

Biomolecular profiling for noninvasive health monitoring

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Biomolecular profiling offers a powerful lens into human physiology, yet current diagnostics often rely on invasive sampling and delayed, centralized analysis. Advances in mass spectrometry (MS), particularly untargeted metabolomics and proteomics, have expanded molecular access to noninvasive biofluids such as sweat, saliva, tears and interstitial fluid, revealing dynamic biomarkers linked to both chronic and acute conditions. In parallel, wearable biosensors enable real-time, on-body chemical sensing, but remain limited to a narrow panel of predefined analytes. This Review highlights how MS-based molecular discovery and wearable sensing serve as complementary approaches—MS enabling high-dimensional untargeted profiling and wearables delivering longitudinal real-time data—and also discusses how their bidirectional integration and co-evolution open new possibilities for personalized noninvasive health monitoring. We discuss advances in sampling strategies, sensing modalities and system integration, and outline criteria for identifying biomarkers amenable to sensor translation. By uniting untargeted discovery with real-world deployment, this convergence shifts personalized noninvasive healthcare from episodic diagnostics to continuous, context-aware monitoring.

In biology and medicine, access governs insight. The ability to monitor molecular processes in real time, within their native physiological context, has long remained out of reach. Most current molecular diagnostics rely on static snapshots—blood draws or biopsies processed in centralized laboratories—that yield delayed interpretations of transient biological events¹. In acute settings such as pneumonia or sepsis, these delays can be life-threatening, underscoring the need for timely and reliable biomarkers that reflect dynamic physiological states.

Even the most sophisticated omics platforms, despite their breadth and sensitivity, are constrained by invasive sampling, limited temporal resolution and disconnect from everyday physiology. These limitations are critical in rapidly evolving conditions such as pain, inflammation, metabolic dysregulation or neuroendocrine stress, where meaningful changes often occur within minutes or hours. Capturing these dynamics requires a shift from episodic measurement to continuous molecular sensing.

This emerging need is driving the convergence of omics-enabled mass spectrometry (MS) and wearable chemical sensing technologies

in a bidirectional framework (Fig. 1). Among omics layers, metabolomics, lipidomics and proteomics most directly reflect phenotype, making them highly relevant for real-time, noninvasive monitoring^{2,3}. Their molecular targets—metabolites, lipids and proteins—act as downstream effectors responsive to physiological stimuli and are present in accessible biofluids. Unlike DNA or RNA, which resides within cells and reflects slow-changing potential, these molecules capture rapid phenotypic responses and can be noninvasively sampled from sweat, saliva, tears, interstitial fluid (ISF), sebum or cerumen. Because the identities of these molecules cannot be inferred from genomic sequence alone, MS has an indispensable role in their empirical characterization. However, despite its diagnostic power, MS-based insights are typically confined to laboratory settings, limiting their translation into real-time, context-aware health applications.

In contrast, wearable sensors offer continuous access to chemical signals *in situ*^{4–6}. Advances in materials, microfluidics and bioelectronics have enabled real-time tracking of electrolytes, metabolites, hormones and certain proteins directly on the skin⁷. These platforms

