

Wearable biomolecular sensing nanotechnologies in chronic disease management

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Jiaobing Tu^{1,8}, Connor D. Flynn^{2,3,8}, Jeonghee Yeom¹, Zhenwei Wu^{3,4}, Shana O. Kelley^{2,3,4,5,6,7}✉ & Wei Gao¹✉

Over the past decade, consumer wearable sensors have become increasingly ubiquitous in health monitoring, enabling the widespread tracking of key biophysical parameters. The transition towards next-generation body-interfaced biomolecular sensing technologies, fuelled by the integration of reagentless sensing strategies with advanced nanomaterials, marks the next substantial leap forward. These innovations enable unobtrusive, multimodal monitoring of both physiological parameters and biochemical disease markers in real time. This Review examines the current generation of body-interfaced biomolecular sensing technologies, with a particular emphasis on materials innovation and nanotechnological advancements, and discusses their pivotal role in chronic disease monitoring. The discussion extends to the challenges and prospects in this rapidly evolving field, highlighting the potential for materials-focused approaches to transform the landscape of chronic disease monitoring and management with body-interfaced bioelectronics. By harnessing the power of materials and nanotechnological innovations, these biomolecular sensing technologies promise to enhance diagnostic capabilities and foster a more proactive, personalized approach to combating these diseases.

Chronic diseases, such as cardiovascular disease and diabetes, rank among the leading causes of premature deaths globally, placing immense strain on both patients and healthcare infrastructure¹. The growing prevalence of these conditions, fuelled by a rapidly growing ageing population, necessitates more independent and affordable healthcare solutions. Although early preventive measures and health promotion approaches can decrease the incidence of chronic diseases and ease the burden on the healthcare system, the ongoing

challenge lies in effectively monitoring these diseases and tracking their progression.

The fusion of nanotechnologies with wearable bioelectronics has catalysed a paradigm shift towards proactive and personalized healthcare, with the potential to drastically improve chronic disease management. Traditionally, chronic disease management has relied heavily on the clinical evaluation of vital signs and specific biomarkers in blood. Recent advances in nanosensing technologies and biomarker discovery

¹Andrew and Peggy Cherng Department of Medical Engineering, Division of Engineering and Applied Science, California Institute of Technology, Pasadena, CA, USA. ²Department of Chemistry, Weinberg College of Arts and Sciences, Northwestern University, Evanston, IL, USA. ³Chan Zuckerberg Biohub Chicago, Chicago, IL, USA. ⁴Department of Biomedical Engineering, McCormick School of Engineering, Northwestern University, Evanston, IL, USA. ⁵Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada. ⁶Department of Biochemistry and Molecular Genetics, Feinberg School of Medicine, Northwestern University, Evanston, IL, USA. ⁷International Institute for Nanotechnology, Northwestern University, Evanston, IL, USA. ⁸These authors contributed equally: Jiaobing Tu, Connor D. Flynn.

✉e-mail: shana.kelley@northwestern.edu; weigao@caltech.edu

have opened new avenues for more comprehensive condition-specific health assessments.

This Review begins with an overview of the global landscape of chronic diseases, highlighting key conditions and their associated molecular signatures. We then discuss body-interfaced sensing technologies relevant to the monitoring and management of these chronic conditions. Since body-interfaced physical sensors, such as those monitoring vital signs, have been extensively covered in the existing literature^{2,3}, this Review focuses on the evolving landscape of biomolecular sensing. We focus our discussion on the role of nanomaterials in enhancing sensor sensitivity, while also highlighting their potential to improve flexibility and biocompatibility—key factors in overcoming limitations of conventional sensing platforms.

We also examine the relevant form factors of body-interfaced biomolecular sensing devices, emphasizing the importance of design and engineering in optimizing their performance and user experience. Additionally, we outline the transformative potential of these sensors in chronic disease management and discuss the challenges and opportunities associated with their integration and commercialization. This Review is not intended to be exhaustive, but instead aims to provide a focused perspective on how nanotechnology can address key sensing challenges and unlock new possibilities for the continuous, body-interfaced monitoring of chronic diseases. Through selected examples and thematic analysis, we highlight both the promise and current limitations of these emerging technologies. We aim to emphasize the importance of translating these innovations into practical healthcare solutions that deliver tangible benefits to patients and healthcare systems alike.

Molecular signatures of chronic diseases

Biomarkers are essential for diagnosing, monitoring and managing chronic diseases, providing insights into disease progression and enabling personalized treatment⁴. Traditional biomarker analysis has primarily focused on disease-specific markers (for example, troponin for cardiovascular disease); although these markers correlate with disease state, they often fail to capture the entirety of the disease. As medical science continues to elucidate the interconnectedness of the molecular world, it has become increasingly clear that diseases are best viewed through an eclectic approach that combines multiple body systems. For example, analysis of indirect surrogate biomarkers in other body systems (for example, C-reactive protein and choline) can provide valuable insight into cardiovascular disease progression (for example, vessel integrity) that can facilitate disease treatment and prevention. Here we highlight key biomarkers relevant to chronic disease (Fig. 1) and emphasize the importance of adopting a system-wide approach to disease monitoring and management.

Signatures of cardiovascular diseases

Cardiovascular disease, including coronary artery disease, heart valve disease and heart failure, is the leading cause of death worldwide⁵. Monitoring cardiovascular health can help to track disease progression and predict acute events, such as heart attack and stroke⁶. Cardiovascular biomarkers include cardiac dysfunction and tissue damage indicators, including B-type natriuretic peptide and its amino-terminal partner fragment—peptides generated through excessive heart muscle stretching—and troponin I, troponin T and creatine kinase-myocardial band—proteins released due to heart muscle degradation^{6,7}. In the peripheral cardiovascular system, vessel stenosis can be caused by either atherosclerotic plaque formation—identified through lipid-based biomarkers such as low-density lipoproteins and apolipoprotein B⁸—or thrombus formation—identified via biomarkers such as thrombin and D-dimer proteins⁹. Surrogate biomarkers of the digestive system (for example, microbiota-derived trimethylamine-*N*-oxide and its precursor, choline¹⁰) and skeletal system (for example, osteopontin and osteoprotegerin¹¹) are also emerging as useful indicators of vessel stenosis and calcification, respectively.

Signatures of metabolic disorders and autoimmune diseases

Metabolic disorders, such as diabetes mellitus, pose substantial systemic risks to patients and often require diligent molecular monitoring (for example, glycaemic control) to avoid complications¹². Glucose, glycated haemoglobin (HbA1c) and insulin are traditional biomarkers of diabetes; however, recent years have seen the emergence of alternative markers, including β -hydroxybutyrate¹³, hyocholic acid¹⁴ and leptin¹⁵, related to obesity and diet that can inform diabetic progression.

Biomolecular monitoring can also help to manage autoimmune disorders, such as arthritis (for example, rheumatoid arthritis and gout) and lupus, by tracking disease progression, predicting flare-ups and guiding proactive treatment. Autoimmune biomarkers often include autoantibodies (for example, rheumatoid factor and anti-citrullinated protein antibodies for arthritis^{16,17} and anti-DNA antibodies for lupus¹⁸). In addition to monitoring disease progression and activity, sensors may also be employed in the management of chronic symptoms (for example, chronic wounds¹⁹ and kidney damage²⁰).

Signatures of neurological disorders

Biomolecular monitoring of neurological disorders, including Alzheimer's disease, Parkinson's disease and multiple sclerosis, can identify and track neurodegeneration, allowing clinicians to address neurological symptoms in a timely manner. For example, neuron-specific protein markers, such as neurofilament light chain^{21,22}, can indicate neuron breakdown and predict neurological dysfunction. The aggregation of other markers, such as amyloid beta and tau proteins in Alzheimer's disease²³ or α -synuclein in Parkinson's disease²⁴, can begin years or even decades before symptom onset and serve as a key indicator of disease imminence. MicroRNAs have also emerged as promising biomarkers of neurodegenerative diseases; for example, increased expression of miR-34a and miR-124 has been linked to the onset of Alzheimer's and Parkinson's, respectively^{25,26}.

Signatures of mental health

Biomolecular monitoring is poised to revolutionize mental healthcare by enabling accurate diagnosis and personalized treatment of anxiety, depression and bipolar disorders through comprehensive biomarker profiling^{27–29}. Fluctuations in neurotransmitters such as dopamine, serotonin and gamma-aminobutyric acid are typical identifiers of mental health conditions³⁰; however, these markers alone cannot adequately stratify patients with more complex issues (for example, treatment-resistant depression)³¹. Emerging biomarkers, including brain-derived proteins (for example, brain-derived neurotrophic factor), endocrine molecules (for example, cortisol) and inflammatory markers (for example, cytokines), have shown strong correlative relationships with mental health conditions and represent promising clinical indicators²⁹. The importance of the gut–brain axis has also become increasingly clear, with microbial metabolites such as short-chain fatty acids and uraemic toxins (for example, indoxyl sulfate) being shown to influence individual mental state³².

