization, which aims to protect individuals by decreasing the amount of available information about them. Research teams need to demonstrate the necessity of the data they collect and balance it carefully against potential privacy risks. Patients need to be provided thorough information about data use and access; they need to be presented not only with benefits and efficiency arguments but also with the risks associated with the continuous collection of sensitive molecular data. Consideration should also be given to the feeling of surveillance that participants might develop when under continuous monitoring. An additional ethical issue regards equitable access: whose biomarkers are being talked about, and whether digital markers increase the equity of access to healthcare or exacerbate disparities. These are important considerations with implications for the recruitment of participants, the diversity of participant populations and the types of biomarker studied. Issues of access to technology must also be considered, especially in the context of persisting digital divides within and between countries.

Regulatory

Unlike biophysical sensors such as the electrocardiogram, portable devices analysing body fluids are regulated in Europe as in vitro diagnostic medical devices under In Vitro Diagnostics Regulation (IVDR) (EU) 2017/746. Their accuracy and reliability in clinical and/or laboratory settings depend on well-implemented verification and validation strategies. Correct documentation of the results obtained and a description of the verification and validation methods—together with a risk–benefit analysis—are at the heart of technical documentation, and, as such, form the basis for review by the notified body during the certification process. Verification and validation includes separate checks for sensor and software components (verification) and whole-device validation (real-world testing).

Sensor verification involves rigorous testing to confirm the accuracy of measurements of biomarkers in body fluids. Calibration, sensitivity and specificity, and performance are investigated under varying conditions. The the software responsible for processing the data and displaying the results—including artificial-intelligence algorithms for data interpretation—must also be thoroughly tested, meet predefined

Box 2

Artificial-intelligence-based wearable data processing to interpret, detect, predict and visualize clinical outcomes

Wearable sensors can generate a large amount of data, which is ideal for creating artificial-intelligence-based predictive models. Artificial intelligence typically offers two types of learning: supervised learning, in which the algorithm learns the relationship between sets of known inputs and outputs (either quantitative or classification-based); and unsupervised learning, in which the algorithm learns underlying patterns inherent within an input dataset (no output is required).

Supervised learning can use wearable-derived data to improve every aspect of health monitoring. At the sensor level, models can be trained to improve sensitivity and mitigate noise that wearables often pick up from the surrounding environment (for example, chemical interference)[117], as well as to reduce or even eliminate the need for frequent sensor calibration. The latter is a known problem for glucose sensors, for example[118]. Classification algorithms, such as support vector machines, are also frequently used to improve disease screening and diagnostics. Such algorithms have been applied to cross-reactive volatile-organic-compound sensors, for example, to successfully detect in the breath and classify multiple diseases including cancer, asthma and COPD[117] and COVID-19[119], as well as conditions such as pre-eclampsia[120]. In addition, supervised learning can help with chronic-disease management. As sensors can predict adverse outcomes before they occur, they can be paired with therapeutic devices to achieve a closed-loop system that improves patients' health by keeping their symptoms within the normal range. This is being seriously explored in CGM and has even been integrated commercially into a diabetes management system[121].

Unsupervised learning has less direct effects on health outcomes but is very powerful in its ability to derive important abstractions from complex datasets, improving our understanding of many diseases and conditions and leading to better decision-making. Most often, unsupervised methods such as neural networks, principal component analysis and *k*-means clustering algorithms are used to extract features from wearable data that can then be used as inputs to a supervised learning model to improve its prediction accuracy[122–125]. Deep neural networks—neural networks that contain multiple hidden layers to achieve more abstract and nonlinear representations of data—are currently being explored to steer away from overly generalized symptoms of disease and, instead, use comprehensive datasets (enabled by continuous patient monitoring) to train models that are specific to the individual patient[126,127]. Such models can be used to provide a comprehensive and customized health profile unique to each patient, assisting clinicians in eliminating the risk of inaccurate and delayed diagnoses as well as in optimizing therapeutic treatments[128].

performance standards, and address data variability and cybersecurity considerations, either as 'software in the medical device' or 'software in the in vitro diagnostic device'.

Final validation ensures that the entire device, with its sensors, software and wearable platform, works correctly in the real world and complies with regulations and standards such as IVDR and International Organization for Standardization (ISO) 20916:2019. The unique characteristics of each fluid type require tailored validation protocols that address sample collection, handling and analysis to ensure the accuracy and safety of the device in clinical and laboratory use.

Despite optimal design and manufacturing, there will be residual risks. A benefit–risk analysis, part of the post-validation risk management process, assesses whether the benefits outweigh the risks and informs the decision to market the device. This analysis, together with the technical documentation, needs to be prepared by the manufacturer and submitted to the notified body for evaluation and assessment.