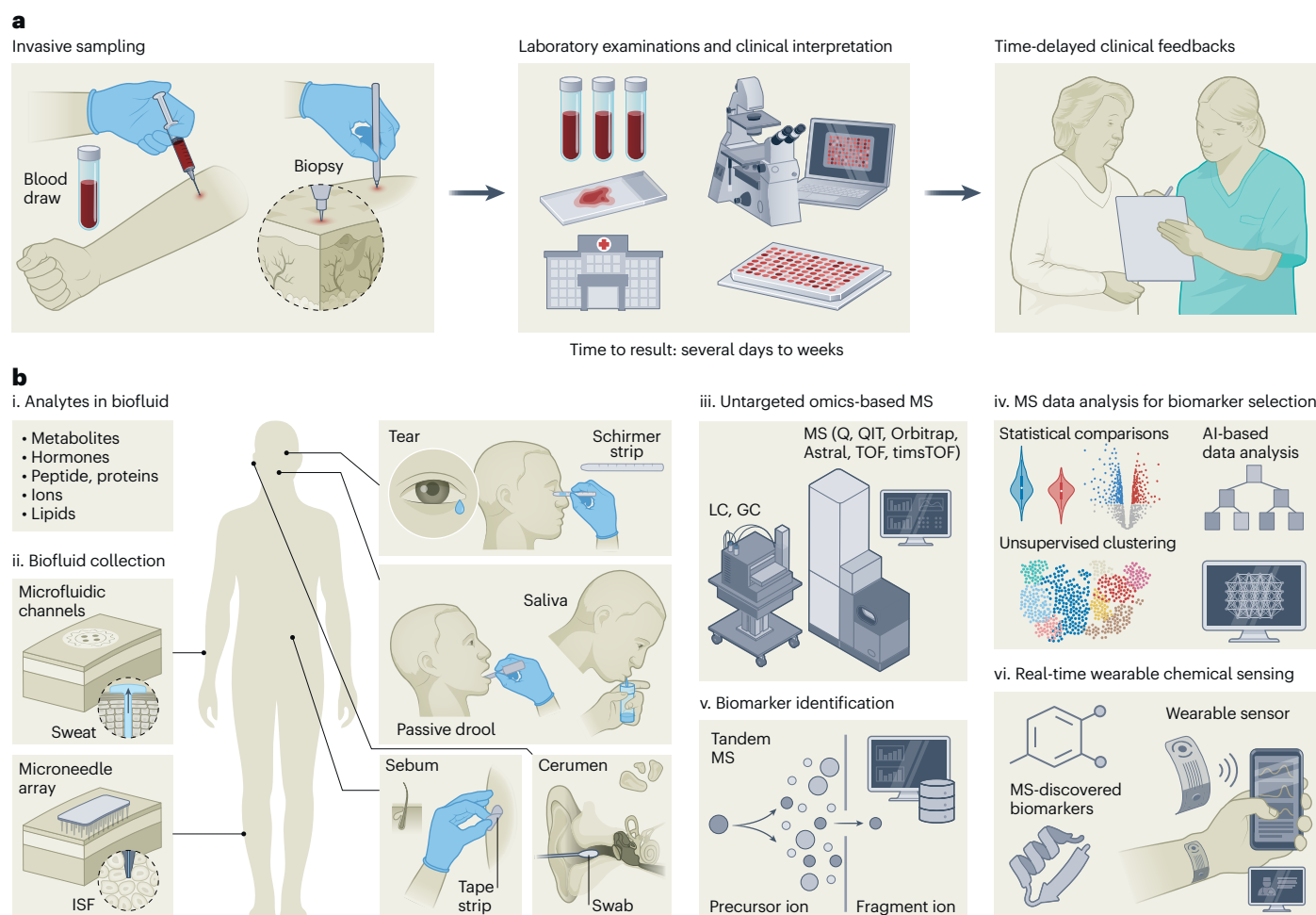


Fig. 1 | From molecular discovery to real-time sensing—an omics-to-wearables translation loop. **a**, Conventional clinical diagnostics relying on invasive procedures such as blood draws or biopsies followed by centralized laboratory analysis, resulting in delayed feedback over days to weeks and limiting detection of rapid or transient physiological changes. **b**, Continuous molecular monitoring by integrating untargeted MS with wearable chemical sensors. **i**, key analyte classes in noninvasive biofluids include ions, metabolites, hormones, lipids, proteins and peptides. **ii**, Biofluids are collected through microfluidics for sweat, microneedles for ISF, passive drool for saliva, Schirmer strips for tears, tape strips for sebum and swabs for cerumen. **iii**, Untargeted MS platforms such as Q, QIT, Orbitrap and TOF enable omics-scale profiling. Advanced architectures

such as TIMS (for example, timsTOF Pro 2) and Orbitrap–Astral hybrid analyzers further enhance ion use and MS/MS acquisition speed, enabling high-throughput analysis of low-volume, noninvasive biofluids. **iv**, Biomarker discovery is driven by statistical comparisons and AI-based analyses. **v**, Tandem-MS supports structural annotation. **vi**, Validated biomarkers are ultimately translated into wearable sensors for longitudinal, on-body monitoring. Together, these steps form a closed-loop pathway from molecular discovery to continuous, real-time health sensing. Figure created in BioRender; Kim, M.J. <https://BioRender.com/83fkyaq> (2026). Q, quadrupole; QIT, quadrupole ion trap; TIMS, trapped-ion-mobility spectrometry.

operate outside clinical infrastructure, providing longitudinal biochemical insight during daily life. While their primary role has been real-time monitoring, recent progress suggests that wearable platforms—especially with multimodal sensing and artificial intelligence (AI)-driven interpretation—can also support discovery by revealing meaningful molecular signatures in real-world conditions. However, most current wearable devices are limited to a narrow panel of preselected analytes and lack discovery capacity. Integrating the two—untargeted MS discovery and on-body sensing—offers a path for translating molecular insights into real-time diagnostics.