Signatures of women's health

Continuous monitoring of women's health markers can enhance the management of menstruation, pregnancy and menopause-related chronic conditions, many of which are currently underdiagnosed or overlooked. Menstruation-related ailments (for example, polycystic ovary syndrome, endometriosis and dysmenorrhoea) are associated with hormone (for example, sex hormone-binding globulin and oestradiol), prostaglandin (for example, prostaglandin E2 and F2 α) and inflammatory (for example, leukotriene B4) markers^{33,34}. Pregnancy-related chronic conditions (for example, pre-eclampsia, hyperemesis gravidarum and gestational diabetes) are associated with placental (for example, placental protein 13) and regulatory proteins (for example, soluble fms-like tyrosine kinase 1 and soluble endoglin)³⁵. Menopause-related conditions, including premature ovarian

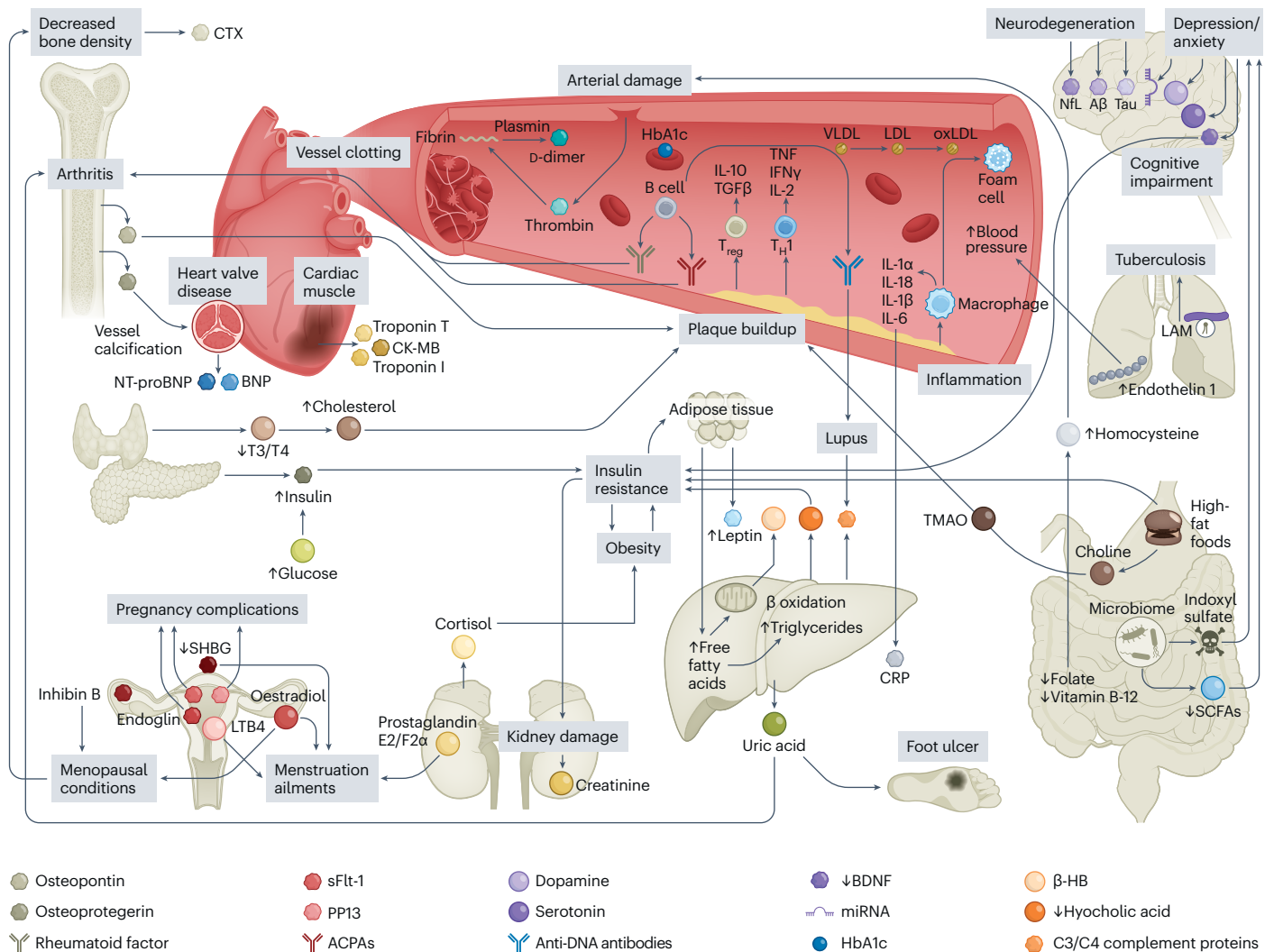


Fig. 1 | Molecular signatures of chronic diseases. Schematic of the established molecular biomarkers associated with chronic diseases, highlighting their interconnected relationships across various body systems, complications, symptoms and disorders. Many biomarkers lend themselves to multiple pathological processes and serve to trigger or exacerbate new or existing symptoms elsewhere in the body. Comprehensive analysis of indirect surrogate biomarkers provides a holistic view of chronic disease state, enhancing our understanding and improving clinical outcomes. Cardiovascular conditions can be monitored through biomarkers from other body systems (for example, hypertension monitoring via lung-derived endothelin 1)¹²⁴. Autoimmune activity can be monitored through both small-molecule (for example, uric acid¹⁰³) and protein biomarkers (for example, C3/C4 complement proteins¹²⁵). Neurological disorders have been linked to peripheral small-molecule markers such as uric acid²⁶ and homocysteine²⁷ that may prove valuable as future preventive biomarkers. Infectious diseases are typically diagnosed using pathogen-related antigens, such as p24 capsid protein or lipoarabinomannan (LAM) for human immunodeficiency virus (HIV) and tuberculosis, respectively³⁸. Infection progression may be monitored through general immune system biomarkers

(for example, leukocytes and cluster of differentiation (CD) proteins)³⁸ or condition-related biomarkers (for example, neurofilament light chain (NFL) for HIV-induced neurodegeneration)²². In addition to cytokines, inflammatory biomarkers include downstream molecules produced during acute-phase processes; for example, C-reactive protein (CRP) is produced by the liver in response to IL-6 signalling and is associated with numerous chronic diseases^{39,40}. Aβ, amyloid beta; ACPs, anti-citrullinated protein antibodies; β-HB, β-hydroxybutyrate; BDNF, brain-derived neurotrophic factor; BNP, B-type natriuretic peptide; CK-MB, creatine kinase-myocardial band; CTX, C-terminal telopeptide of type I collagen; IFNγ, interferon gamma; LDL, low-density lipoprotein; LTB4, leukotriene B4; miRNA, microRNA; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; oxLDL, oxidized LDL; PP13, placental protein 13; SCFAs, short-chain fatty acids; sFlt-1, soluble fms-like tyrosine kinase 1; SHBG, sex hormone-binding globulin; TMAO, trimethylamine-*N*-oxide; TNFα, tumour necrosis factor alpha; VLDL, very-low-density lipoprotein. Arrows in the figure represent established links between biomarkers and conditions. ↑ or ↓ next to a biomarker indicates increased or decreased levels, respectively, while biomarkers without such symbols are shown as associated with the condition for simplicity.

insufficiency and postmenopausal osteoporosis, can be monitored through ovarian (for example, follicle-stimulating hormone and inhibin B) and bone integrity markers (for example, C-terminal telopeptide of type I collagen), respectively³⁶.

Inflammatory signatures

Inflammation monitoring has emerged as a promising surrogate for tracking chronic disease and infection progression due to the ubiquitous nature of inflammation in diseases^{37–39}. Inflammation

biomarkers are typically cytokines such as interleukins (for example, interleukin 6 (IL-6)), tumour necrosis factor family (for example, tumour necrosis factor) and interferons (for example, interferon gamma)⁴⁰. Many cytokines exhibit polycasual fluctuations due to the systemic nature of inflammation, and ongoing research has focused on elucidating disease-associated diagnostic cytokine patterns⁴. For example, increased levels of interferon gamma, IL-1β, IL-6 and tumour necrosis factor are strongly correlated with atherosclerotic plaque formation in cardiovascular disease³⁷.

Exogenous signatures

Exogenous markers, including externally introduced drugs and nutrients, can also prove valuable in the context of biomolecular sensing by allowing users to monitor materials entering their body and measure their subsequent effects^{41–43}. Continuous drug monitoring, such as the sensing of chemotherapy agents, allows clinicians to track drug dosage over time after initial administration⁴². This analysis can be coupled with the sensing of other health indicators (for example, inflammation levels) to simultaneously assess drug effectiveness and optimize dosing while minimizing deleterious effects. Monitoring diet-derived biomarkers (for example, vitamin D and omega-3 fatty acids) can also guide preventive medicine approaches through the development of personalized nutrition regimens^{42,44}.

Biomarker considerations

When identifying appropriate biomarkers, factors such as molecular relevance, specificity and timescale must be carefully considered. Not all biomarkers are well suited for continuous monitoring; for example, binary biomarkers such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein indicate a disease state based on presence or absence, making continuous assessment unnecessary⁴⁵. Continuous monitoring is most valuable for biomarkers whose concentrations fluctuate meaningfully with disease progression. However, distinguishing which biomarkers fall into this category can be extremely challenging due to the body's inherent complexity—numerous biomarkers fluctuate for various reasons unrelated to disease. Adding to this complexity, many biomarkers (for example, cytokines) exhibit polycasual fluctuations, such that their changing levels are indicative of a general response (for example, inflammation) not easily assigned to a specific disease state^{4,46}. Furthermore, the same biomarker may fluctuate at drastically different timescales (that is, minutes versus hours) for different disease states, making it challenging to discern whether changes are due to acute or chronic processes⁴⁶. This assessment underscores the importance of implementing robust clinical validation alongside sensor development⁴⁷. A deeper understanding of temporal biomarker dynamics is still in progress, and continuous monitoring helps to establish a cyclic system—allowing sensors to elucidate biological mechanisms that, in turn, can guide further sensor development and improve diagnostic and treatment capabilities⁴.