Commercialization

Recent progress in microfluidic roll-to-roll process innovation and the rapid printing of flexible bioelectronics have led to classes of wearable biochemical-sensing solutions that exploit colorimetric and electrochemical sensing capabilities for the real-time biochemical analysis of body fluids[10,15,94]. Commercialization efforts for highly miniaturized, non-invasive sweat-sensing devices are underway in consumer health and wellness, sports and fitness, connected-worker, and healthcare applications. Achieving the successful translation and scale-up of these classes of devices will require not only innovation in the manufacturing process but also hardware system certifications, validation in field studies, system integration with algorithms and smartphone mobile applications, and cloud development to support the collection and longitudinal sorting of these large datasets[95]. Colorimetric-assay integrated sweat patches, which have been demonstrated to measure whole-body sweat rate and sodium loss in sports and fitness, provide one example of successful commercialization. A few electrochemical sensing platforms have also entered the commercialization phase of deployment in sweat sensing, with similar systems focused on ISF (beyond glucose), saliva and breath analysis. Large-scale validation studies during physical exercise and within the ruggedized context of industrial work (for example, oil and gas field work, firefighter training, and chemical factory work) are exploring continuous sweat- and electrolyte-loss monitoring along with the tracking of biophysical markers including skin temperature, motion and heart rate[96]. These microfluidic electrochemical sensing platforms, in combination with sweat induction and extraction strategies, serve as a foundation for real-time electrolyte, metabolite, hormone and proteomics monitoring, allowing for fully automated performance, nutrition, stress and health management.

Discussion

Wearable devices offer a non- or minimally invasive, continuous, lab-independent and precise molecular analysis of various body fluids. The devices' connectivity with computer tablets, software and artificial-intelligence algorithms enables immediate data analysis, interpretation, and prediction of health and disease independently of healthcare institutions or trained healthcare workers. The combination of molecular analysis with biophysical measures such as heart rate allows for a comprehensive understanding of the meaning of the measurements in a holistic health context and will most likely add clinical value. Although wearable devices for body-fluid analysis have come a long way, several challenges to their broad clinical application remain on the levels of the devices themselves, their translation and the clinics involved.

Challenges

Wearable devices. Challenges remain pertaining to (1) materials and their fabrication to assure conformity, flexibility and conductivity,

(2) aspects of the electronics involved, including noise and lack of flexibility during real-time operation, (3) the stability of the biological sensing components during long-term use and storage, (4) the sensors' compatibility with anatomical and physiological conditions, (5) wearer acceptance, and (6) adequate power supply and charging. The latter has been a challenge when introducing wearable devices into clinical use, especially when remote unsupervised monitoring is conducted. An adequate, and autonomous, power supply ensures diagnostic availability and longitudinal multiplex analysis in various settings for various device forms and sizes—for example, in resource-scarce areas using smart lenses, patches or facemasks. While chargeable lithium batteries are broadly used, self-powered devices would enable resource-independent operation. To this end, several approaches have been discussed, including triboelectric nanogenerators, biofuel and solar cells, and hybrid energy harvesters[97]. A recent study involving perovskite solar cells powering sweat sensors demonstrated a runtime of more than 12 hours in ambient light[98]. Although this approach represents a significant innovation, the runtime of self-powered devices would have to reach at least 24 hours, and preferably a week or more, to allow for their expedient clinical application. Ultimately, meeting the growing power demands of wearable sensor systems requires the rational pairing of multiple energy harvesters and storage devices to allow for self-powered autonomous operation[99].

Translation. Here it is crucial that (1) data reproducibility and (2) added clinical value be demonstrated.

(1) Data reproducibility can be impaired by technological aspects of the sensor, such as discussed above, and a lack of understanding of the underlying physiology. Both challenges should be addressed through thorough testing in various settings, ranging from determining sensors' accuracy and reliability in solutions with different pH values to targeted population studies at-scale, including the assessment of the physio-environmental context[100]. There are a couple of considerations regarding physiological understanding, which shall be addressed. It is important to consider body-fluid cross-contaminations, for example, in sweat, saliva and breath. For sweat, there are three types of sweat gland (eccrine, apocrine and apo-eccrine), which are distributed differently along the skin surface, and each of them secretes sweat with specific biochemical compositions[101]. Furthermore, sebaceous glands in the skin, which are not sweat glands, secrete talcum to the skin surface. For saliva, blood contaminations, which might occur such as in cases of gingivitis or microinjury, can lead to changes of biomarker concentrations[102,103]. For breath, EBC biomarker measurements can probably be contaminated by salivary biomarkers[104]. An understanding of tissue characteristics is of further importance when interpreting the correlations between, for example, sweat and blood. When tissue is inflamed, increased blood-vessel permeability is induced that is likely to lead to an increased exchange between blood and tissue and an increased concentration of blood-derived biomarkers in sweat. In contrast, decreased permeability can be expected in atherosclerotic vessels. For breath analysis, the pathological loss of lung tissue surface and exchange area such as in patients with COPD must also be considered. And although the active stimulation of sweat glands has already been used for sweat analysis with high promise to increase biomarker correlations between sweat and blood[67], other body fluids are not responsive to such stimulative approaches yet. However, mechanotransduction using soundwaves may enable the advance of sampling standardization by induction in most body fluids[105].