This review article frames MS and wearable sensing as complementary approaches to molecular discovery and monitoring. We examine how high-dimensional MS workflows can inform analyte selection for on-body sensing, and how advances in materials, microfluidics and electronics are enabling next-generation wearable systems. While distinct in scope, resolution and real-time capability, their integration and co-evolution offer unique opportunities (Table 1)^{6,8–27}. By combining the expansive discovery power of MS with the immediacy of wearable

platforms, we outline a synergistic paradigm that moves beyond detecting static biomarkers to continuously interpret health in motion.

Untargeted omics through MS as a discovery engine

Untargeted MS for panel-level and dynamic biomarker discovery

Biomarkers offer a molecular lens into physiology and disease, yet identifying reliable and specific ones remains challenging. Pathological states follow heterogeneous trajectories shaped by genetics, environment and comorbidities. For example, elevated lactate may indicate sepsis-related anaerobic metabolism but can also arise from exercise or hypoxia²⁸. Similarly, levels of inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor rise across diverse conditions, limiting their diagnostic specificity^{29,30}. These overlaps highlight the biological complexity that targeted assays often struggle to resolve, reinforcing the need for unbiased, comprehensive profiling capable of capturing context-specific molecular patterns.

Table 1 | Comparative summary of various MS and wearable sensing platforms

Modalities	Analyte scope	Advantages and challenges	Biofluid (analytes)	Sampling	Biomedical relevance
MS					
LC-MS	Wide range of polar to moderately nonpolar small molecules and peptides/proteins	Advantages: broad molecular weight and chemical class coverage; high dynamic range and sensitivity Challenges: limited suitability for real-time analysis; multistep sample preparation (for example, quenching, extraction, purification, chromatographic separation); moderate sample-volume requirement (5–200 µl); time-consuming and labor-intensive workflows; potential sample loss or degradation before analysis	Sweat (caffeine, theobromine, paraxanthine, theophylline, etc.) ⁸	Passive sweat sampling from fingertip using prewetted filter ⁸	Caffeine metabolism ⁸
			Sweat (urocanic acid, tetrahexose, histidine, trisaccharide phosphate, suberic acid, taurine, phenylalanine, citrulline, muconic acid, etc.) ⁹	Iontophoresis ⁹	Lung cancer ⁹
			Saliva (lactate, pyruvate, acetylated polyamines, amino acids, succinate, etc.) ¹⁰	Straw-assisted passive saliva collection ¹⁰	Colorectal cancer, adenoma ¹⁰
			Tears (3-dehydroquinic acid, anthranilic acid, citric acid, L-isoleucine, etc.) ¹¹	Capillary collection from lower tear meniscus ¹¹	Chronic dacryocystitis ¹¹
			ISF (albumin, immunoglobulins, EDNR-listed and FDA-approved protein biomarkers, SARS-CoV-2 neutralizing antibodies) ¹²	Microneedle array and vacuum-assisted skin patch ¹²	COVID-19 immunity ¹²
			Sebum (DGs 30:1, 31:1, 32:1, 34:1, etc.) ¹⁸	Passive collection using Sebustape adhesive patches ¹⁸	Skin acne ¹⁸
GC-MS	Volatile and thermally stable small molecules (often nonpolar)	Advantages: ideal for volatile and semi-volatile compounds; effective in profiling EBC and saliva Challenges: limited suitability for real-time analysis; limited to analytes compatible with gas-phase analysis; requirement for derivatization; high sample-volume demand (100–500 µl); time-consuming and labor-intensive workflows; potential sample loss or degradation before analysis	Exhaled breath (aldehydes, C5–C7 hydrocarbons, C3–C5 carbonyls, etc.) ¹³	ReCIVA (Owlstone Nanotech) breath sampler with clean air ¹³	Acute heart failure, asthma, COPD, pneumonia ¹³
			Saliva (4-hydroxyphenylethanol, adenosine, adenine, hexanoic acid, amino acids, glucose 6-phosphate, tyramine, etc.) ¹⁴	Unstimulated spitting ¹⁴	Smoking-associated metabolic alterations ¹⁴
			Sebum (cyclohexanone dimer/monomer, acetone, ethanol dimer, (E)-2-hexenal monomer, acetoin dimer, etc.) ¹⁹	Passive collection using medical gauze swab ¹⁹	Parkinson's disease ¹⁹