Nanoscale sensing systems for body-interfaced monitoring

Early diagnosis and the continuous monitoring of chronic diseases hinge on the accurate measurement of physicochemical signals and related biomarkers. The integration of nanomaterials and nanostructures into body-interfaced sensors has emerged as a powerful tool, enhancing sensor performance through the use of multifunctional materials and optimized interactions with target analytes.

Harnessing nanomaterials and biomolecules for nanoscale sensing

Many physiological analytes of interest require detection at sub-nanomolar or even picomolar levels. Over the past few decades, extensive research has focused on developing high-resolution sensors that surpass the limitations of bulk and planar sensing platforms through the intervention of nanotechnology⁴⁸. Nanoengineered devices enhance the signal-to-noise ratio to achieve superior sensitivity, down to the femtomolar level and even the single-molecule level, by leveraging their size-matched interaction with target molecules and often overcoming analyte transport limitations. This section highlights the synergistic combination of nanomaterials, nanostructures and bio-affinity elements for the detection of minute targets, as well as the application of nanoscale materials and nanoengineered surfaces for in situ and real-time monitoring of chronic disease biomarkers. It also emphasizes various sensing approaches that facilitate their detection (Box 1).

Nanomaterials play a crucial role in improving sensor performance due to their unique, nanoscale-driven physicochemical properties. These materials possess large surface-to-volume ratios and high electron mobilities and are easily modified with recognition elements to produce active target recognition materials (Fig. 2a). Common nanomaterials employed in sensors include quantum dots, nanoparticles, nanowires, graphene, MXenes and metal–organic frameworks. These materials serve as important scaffolds for sensor functionalization, providing both versatile binding sites and structural stability. Nanomaterials can also play an active role in sensing systems, serving as conductive electrodes, active sensing layers or functional additives that enhance target binding and signal transduction.

Biological and synthetic recognition elements are also nanoscale entities and exhibit strong affinity or high catalytic activity for specific targets, enabling sensitive and specific recognition of key physiological markers. Nanoscale recognition elements encompass a diverse range of biological and synthetic molecules, including ionophores, peptides, nucleic acids, aptamers, antibodies, enzymes, molecularly imprinted polymers (MIPs) and whole cells. These components interact with specific target analytes, enabling the detection of a wide range of substances through innovative sensing strategies.

The interplay between nanomaterials and recognition elements enables the development of highly robust sensing systems capable of precise biomarker quantification, achieving sensitivities compatible with the targets of interest. For example, nanozymes (that is, catalytically active nanomaterials) have emerged as promising alternatives to natural enzymes, overcoming the limitations of traditional enzymatic systems (Fig. 2b)⁴⁹. Nanozymes offer enhanced stability, tunable activity and lower cost, making them suitable for diverse applications; however, their substrate selectivity remains a challenge. Hybrid approaches that combine nanozymes with natural enzymes⁵⁰, other nanozymes or synthetic receptors, such as MIPs⁵¹, can enhance selectivity and functionality. In an example, core–shell nanoparticles with built-in dual functionality—featuring an MIP shell for customizable target recognition and a nickel hexacyanoferrate core for stable electrochemical transduction—were reported for the continuous monitoring of circulating nutrients and therapeutic drugs⁵¹.

Nanomaterials also play a crucial role in enhancing energy transfer for ultrasensitive optical detection. In Förster resonance energy transfer-based biosensors, nanomaterials such as quantum dots and upconversion nanoparticles serve as efficient donors, whereas gold nanoparticles (AuNPs) act as acceptors, enabling non-radiative energy transfer within 10 nm. Compared with organic dyes, these nanomaterials offer superior photostability, tunable spectra, chemical stability, low toxicity and high quenching efficiency⁵² (Fig. 2c).

Engineered nanostructures facilitate electron and photon transfer, manipulating light-matter interaction to enhance sensor performance. A variety of nanostructures and patterns can be fabricated using multiple nanofabrication techniques: top-down and bottom-up approaches⁵³. Top-down methods, such as photolithography (ultraviolet light), electron beam lithography (electrons) and the focused ion beam technique (ions) enable precise construction of nanostructures, but are often limited by high costs and low throughput. Bottom-up approaches can create versatile patterns, ranging from the self-assembly of simple hexagonal patterns using nanoparticles, to complex arbitrary designs via DNA scaffolding (for example, DNA origami)⁵⁴; however, these methods still face scalability challenges. High-throughput techniques such as roll-to-roll imprinting, roll transfer and inkjet printing offer promising solutions for cost-effective, large-area sensor fabrication when coupled with robust nanomaterials-based formulations.

The morphology at the sensor interface is critical for both electrochemical and photonic devices. Nanostructured surfaces enhance electric signals by modulating the electric double layer⁵⁵. Nanoporous structures enable sensing beyond traditional Debye-length

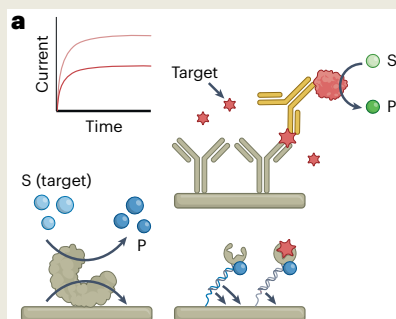
BOX 1

Key sensing modalities in body-interfaced sensing

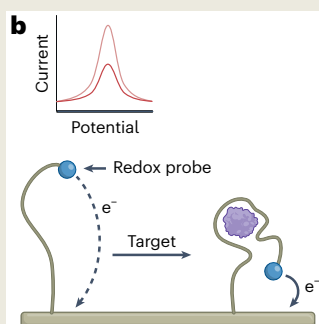
Sensor development is a nuanced endeavour, requiring diverse sensing modalities tailored to biomarker type, physiological application and receptor characteristics. To address these challenges, scientists have engineered nanoscale transduction systems capable of enhancing sensitivity, improving selectivity and enabling real-time detection in complex biological environments.

Electrochemical sensing strategies

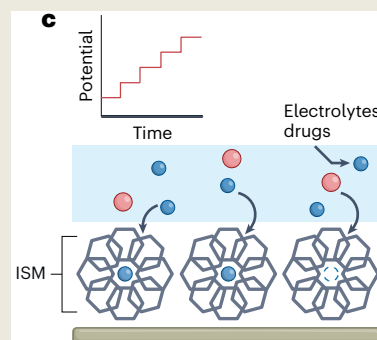
Electrochemical sensors dominate the current-sensing landscape and are favoured in wearable electronics applications due to their ease of use, low cost, rapid response and high sensitivity. Electrochemical sensors transduce biological interactions into electric signals and can be categorized based on the electric property they measure, with amperometry, voltammetry, potentiometry and impedimetry being the primary techniques.



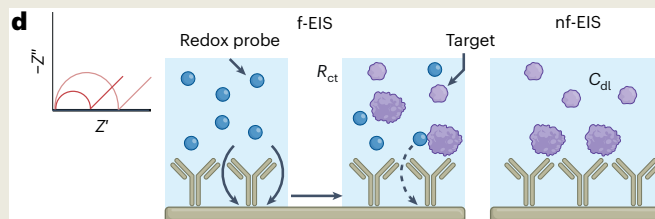
Amperometric sensors. Amperometric sensors (panel **a**) measure current as a function of time, often from the oxidation or reduction of redox reporters, and rely on target-induced changes in the amount or extent of redox reactions. For example, amperometry is the predominant transduction method for enzymatic glucose sensors, with the current being proportional to the glucose concentration. Amperometric measurements are fast and minimally interrogative, making them ideal for continuous monitoring applications; as such, they have been widely utilized to monitor metabolites, such as glucose, lactate and uric acid, in body fluids^{19,65,131}. Despite the success of enzymatic amperometric sensors, expanding the range of detectable analytes remains challenging due to the limited availability of redox enzymes. Affinity receptors, such as aptamers and antibodies, can be linked to enzymes to enable signal transduction⁹⁹. Other techniques, such as the molecular pendulum method, have been developed to detect various biomolecules without enzymes¹³². This approach utilizes time-resolved current changes based on hydrodynamic differences in receptor-bound DNA constructs to monitor and quantify analyte binding¹³³. P, product; S, substrate (target molecule).



Voltammetric sensors. Voltammetric sensors (panel **b**) measure current as a function of potential, using techniques such as cyclic voltammetry, differential pulse voltammetry and square wave voltammetry. By changing potential, voltammetric sensors can easily profile redox reactions to obtain distinct redox peaks. Voltammetric methods can be used to directly detect electroactive species; for instance, differential pulse voltammetry with laser-engraved graphene electrodes can detect micromolar-level uric acid in sweat, which is relevant to gout and cardiovascular disease monitoring¹⁰³. Selectivity challenges can arise in the presence of interferents with similar redox potentials, but this can be improved by utilizing specific bioreceptors, such as MIPs⁴³, aptamers⁶² and antibodies³⁹. Voltammetric methods may also employ redox reporters, such as with electrochemical aptamer-based sensors, which rely on binding-induced conformational changes to alter the efficiency of redox activity⁹².



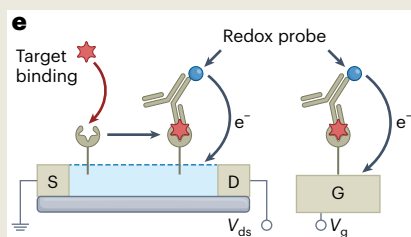
Potentiometric sensors. Potentiometric sensors (panel **c**) measure the interfacial potential between the working electrode and reference electrodes in the absence of current. Solid-state potentiometric ion-selective electrodes are commonly used in wearable sensors to monitor electrolytes in body fluids (for example, Na⁺, K⁺, Ca²⁺ and NH₄⁺)⁹⁸. The ion-selective membrane (ISM) on the working electrode selectively traps ions of certain size and charge, with the ion-binding event transduced to a voltage change following the Nernst equation.