(2) Proof of benefits accrued by each of the various stakeholders—from patients to physicians and healthcare payers—is essential and will help to overcome remaining and unforeseen implementation challenges. For this, it is crucial to understand (1) what matters to patients and research participants, (2) what matters to care providers in the context of common clinical standards of care, (3) public health challenges and structures (including societal and global health challenges and challenges of resource availability, politics and reimbursement strategies), and (4) the regulatory hurdles to be overcome to reach a full medical-device validation that would render wearable devices reimbursable; overcoming these will involve large-scale clinical validation studies. High costs are to be expected when conducting large-scale clinical trials for regulatory approval (phase III trials in drug development incur median costs of US$21.4 million)[106]. Furthermore, the sensor needs to be rendered scalable in terms of time as well as affordability. Here, 3D-printed sensor production for skin-compatible classes of microfluidic platforms have recently been proposed that would enable a standardized and cost-effective, scalable solution[107,108]. Finally, post-market-approval investigations to assess safety and enable device repurposing must be carried out.

Clinical implementation. One important consideration pertaining to wearable devices and their clinical use for remote health monitoring is that high false-positive rates would lead to potentially preventable, burdensome and costly doctor's visits. Reliable test accuracy demonstrated during the translational phase will be essential to convince care providers and payers such as health insurance companies to back the use of these devices. In addition, although body-fluid analysis by wearable devices allows for the continuous collection of large datasets, more data does not necessarily lead to better clinical outcomes. From a clinical-application point of view, it will be crucial to investigate and integrate disease dynamics into the setting up of continuous monitoring to define sample frequencies relevant to the disease and its treatment and provide clinical management that is tolerated by patients and research participants and is sustainable in terms of the availability of resources[53]. Finally, it is crucial to ensure safe data analysis, exchange and storage, with an emphasis on data interoperability.

Although body-fluid analysis by wearable devices is evolving from invention to clinical innovation, alternative diagnostic approaches such as implantable and ingestible sensors are also under investigation. Early efforts have focused on developing implantable sensors for continuous biomarker monitoring[109,110]. Such in vivo devices can measure the chemical dynamics of important physiological analytes and are often used for bedside monitoring or probing brain chemistry. However, implantable sensors are invasive, and as 'foreign bodies' lead to inflammation responses; moreover, they suffer from limited stability owing to surface biofouling effects. Ingestible capsules have received considerable attention recently for accessing and monitoring the gut microbiota microbiome. Such devices are used primarily for gathering images and monitoring gastrointestinal fluid for gases and electrolytes[110]. Such chemical-sensing technology is extremely useful for monitoring gut health but (unlike common wearable chemical sensors) is usually not correlated with gold-standard blood diagnostics. Although these sensors could provide important stand-alone feedback about health, they will more likely add significant understanding to a multimodal and holistic monitoring approach in combination with body-fluid analysis by wearable devices.

Conclusion

A broad range of wearable devices for non- or minimally invasive body-fluid analysis have been developed, enabling remote and precise biochemical monitoring and providing a next generation of digital biomarkers[111]. The application of body-fluid analysis by wearable devices not only facilitates access to remote molecular monitoring but also allows for the derivation of biomarkers that may expand our understanding of health and disease. Applied body-fluid analysis by wearable devices represents the next paradigm shift in remote healthcare monitoring.

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Competing interests R.G. is co-founder and CEO of Epicore Biosystems. J.W. is founder and chief scientific officer at Persperion. W.G. is co-founder and advisor at Persperity Health. E.V. serves in the ethics advisory panel of Merck AG and in the ethics advisory panel of IQVIA. J.A.R. is a co-founder and advisor to Sibel Health, Sonica and Epicore Biosystems, and holds patents associated with these companies. The other authors declare no competing interests.

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