			Cerumen (cis-9-hexadecenoic acid, cis-10-heptadecenoic acid, cis-9-octadecenoic acid, etc.) ²⁰	Manual removal ²⁰	Meniere's disease ²⁰
(MA)LDI-MS	Large proteins, peptides, polymers, nucleic acids (in MALDI-MS); small to midsized molecules, metabolites, lipids (in LDI-MS)	Advantages: direct, label-free analysis with minimal sample preparation; small sample-volume requirement (<1 µl); rapid analysis suitable for high-throughput screening; enhanced ionization with engineered nanomaterials (in LDI-MS) Challenges: limited suitability for real-time analysis; organic matrix background interference in MALDI-MS; lower coverage than LC-MS/GC-MS; less robust quantification	Urine (urea, citrate, glycine, 4-hydroxyphenylacetate, hippurate, mannitol, trigonelline, etc.) ¹⁵	Passive collection ¹⁵	Bladder cancer ¹⁵
			Tears (3-mercaptoplactic acid, 3-sulfinylpyruvic acid, barbituric acid, dihydroxyacetone phosphate acyl ester, lactic acid, threonine, etc.) ¹⁶	Capillary collection from inferior tear meniscus ¹⁶	Glaucoma ¹⁶
			Saliva (17-hydroxyprogesterone, 3β-hydroxy-5-choleonic acid, adenosine diphosphate, creatinine, creatine, glucose, etc.) ¹⁷	Passive drool collection ¹⁷	Parkinson's disease ¹⁷
Wearable sensor					
Electrochemical sensing	Electroactive species, redox-active small molecules, proteins/peptides, nucleic acids	Advantages: high sensitivity and specificity for target analytes; rapid, real-time signal transduction; compatible with miniaturized, low-power wearable platforms; selective detection achievable through enzyme or aptamer functionalization Challenges: limited to electroactive or enzyme-targetable molecules; potential interference from ions and biofouling in complex biofluids; sensor drift and degradation over time; frequent calibration requirement	Sweat (CRP protein) ¹⁸	Iontophoresis ¹⁸	COPD, heart failure, infection ¹⁸
			Sweat (glucose, lactate, uric acid, sodium ions, potassium ions and ammonium ions) ¹⁹	Iontophoresis ¹⁹	Physiological stress (for example, CPT, VR, exercise) ¹⁹
			Sweat (cortisol, glucose) ²⁰	Physical exercise ²⁰	Diabetes ²⁰
			ISF (calcium ions, chloride ions) ²¹	Reverse iontophoresis ²¹	Cystic fibrosis screening ²¹
			Saliva (sodium ions, potassium ions) ²²	Pacifier-assisted collection ²²	Neonatal intensive care unit monitoring ²²
			EBC (nitrate ions, ammonium ions, protons, alcohol) ⁶	Wearable mask with cooling ⁶	Respiratory inflammation (for example, COPD, post-COVID, asthma, smoking) ⁶
			Wound exudate (IL-6, IL-8, TNF, TGFβ1, <i>Staphylococcus aureus</i>) ²³	Capillary action-based exudate sampling ²³	Chronic wound infection ²³
Optical sensing	Optically active analytes, ions, metabolites, proteins/peptides, nucleic acids	Advantages: label-free detection through absorbance, fluorescence or colorimetry; visually interpretable outputs; minimal electronic complexity Challenges: susceptible to ambient light interference and photobleaching; less precise quantification; limited sensitivity for low-abundance analytes; dependent on skin tone and contact quality	Sweat (lactate, glucose, protons, chloride ions) ²⁴	Physical exercise ²⁴	Dehydration, electrolyte imbalance, metabolic monitoring during exercise or heat exposure ²⁴
			Sweat (vitamin C, calcium ions, zinc ions, iron ions) ²⁵	Sauna ²⁵	Nutritional monitoring ²⁵
			ISF (<i>Plasmodium falciparum</i> histidine-rich protein 2) ²⁶	Microneedle array ²⁶	Infectious malaria ²⁶
			Tears (sodium ions, potassium ions, calcium ions, magnesium ions, zinc ions) ²⁷	In situ capture through scleral lens ²⁷	Dry eye severity ²⁷

Representative MS modalities, including LC-MS, GC-MS and MALDI-MS, are contrasted with wearable chemical sensors. MS enables high-dimensional, untargeted molecular profiling with broad analyte coverage, whereas wearable sensors prioritize real-time monitoring, minimal invasiveness and point-of-use operation. LDI, laser desorption/ionization; COVID, coronavirus disease; DG, diacylglycerol; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CPT, cold pressor test; VR, virtual reality; TNF, tumor necrosis factor; TGFβ1, transforming growth factor-β1; EDNR, Early Detection Research Network; FDA, Food and Drug Administration.