Impedimetric sensors. Impedimetric sensors (panel **d**) measure changes in electrode surface properties due to target binding using electrochemical impedance spectroscopy (EIS). Faradaic EIS (f-EIS) involves the incorporation of redox reporters, often quantifying redox efficiency through charge transfer resistance (R_{ct}), whereas non-faradaic EIS (nf-EIS) focuses primarily on double-layer capacitance (C_{dl}) changes (for example, surface dielectric properties or charge distribution). These label-free sensors are information rich and miniaturizable; however, they can face issues with non-specific interferants due to their indiscriminate nature⁴.

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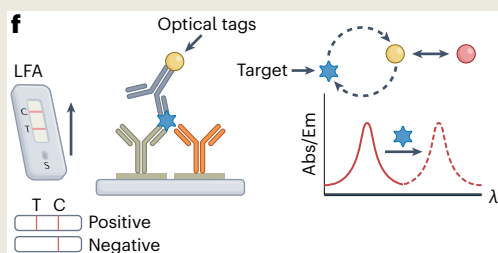
In the figure panel, Z' and $-Z''$ correspond to real impedance and imaginary impedance, respectively.



Organic electrochemical transistors. Organic electrochemical transistors (OECTs) are electronic transistors capable of amplifying minute biomarker concentration changes¹³⁴, offering high sensitivity and specificity. OECTs can be modified with biorecognition probes (aptamers, nanobodies, antibodies and MIPs) on either the channel or gate in a versatile fashion¹³⁵. Target–probe interactions effectively facilitate or impede electron transfer, altering the channel current, gate voltage or response time¹³⁴. OECTs have been actively utilized to monitor metabolites, such as glucose, lactate, uric acid and cholesterol, with ultrahigh sensitivity¹³⁵. Panel e shows schematics of OECT-based sensors utilizing immobilized detection probes on the channel or gate electrode. D, G and S represent the drain, gate and source electrodes, respectively. V_g and V_{ds} correspond to the gate voltage and drain–source voltage, respectively.

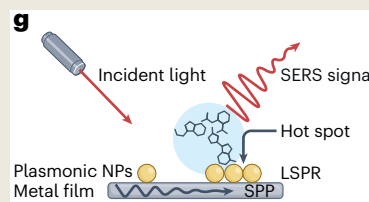
Optical sensing strategies

Optical sensors rely on the modulation of optical signals, through altered absorbance, quenching, enhancement or energy transfer, in response to target recognition events. These systems often employ optical tags, such as chromophores, fluorophores, quantum dots or AuNPs, as reporter molecules.

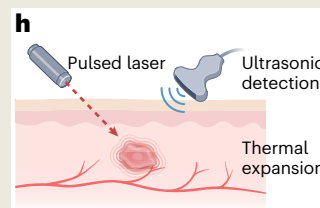


Colorimetric sensors. Colorimetric sensors rely on the generation or alteration of colour to signal analyte presence or concentration. Lateral flow assays, such as pregnancy and coronavirus disease 2019 tests, are the most well-known colorimetric sensors; these use AuNPs and other plasmonic nanomaterials for visual detection, but are semi-quantitative, with limited sensitivity⁴⁵. Colorimetric sensors can also be implemented into wearable form factors, such as with the use of chromogenic reagents embedded in a hydrogel and cellulose matrix to monitor sweat components (for example, water, chloride, pH, lactate, glucose or creatine)¹³⁶. Panel f shows schematics of

optical signal transduction strategies, including colorimetric/fluorometric sensing with optical tags, nanostructure-assisted SERS sensing and photoacoustic imaging-based sensing. Abs, absorption; C, control; Em, emission; λ , wavelength; LFA, lateral flow assay; T, test



SERS. SERS (panel g) provides high sensitivity and molecular fingerprinting capabilities without the need for optical tags⁵⁶. Nanoengineered metal structures exhibit plasmonic effects that amplify Raman signals at hot spots, enabling highly sensitive molecular-level detection. Hybrid architectures combining semiconducting materials (for example, ZnO and TiO₂) with noble metals further enhance SERS effects, achieving an enhancement factor of 10^{11} and allowing for the label-free detection of antibiotics¹³⁷. To address challenges in surface biofouling, wearability and sample collection and processing, SERS structures are often integrated into flexible or stretchable substrates¹³⁸ and sweat-extracting hydrogels¹³⁹, creating wearable biosensors capable of detecting trace amounts of substances such as drugs in human sweat. LSPR, localized surface plasmon resonance; NPs, nanoparticles; SPP, surface plasmon polariton.



Photoacoustic imaging. Photoacoustic imaging (panel h) combines optical excitation with ultrasonic detection to provide high-resolution imaging of biomolecules¹⁴⁰. Short-pulsed laser light induces thermal expansion in tissues, generating photoacoustic waves that are detected by an ultrasonic transducer. By combining target-specific recognition probes with nanoparticles (for example, AuNPs) or fluorescent dyes, photoacoustic imaging allows for the non-invasive, in vivo detection of specific targets for diagnosing and treating conditions such as cancer.

Continuous sensing strategies. Although CGMs enable real-time glucose monitoring through compatible redox enzymes, the continuous and stable detection of other small molecules and large biomolecules remains a challenge, primarily due to the slow equilibration times of affinity reagents and the instability of the redox probes or bioreceptors. Emerging approaches for receptor stabilization or regeneration involve applying external energy, such as increased temperature or alternating electric fields, to reset the sensor baseline and enable sequential measurement^{43,141,142}.

limitations, thereby reducing screening effects and enhancing charge transfer at the electrode (Fig. 2d). Furthermore, integrating a single nanowire or nanotube as the field-effect transistor gate facilitates single-molecule detection through local surface potential changes during binding events.

Furthermore, sub-wavelength nanoengineered surfaces are employed for precise light control to amplify signals, enabling

single-molecule-level detection. For example, surface plasmon resonance on nanostructured metallic surfaces enables label-free, real-time biomolecular detection via enhanced light-matter interaction⁵⁶. Plasmon-enhanced fluorescence further amplifies the fluorescence of nearby fluorophores using metallic nanostructures, such as AuNPs and AgNPs, nanohole arrays and nanorod arrays, thereby boosting sensitivity in fluorescence-based sensors⁵⁷. Advanced

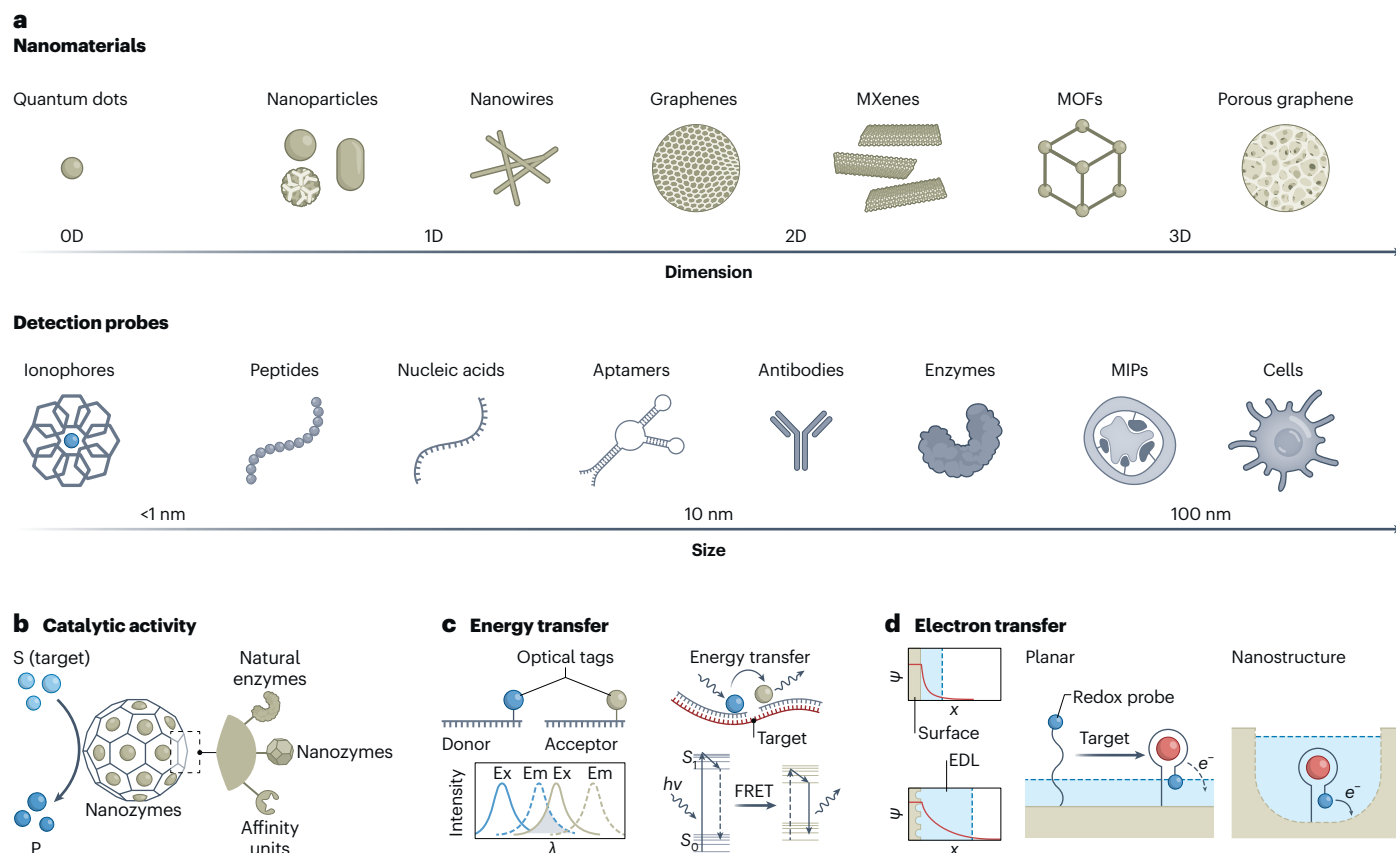


Fig. 2 | Introduction of nanomaterials and nanotechnologies in body-interfaced monitoring. **a**, Schematics of nanomaterials and detection probes for sensitive body-interfaced sensors. **b**, Nanozymes that mimic the catalytic activity of natural enzymes. Modification of nanozymes with natural enzyme structures can impart high selectivity. **c**, Energy transfer mechanisms, such as Förster

resonance energy transfer (FRET), between light-sensitive donor and acceptor molecules during target recognition events. **d**, Nanostructured surfaces designed to enhance electron transfer for improved electrochemical sensing performance. Em, emission; Ex, excitation; MOFs, metal–organic frameworks; S, substrate; P, product; S_0 , ground state; S_1 , excited state; x , distance; ψ , potential.

techniques, such as the integration of plasmonic light-trapping techniques (for example, plasmonic tweezers) with surface-enhanced Raman spectroscopy (SERS), achieve single-molecule resolution by confining and amplifying molecular signals at nanoscale hot spots⁵⁸.

The integration of nanomaterials, bio-affinity elements and nanostructures has led to the development of highly sensitive biomolecular sensing platforms capable of detecting key biomarkers with remarkable advancements in sensitivity. Box 1 introduces popular and emerging transduction strategies for identifying specific molecular targets.

Body-interfaced platforms for chronic healthcare

Integrating sensors into daily life requires form factors that are unobtrusive for effective health monitoring. Building on the foundation of point-of-care devices, new body-interfaced technologies are emerging for the management of chronic diseases. Although most remain laboratory prototypes (Table 1), some, such as continuous glucose monitors (CGMs), have reached practical application. Here we explore form factors that can be interfaced with various locations on the human body, discussing the design challenges and considerations associated with different biological samples and analytes of interest (Fig. 3a).

Wearable devices. Wearable sensing platforms enable non-invasive monitoring of chronic diseases with high adherence and data accessibility. Their integration with soft, stretchable materials enhances comfort and usability.

Sweat monitoring. On-skin sweat analysis has been achieved using form factors such as skin patches, tattoos, earpieces and socks⁵⁹. The passive

collection of natural sweat faces challenges such as limited temporal resolution and accuracy issues due to sweat mixing and insufficient volumes for continuous sensing. To address this, hydrogels can be integrated into electronic interfaces for low-volume sampling⁶⁰ or detecting solid-state analytes⁶¹. Exercise or thermal stimuli can induce profuse sweating, but large variations in sweat rate complicate analyte quantitation. Controlled sweat induction and analysis via iontophoresis, which delivers cholinergic drugs loaded via small currents, allows for sustained local sweat stimulation and in situ sampling of biomarkers for monitoring conditions such as metabolic syndrome, gout and inflammation^{39,43,62}.

Interstitial fluid monitoring. Interstitial fluid (ISF) closely mirrors blood in biomarker composition, with less cellular interference⁶³. ISF extraction is challenging due to hydraulic resistance from the extracellular matrix and limited quantity, but research into improved methods, such as microneedles and microdialysis, is ongoing⁶⁴. CGMs—a commercial success—use an enzyme-coated sensor needle for glucose monitoring in ISF. However, these devices require frequent replacement due to sensor drift, foreign body rejection and epidermal shedding. Microneedles offer minimally invasive ISF sensing, but inconsistencies in skin penetration can affect accuracy and reliability⁶⁵. Reverse iontophoresis, which uses applied current to generate the electro-osmotic flow of ISF through the epidermis, often results in highly diluted samples⁶⁶ and can preferentially extract charged or zwitterionic small molecules, further complicating analysis.

Wound exudate monitoring. Skin-interfaced devices such as bandages and dressings can monitor exudate in chronic wounds linked

Table 1 | Current body-interfaced chronic-disease-monitoring technologies

Technology	Form factor	Biological sample(s)	Materials	Measured biomarkers and their physiological levels	Correlation(s)	Chronic disease application	Development status and limitations
SEB sensor ⁶¹	Epidermal patch	Solid-state epidermal biomarkers	Ionic conductive hydrogel and electronically conductive hydrogel bilayer	Lactate and cholesterol	Solid-state lactate against serum lactate ($r=0.89$; $n=21$) and solid-state cholesterol ($r=0.95$ before intake and $r=0.92$ after intake; $n=21$)	Lactic acidosis, risk factor monitoring for cardiovascular diseases, diabetes and metabolic syndrome	Laboratory prototype stage with early human testing; Limited 2- to 4-h operational time
NutriTrek ⁴³	Smart watch	Sweat	Laser-engraved graphene and Prussian blue nanoparticles	Tryptophan (5–80 μM), leucine (10–300 μM) and total BCAAs (0.2–0.8 mM)	Sweat leucine versus serum leucine ($r=0.66$; $n=65$) and sweat BCAAs versus serum BCAAs ($r=0.69$; $n=65$)	Metabolic syndrome and diabetes	Laboratory prototype stage with early human testing; Lack of long-term validation
InflaStat ³⁹	Wearable patch	Sweat	Graphene–gold nanoparticle composite	CRP (0.5–20.0 ng ml^{-1})	Sweat CRP versus serum CRP ($r=0.841$; $n=80$)	Inflammatory diseases and infection monitoring (for example, COPD, heart failure and COVID-19)	Laboratory prototype stage with early patient studies; Single-point measurement
Multiplexed microneedle-based wearable sensor system ⁶⁵	Microneedle array	ISF	PMMA microneedle array with electrodeposited PPD working electrode	Lactate (0.3–1.3 mM), alcohol (0–0.02%) and glucose (3.9–7.1 mM)	Lactate ($r=0.94$; $n=105$ paired datapoints against blood lactate), glucose (MARD = 8.83%; $n=95$ paired datapoints) and alcohol ($r=0.94$; $n=95$ datapoints against breath analyser)	Diabetes, lactic acidosis, pre-diabetes, metabolic syndrome and risk factor monitoring	Laboratory prototype stage with early human testing; Lack of long-term validation; Not yet capable of real-time self-calibration
Pixel-based graphene array for ISF glucose monitoring via reverse iontophoresis ⁶⁶	Wearable patch	ISF	Platinum nanoparticle-decorated graphene array	Glucose (by reverse iontophoresis; $\leq 50 \mu\text{M}$)	–	Diabetes	Laboratory prototype stage with early human testing; Lack of long-term validation beyond 6 h
VeCare ⁶⁷	Wound dressing	Wound fluid	Electrochemically exfoliated graphene–gold nanoparticle nanocomposite	TNFr, IL-6, IL-8, TGF β 1, <i>Staphylococcus aureus</i> , and pH	–	Chronic wounds and venous ulcers	Pre-clinical stage with pilot human testing; Single-time-point measurements
Fully integrated, stretchable, wearable bioelectronic system ¹⁹	Wearable patch	Wound fluid	Gold electrodes on SEBS substrate	Glucose ($\leq 50 \text{ mM}$), lactate (2–4 mM), uric acid (40–80 μM), NH_4^+ (2–5 mM) and pH (7–8)	–	Chronic wounds and diabetic foot ulcers	Laboratory prototype stage with in vivo animal studies; Lack of long-term validation and human studies
iCares ¹²⁰	Wearable patch	Wound fluid	Inkjet-printed gold nanoparticles and laser-engraved graphene	NO (1–40 μM), H_2O_2 (5–70 μM), O_2 (0.8–3.0 ppm) and pH (5.5–8.0)	–	Chronic wounds, including diabetic and venous wounds	Pre-clinical stage with pilot human testing; Lack of long-term validation
Electroreregurable, printable, MIP-based, wearable biosensing platform ⁵¹	Wearable patch	Sweat	Inkjet-printed, core-shell, Prussian-blue-analogue MIP nanoparticles	Ascorbic acid (50–70 μM), creatinine (40–100 μM) and tryptophan (5–80 μM)	Sweat ascorbic acid versus serum ascorbic acid ($r=0.945$; $n=9$), sweat creatinine versus serum creatinine ($r=0.723$; $n=14$) and sweat tryptophan versus serum tryptophan ($r=0.858$; $n=12$)	Nutrition monitoring and therapeutic drug monitoring	Laboratory prototype stage with animal and human studies; Lack of long-term validation beyond 3 h
Wearable salivary uric acid mouth guard biosensor ⁷¹	Mouth guard	Saliva	Screen-printed Prussian blue-graphite working electrode	Uric acid (30–180 μM) ²¹	–	Hyperuricaemia and gout	Laboratory prototype stage with early human testing; Lack of long-term validation beyond 4 h

Table 1 (continued) | Current body-interfaced chronic-disease-monitoring technologies