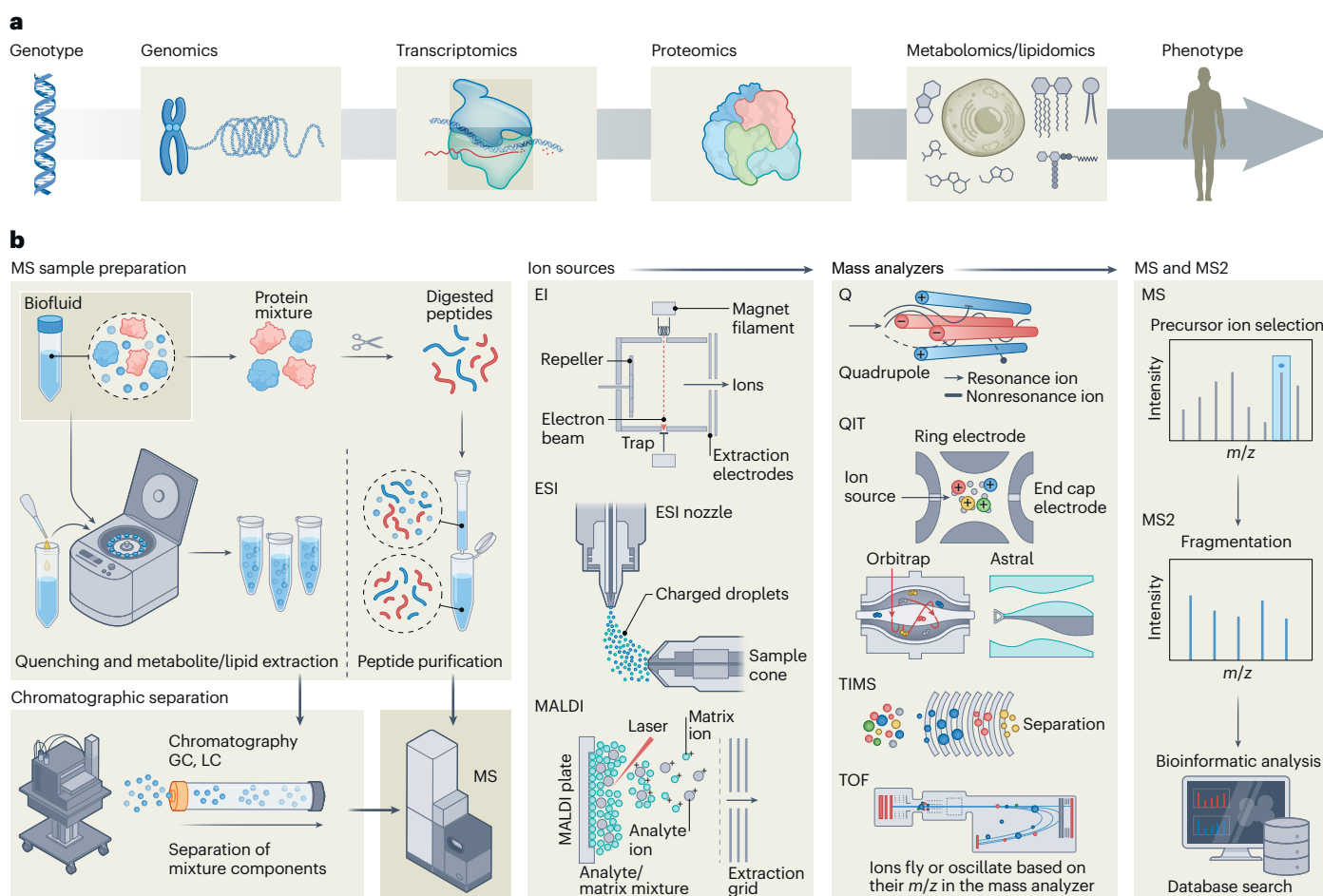


Fig. 2 | Untargeted metabolomics, lipidomics and proteomics. **a**, Multiscale omics cascade from genome to phenotype, showing how protein and metabolite/lipid states reflect both genetic programs and environmental cues, ultimately determining phenotypic expression. **b**, Experimental workflow of MS-based untargeted metabolomics, lipidomics and proteomics. Biofluids undergo metabolite/lipid extraction or protein digestion and purification, followed by chromatographic separation and ionization such as EI, ESI and MALDI. Ions