Technology	Form factor	Biological sample(s)	Materials	Measured biomarkers and their physiological levels	Correlation(s)	Chronic disease application	Development status and limitations
Biotransferrable graphene wireless nanosensor ⁷⁰	Tooth enamel tattoo	Saliva	Graphene on water-soluble silk, modified with antimicrobial peptide	<i>S. aureus</i> and <i>Helicobacter pylori</i>	–	Dental caries and periodontal diseases	Laboratory prototype stage; Lack of continuous monitoring and long-term validation
EBCare ⁷⁵	Face mask	EBC	PDMS–Al ₂ O ₃ radiative cooling coating and inkjet-printed carbon electrode and platinum-based electrode with NH ₄ ⁺ ISM	NH ₄ ⁺ (14–1,220 μM), nitrite (0.42–11.8 μM), alcohol and pH	Paired datapoints for EBC ammonium–blood urea (<i>r</i> =0.846; <i>n</i> =35) and EBC nitrite–FeNO (<i>r</i> =0.795; <i>n</i> =31)	Chronic kidney disease and airway inflammation (asthma, COPD and COVID-19)	Laboratory prototype stage with early human testing and patient studies; Lack of long-term validation
Cell-free synthetic biology-based face mask ⁷⁴	Face mask	EBC	Freeze-dried, cell-free genetic circuits on cellulose substrates	SARS-CoV-2 RNA	–	Respiratory infectious diseases	Laboratory prototype stage; Single-time-point measurements (not continuous monitoring)
Field-effect-transistor-based contact lens ⁷⁷	Contact lens	Tears	Graphene–silver nanowires	Glucose (0.18–0.70 mM) ⁷²	–	Diabetes	Laboratory prototype stage with animal testing; Lack of long-term biocompatibility and stability data in humans
Smart contact lens ⁸¹	Contact lens	Tears	Screen-printed Prussian-blue-modified carbon working electrode on silicone elastomer (Interjo)	Glucose (0.18–0.70 mM)	Healthy rabbit (<i>r</i> =0.946), diabetic rabbit (<i>r</i> =0.944), healthy beagle (<i>r</i> =0.961), diabetic beagle (<i>r</i> =0.924) and healthy human (<i>r</i> =0.954)	Diabetes	Pre-clinical stage with pilot human testing; Lack of long-term continuous monitoring beyond 2 h
Ingestible electronic capsule for gas sensing ⁸²	Ingestible capsule	Gastrointestinal gases	Metal-oxide-based semiconducting and thermal-conductivity-sensing elements	O ₂ , H ₂ and CO ₂	–	Dietary intake, IBD and gastrointestinal infections	Pre-clinical stage with pilot human testing; Battery-constrained operational lifetime (~4 d)
PillTrek ¹²³	Ingestible capsule	Intestinal fluids	Inkjet-printed gold nanoparticles	Glucose, serotonin, pH and ionic strength	–	Metabolic and mental disorders	Pre-clinical stage with rabbit model; Lack of long-term validation in large animals and human patients
Ingestible micro-bioelectronic device ⁸⁷	Ingestible capsule	Gastric fluid	Genetically engineered probiotic <i>Escherichia coli</i> embedded within a semi-permeable membrane	Haeme, thiosulfate and acyl-homoserine lactone	–	Gastric bleeding and digestive system disorders (reflux, ulcers and cancer)	Pre-clinical stage with pilot large animal testing; Short-term functionality up to 2 h
NeuroString ⁸⁹	Tissue-like strings	Cerebrospinal fluid and intestinal fluid	Transition-metal-nanoparticle (Fe ₃ O ₄ and NiO)-decorated, laser-induced graphene networks in a SEBS elastomer matrix	Dopamine, serotonin, norepinephrine and epinephrine	–	Gut-brain axis communication, psychiatric and neurological disorders, including addiction, major depressive disorder and Parkinson's disease	Pre-clinical stage with pilot large animal testing; Limited miniaturization due to wired data acquisition

BCAAs, branched-chain amino acids; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; EBC, exhaled breath condensate; FeNO, fractional exhaled nitric oxide; IBD, inflammatory bowel disease; ISM, ion-selective membrane; PDMS, polydimethylsiloxane; PMMA, poly(methyl methacrylate); PPD, poly(*o*-phenylenediamine); SEBS, solid-state epidermal biomarkers; SEBS, styrene–ethylene–butylene–styrene; TGFβ1, transforming growth factor β1; TNFα, tumour necrosis factor alpha; MARD, mean absolute relative difference.

to conditions including diabetes, vascular diseases and pressure injuries⁴⁸. Soft microfluidic biomolecular sensors enable on-site monitoring of biomarkers in wound exudate, aiding clinical assessment and intervention^{67,68}. Wearable wound sensors can also be integrated with therapeutic components such as drug delivery and electrical or mechanical stimulation to accelerate healing⁴⁹. However, wound exudate sampling in situ is complicated by potential contamination, limited sample volume and a complex composition (including dead cells and debris), which can affect data accuracy.

Oral and breath monitoring. Devices such as mouth guards and tooth tattoos enable the direct monitoring of exogenous compounds (for example, food and drug intake⁶⁹), markers of localized diseases (for example, dental caries⁷⁰ and salivary biomarkers⁷¹). Current intraoral sensors primarily detect liquids while neglecting solid foods; therefore, future research should focus on developing solid-state sensors. Stability challenges, due to daily wear and tear and salivary contamination, also need to be addressed.

Breath analysis offers metabolomic and respiratory insights, detecting pathogen biomarkers and volatile organic compounds linked to disease onset and progression⁷². In situ analysis via face masks provides real-time data while avoiding storage-related errors and contamination⁷³. However, detecting gaseous analytes in breath requires complex sensor engineering for selectivity, as few materials have successfully distinguished gaseous products in real human breath. Exhaled breath condensate, collected using fluid sampling or cooling modules integrated into face masks, enables rapid analysis of pathogens (for example, SARS-CoV-2 virus⁷⁴), nitrite and ammonia⁷⁵. However, the exhaled breath condensate biomarker concentration varies with breathing route, respiration rate and breath portion⁷⁶, necessitating standardized collection protocols for reliable quantification.

Tear analysis. Tear analysis gained popularity in the 2010s, exemplified by Google's smart contact lens (SCL) initiative. The easy accessibility of the eye presents an opportunity for real-time tracking of ocular biomarkers for diseases such as glaucoma⁷⁷ and systemic metabolites for conditions such as diabetes⁷⁸. Eyeglasses-based tear analysis utilizes fluid sampling units at the nose pads for stimulated tear collection⁷⁹. SCL-based biomolecular sensors offer a direct sample interface for continuous monitoring. However, integrating bulky batteries and electronic circuitry into a small ocular cavity remains a challenge. Miniaturized powering units, such as wireless power transmission and biofuels, coupled with wireless data transmission methods, such as near-field communication and radio frequency identification, could enable data transmission and real-time sensing⁸⁰. The clinical use of SCLs for diabetes monitoring is hindered by discrepancies between tear and blood glucose levels. As such, proper sampling without stimulation and personalized lag time correction are crucial for accurate glucose analysis⁸¹.

Ingestible devices. Ingestible devices provide real-time data on local biomarkers by passing through the digestive system without disrupting daily activities. Ingestible electronic pills that can monitor gastrointestinal gases, have revealed interindividual fermentative patterns in humans in response to different diets⁸². Additionally, ingestible capsules equipped with radio frequency identification chips, such as the Proteus Discover system, monitor medication adherence by transmitting an identification code upon contact with gastric fluids⁸³.

Faecal analysis has demonstrated the diagnostic value of liquid-phase biomarkers (for example, calprotectin, microRNA and microbiomes) for gastrointestinal conditions linked to inflammation, infection and cancer⁸⁴. However, challenges in sensing liquid-phase markers include maintaining the stability of biological components

under harsh environments, providing sustained power and addressing potential gastrointestinal tract obstruction due to size constraints⁸⁵. These challenges are currently being addressed with materials-based solutions such as biofuel cell powering⁸⁶ and the use of durable, selective membranes that allow the incorporation of living genetic sensors in vivo^{87,88}. Integrating nanomaterials into ingestible devices could enhance sensor sensitivity, stability and power efficiency.

Implantable devices. Implantable devices interface directly with internal tissues or organs, including blood, providing access to unique environments. They typically include a self-contained biomolecular sensor and a wearable data monitor. Key challenges include biocompatibility, mechanical compliance, sensor fouling, size and power limitations, and efficient data transmission. Additional complexities arise from specific absorption rate limits and implantation or retrieval procedures.

Innovations such as functionalized nanomaterials facilitate the long-term monitoring of metabolites⁸⁹ and neurotransmitters⁹⁰, whereas bioresorbable polymer-based electronics eliminate the need for device retrieval⁹¹, enhancing their practicality. Strategies such as microfluidic-enabled liquid-phase filtering and kinetic differential measurement help to reduce sensor fouling and correct signal drift in vivo^{92,93}. A notable example is the Senseonics Eversense CGM—the first fully integrated implantable biomolecular sensing system, which requires only biannual replacement of a small subcutaneous sensor implant.

Integration with existing devices. Integrating sensors into body-interfaced devices suitable for everyday use is crucial for commercialization. Rather than reinventing the wheel, researchers should expand existing architectures by adding new sensing modalities, lowering barriers to entry for novel biomedical devices. CGMs are the most successful commercially available body-interfaced sensors to date, having been extensively optimized in industry and validated in vivo. Whenever possible, these systems should serve as references, leveraging proven functional and design elements.

Other existing biomedical technologies (for example, pacemakers and stents) have long proven viable in vivo and have the potential to serve as platforms for biomolecular sensor integration^{94–96}. For example, incorporating an oxygen sensor into an existing pacemaker system can simplify future medical testing and regulatory clearance by reducing the degree of innovation⁹⁴.

Applications for chronic disease care

Body-interfaced biomolecular sensors offer transformative potential for chronic disease care by enabling real-time monitoring of health parameters directly from the body. This integration supports prevention, monitoring and management strategies across a range of chronic conditions (Fig. 3b).

Chronic disease prevention involves dietary choices, lifestyle changes and risk factor management⁹⁷. Body-interfaced sensors aid in tracking stress^{98,99}, substance use¹⁰⁰ and allergen exposure¹⁰¹. Fitness wearables and ingestibles can also monitor nutrition, motivating healthier behaviours and promoting better outcomes¹⁰².

The real-time tracking of biomarkers such as troponin and uric acid enhances organ health assessment while reducing the need for blood draws^{6,103}. Peripheral biomarkers (for example, inflammation, hormone levels and nutritional status) provide broader insights into physiological states^{39,43,62}. Continuous monitoring helps to differentiate between transient changes and chronic pathology, guiding treatment decisions and supporting holistic health management.

For drugs with narrow therapeutic windows (for example, antibiotics, immunosuppressants and anticoagulants), real-time monitoring ensures efficacy while minimizing side effects, which is critical for cases during organ transplantation or mental health treatment^{43,104}.

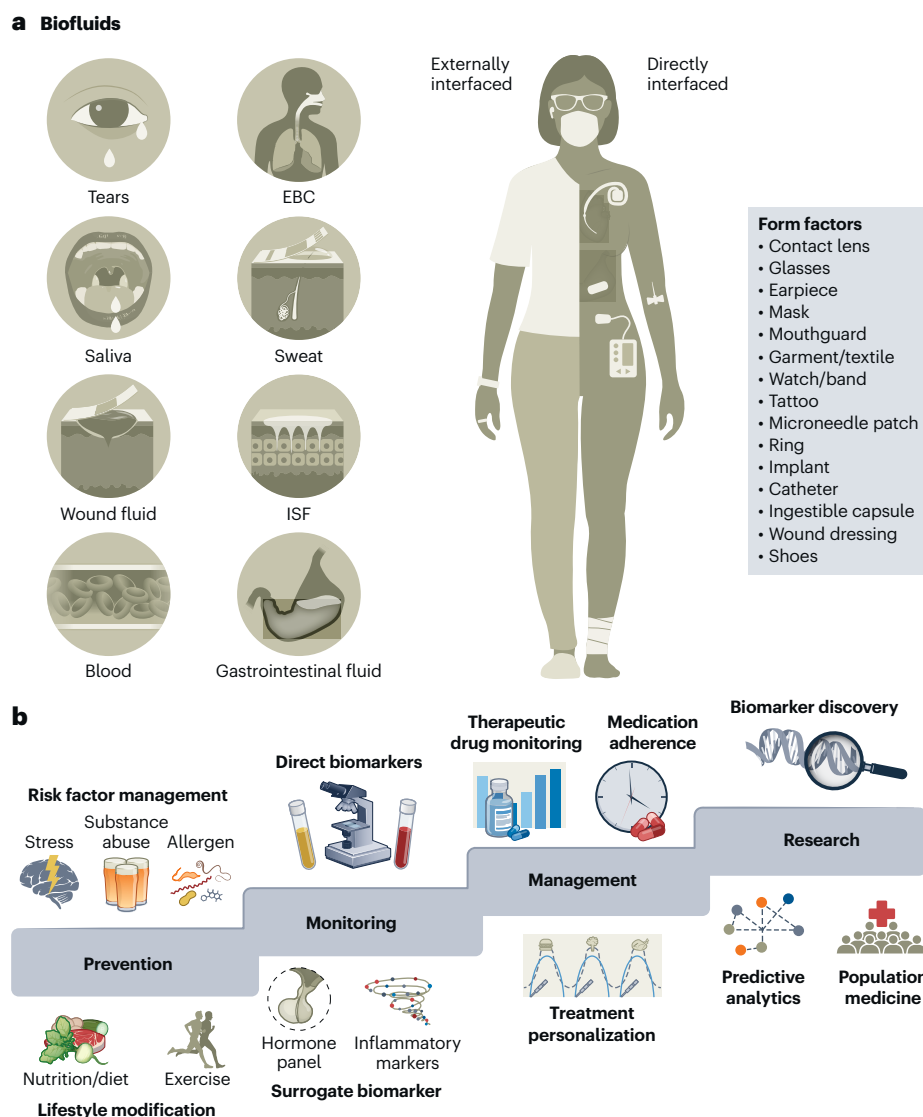


Fig. 3 | Body-interfaced sensor devices for chronic disease care applications.

a, Body-interfaced form factors. Diverse technologies strategically placed on the body allow in situ sampling and analysis of biochemical markers from biofluids such as sweat, saliva, ISF, tears, breath, wound exudate and gastrointestinal fluids (left). These biofluids offer minimally invasive insights into an individual's health, enhancing user comfort and compliance. Form factors include wearable devices (patches, wristbands, tattoos and smart textiles), smart contact lenses for tears, mouth guards for saliva, face masks for breath analysis, ingestible capsules for gastrointestinal monitoring, and implantable sensors. Each approach faces unique challenges in sensor miniaturization, powering, fluid sampling, analyte stability and biocompatibility. **b**, Applications of body-interfaced biomolecular sensors. Body-interfaced sensors play a pivotal role across four key areas: (1) prevention—by tracking stress, substance use (for example, alcohol and drugs)

or allergen exposure, or monitoring nutrition to encourage healthier lifestyle choices; (2) monitoring—by continuously measuring both direct disease biomarkers (for example, troponin or uric acid) and peripheral biomarkers (for example, inflammation, hormonal levels or nutritional status) to support comprehensive health assessment; (3) management—through therapeutic drug monitoring for medications with narrow therapeutic windows (for example, immunosuppressants or anticoagulants), improving medication adherence with ingestible sensors and enabling personalized treatment strategies such as continuous glucose monitoring in diabetes; and (4) research—by facilitating real-world data collection, biomarker discovery and predictive analytics. When paired with machine learning, these sensors can uncover subtle physiological patterns that precede disease exacerbations, ultimately guiding timely interventions and shaping population-level health strategies. EBC, exhaled breath condensate.

Ingestible sensors can confirm medication intake and track physiological responses, thereby improving adherence and facilitating the management of complex regimens¹⁰⁵. CGMs exemplify personalized treatment, enabling immediate dose adjustments and improving outcomes in diabetes.

Continuous, non-invasive sensing is also transforming chronic disease research. Large-scale, long-term data enable the discovery of new biomarkers and metrics (for example, glycaemic variability in diabetes)¹⁰⁶. Deep-learning algorithms and time-series analysis can uncover hidden relationships between physiological patterns and outcomes, allowing the early detection of complications and

guiding timely interventions^{107,108}. At the population level, these sensors provide real-world insights that inform public health strategies by integrating lifestyle, environmental and genetic data (<https://www.joinallofus.org/wear-study>).

Outlook

The integration of nanotechnologies with body-interfaced bioelectronics has ushered in a new era of proactive and personalized healthcare for the management of chronic diseases. Our survey of molecular signatures across various chronic diseases has revealed a complex network of biomarkers that can provide valuable insights into disease

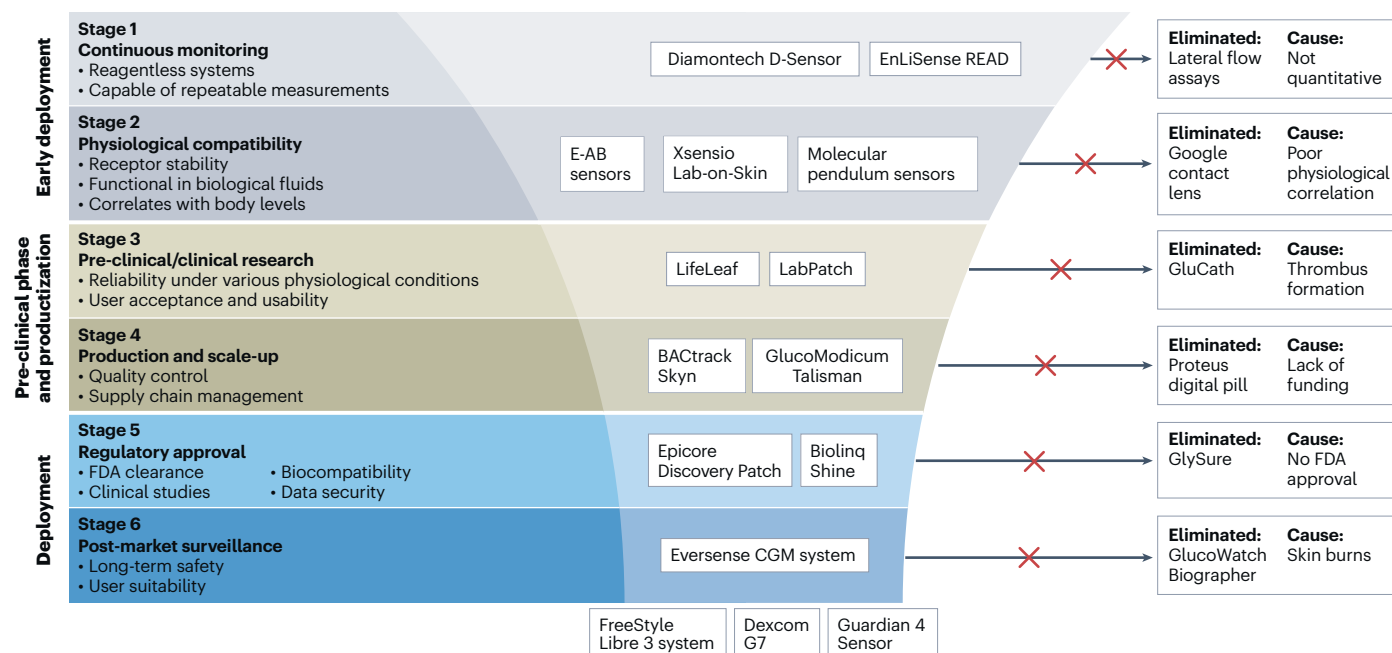


Fig. 4 | Clinical translation sieve for body-interfaced sensing technologies.

Key stages in the commercialization of biomolecular sensing technologies, from early development to market deployment. Each stage represents a set of stringent criteria that must be met for progress towards commercialization. Technologies inside the sieve represent existing technologies currently under development. In the early development phase, sensors must prove to be viable for continuous monitoring applications and exhibit robust physiological compatibility. These include sensors such as Diamontech D-Sensor (<https://www.diamontech.de/en/solutions/d-sensor>), Xsensio Lab-on-Skin (<https://xsensio.com/>) and EnLiSense READ (<https://enlisen.com/>), as well as electrochemical aptamer-based (E-AB) and molecular pendulum sensors. The pre-clinical and productization phase necessitates rigorous pre-clinical and clinical research to assess reliability, user acceptance and usability under real-world conditions. Devices such as LabPatch¹²⁶ and LifeLeaf¹²⁷ are currently addressing these challenges. Following initial validation of safety and efficacy in clinical research, body-interfaced technologies, such as BACtrack Skyn (<https://skyn.bactrack.com/>)

and GlucoModicum Talisman (<https://glucomodicum.com/technology-and-products>), must navigate scale-up challenges and implement quality control measures to transition from the laboratory to commercialization. The deployment phase initially requires regulatory approval, which plays a decisive role in market entry. For instance, the Epicore Discovery Patch has received 510(k) exemption from the Food and Drug Administration (FDA)¹²⁸, and Biolinq Shine was recently granted FDA De Novo classification¹²⁹. Even after commercial deployment, post-market surveillance is required to assess long-term device safety. The Eversense CGM system, which was recently launched¹³⁰, and established products such as the FreeStyle Libre 3 system (<https://www.freestyle.abbott/us-en/home.html>), Dexcom G7 (<https://www.dexcom.com/en-us/g7-cgm-system>) and Guardian 4 Sensor (<https://www.medtronicdiabetes.com/download-library/guardian-4-sensor-transmitter>) continue to be monitored for ongoing safety and efficacy. Technologies shown to the right for each stage represent those that were eliminated at various stages of the commercialization process for failing to meet specific criteria.

progression and overall health status. Innovative strategies for the real-time monitoring of these crucial biomolecules can be developed by leveraging nanoscale sensing systems that employ both biological and synthetic nanomaterials. The seamless integration of nanoscale molecular sensing systems with various unobtrusive body-interfaced form factors has enabled unprecedented access to real-time physiological data under diverse bodily environments. These technologies have the potential to revolutionize disease prevention, monitoring and management by providing timely and accurate data to both patients and healthcare providers.

Despite extensive academic research on continuous body-interfaced biochemical sensing, a notable translational gap remains, with only a few commercial successes to date, including Abbott's FreeStyle Libre series, Medtronic's Guardian series and Dexcom's G-series glucose monitors. The journey from technical innovation to the commercialization of body-interfaced sensing technologies resembles a meticulous sieving process, wherein each stage imposes stringent requirements for advancement (Fig. 4). Even with regulatory approvals, some products have been withdrawn from the market due to issues that could have been pre-emptively addressed during early development. As we look towards the future, it is crucial to examine the critical junctures where advancements in body-interfaced sensing technologies often falter and identify opportunities for improvement.

Early development stages

In the early development stages, researchers should prioritize features that enable clinical translation, such as continuous monitoring and physiological compatibility. Although point-of-care diagnostics have advanced home healthcare, medical-grade body-interfaced sensors can substantially improve patient compliance in chronic disease management; for example, studies have shown improved glycaemic control with CGMs¹⁰⁹.

The design challenges for body-interfaced sensors differ markedly from those encountered in conventional biosensor development, where sample collection and signal stability can be well managed. Body-interfaced sensors must contend with variable biofluid composition, limited and fluctuating sample volumes, and motion artefacts. Implantable and ingestible devices present additional challenges: biocompatibility, immune response, biofouling and long-term powering, as well as data transmission under harsh internal environments, are critical concerns. Nanomaterials provide promising strategies to overcome these hurdles in addition to sensing challenges. Nanostructured antifouling coatings prevent unwanted adsorption¹¹⁰, whereas nanomaterials-based energy harvesters offer a sustainable power solution⁶³. These challenges must be overcome while maintaining high accuracy and sensitivity and minimizing the occurrence of false positives and negatives to ensure robust sensor performance.

Achieving continuous sensing with body-interfaced affinity sensors requires reagent-free approaches for direct in vivo sensing, reversible molecular interactions for repeated sensing and small operational time gaps between readings to ensure continuous data flow with minimal hysteresis^{4,111}. Additionally, overcoming form factor challenges, such as developing mechanically imperceptible interfaces to the body, is essential for user comfort and technology acceptance. Advances in nanostructured materials, such as engineered nanowires and bioinspired adhesives, are critical in the development of ultra-flexible, conformal devices that seamlessly integrate with the body while maintaining high electrical performance⁶³. Extensive validation of biomarker correlation to blood or disease conditions is also crucial, particularly for alternative biofluids such as sweat or tears. For instance, the aim of the Google smart contact lens (SCL) project was to monitor glucose levels through tears, but it was discontinued due to an insufficient correlation between tear and blood glucose levels¹¹².

Pre-clinical and productization stages

Pre-clinical research, which involves rigorous testing of sensor prototypes under laboratory environments and in animal models, is crucial for evaluating the safety and efficacy of body-interfaced sensing technologies. Continuous intravenous glucose sensing, which garnered attention in the 2010s, was explored by several companies that subsequently failed; for example, Glumetrics' GluCath system was shut down due to in vivo thrombus formation¹¹³.

One major hurdle in the transition from laboratory-based prototypes to commercialization is the scalability and cost effectiveness of fabrication methods. Ensuring that these methods can scale up to meet future market demand without compromising quality is crucial. The digital pill industry exemplifies this challenge, with Food and Drug Administration clearance for products such as the Proteus digital pill in the mid-2010s, which ultimately failed to gain traction due to cost concerns¹¹⁴.

The extensive data generated by body-interfaced sensors require robust data interpretation and storage approaches to extract meaningful insights. Current methods rely heavily on supervised learning, which demands costly and biased manual labelling, thereby limiting scalability. Future research should focus on self-supervised learning approaches, leveraging unlabelled data and advanced generative models to handle incomplete data streams effectively to enable reliable forecasting and provide actionable healthcare insights. Beyond technical challenges, concerns about privacy infringement and surveillance paranoia can also lead to end-user reluctance and limited market confidence¹¹⁵. Moreover, continuous monitoring raises questions about user autonomy and the potential for discrimination if sensitive health data are misinterpreted or improperly shared. Companies such as HealthVerity may play a key role in supporting ethical data practices by enabling privacy-protecting record linkage, ensuring Health Insurance Portability and Accountability Act compliance and facilitating secure, de-identified data sharing across healthcare systems¹¹⁶. By adopting technologies and frameworks that prioritize data integrity and patient confidentiality, researchers and developers can mitigate the risk of bias or misuse and foster greater public trust in body-interfaced biosensing systems.

Deployment stages

As new regulatory pathways for expedited approval, such as the Breakthrough Device pathway, become available, the deployment of innovative body-interfaced sensing technologies continues to accelerate. Still, regulatory approval remains a deciding factor in whether a new device makes it to market; for example, GlySure's Continuous Intravascular Glucose Monitoring System failed to receive Food and Drug Administration approval, leading to the company going out of business in 2018 (ref. 117). Regulatory guidelines are expected to evolve to address the unique ethical challenges posed by these emerging technologies, which remain inadequately regulated under current guidelines¹¹⁸.

Continuous monitoring of long-term adverse events and patient outcomes is essential to identify any potential risks or issues that may arise after approval. The case of the GlucoWatch Biographer, discontinued due to reports of skin burns, highlights the necessity of post-market surveillance in ensuring the safety and effectiveness of body-interfaced sensing technologies¹¹⁹. Furthermore, regulatory approval of a device for monitoring a certain physiological parameter does not necessarily guarantee improved patient outcomes. Therefore, post-market surveillance serves as a critical mechanism to assess the real-world impact of these technologies on patient well-being, providing valuable insights into their effectiveness and applicability in chronic disease monitoring.

Ultimately, seamless integration of emerging body-interfaced biomolecular sensors with existing healthcare infrastructure, under proper regulatory oversight, is essential for optimal utilization by healthcare providers. This integration will facilitate efficient data collection, analysis and decision-making processes within established workflows, ensuring that these technologies effectively contribute to improved patient care.

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Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Shana O. Kelley or Wei Gao.

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