are analyzed using various mass analyzers, including Q, QIT, Orbitrap and advanced platforms such as timsTOF and Orbitrap–Astral hybrid analyzers. By maximizing ion use and accelerating fragmentation cycles, these systems enable rapid, quantitative analysis of microscale, noninvasive biofluids. Tandem MS (MS/MS) provides precursor fragmentation and structural identification using spectral databases. Figure created in BioRender; Kim, M. J. <https://BioRender.com/1qraq6> (2026). EI, electron ionization; ESI, electrospray ionization.

Untargeted MS, embedded within omics-scale workflows, has emerged as a leading tool for biomarker discovery (Fig. 2a). While genomics and transcriptomics define regulatory potential³¹, metabolomics, lipidomics and proteomics reveal dynamic, functional phenotypes—signatures that dynamically respond to physiological changes^{2,32}. These molecules are often present in noninvasive biofluids and require no prior hypotheses, enabling comprehensive profiling with high sensitivity and specificity. Moreover, untargeted MS is particularly adept at capturing transient biochemical events over minutes to hours, aligning well with the temporal dynamics targeted by wearable sensing systems.

Diagnostic specificity often fails when single biomarkers overlap across multiple physiological or pathological conditions. Untargeted MS addresses this by resolving multi-analyte, pathway-aware fingerprints together with time-dependent trajectories from a single specimen. One effective approach is the use of product/precursor ratios, which provide more interpretable signals than absolute concentrations. These ratios encode pathway-level constraints and reduce dilution and matrix effects. For example, the lactate/pyruvate ratio is an established indicator of cytosolic redox state (reflecting NADH/NAD⁺ coupling), and often proves more informative than either analyte alone³³. Similarly, in a high-resolution untargeted liquid chromatography (LC)–MS study of myalgic encephalomyelitis/chronic

fatigue syndrome, quantitative assessment of tryptophan-pathway ratios (for example, kynurenine/3-hydroxykynurenine) revealed substantial elevations relative to healthy controls, illustrating how pathway-constrained ratios derived from untargeted data can aid disease discrimination and physiological insight³⁴.

Coregulated metabolite modules summarize coordinated molecular sets into validated panel scores. Because pathophysiology often perturbs pathways rather than isolated nodes, such panel-level fingerprints improve discrimination where single markers overlap across conditions. Module construction is grounded in pathway biology and typically evaluated through statistical controls (for example, multiple testing correction) and independent replication or cross-validation³⁵. For example, untargeted LC–MS of human sweat identified a five-metabolite panel that differentiated lung-cancer patients from at-risk smokers with 80% specificity and 79% sensitivity³⁶, illustrating how multi-analyte fingerprints in accessible biofluids can deliver diagnostic resolution when single metabolites lack specificity.

Dynamic features add complementary value. Metrics such as rise and decay slopes, time-to-peak, recovery half-life and short-window area under the curve (AUC) capture molecular kinetics under standardized challenges. In a cohort of 470 participants undergoing oral glucose tolerance testing, untargeted ultraperformance LC–time-of-flight (TOF)–MS of plasma at 0, 30 and 120 min, respectively, revealed

trajectories strongly correlated with insulin sensitivity, with high informative content in both early ($\Delta 0$ –30) and late ($\Delta 30$ –120) windows³⁷. Such kinetic descriptors distinguish transient physiological activations from sustained pathophysiology and can be further enhanced with statistical and machine learning (ML) approaches.

Altogether, this panel-centric and kinetics-centric perspective defines the core value of MS for biomarker discovery, especially when diagnostic specificity arises from coordinated molecular patterns that evolve over time rather than from single thresholds.

Challenges for MS in wearable-accessible biofluids

Multiple challenges complicate the integration of MS with wearable sensing platforms—not only limitations in instrument sensitivity but also constraints related to small sample volumes, sample purity and the difficulty of achieving reliable quantification under variable biofluid secretion.

Sample-volume constraints. A key barrier to MS–wearable integration is the mismatch between the small volumes of noninvasive biofluids and the larger sample volumes traditionally required for mass spectrometric assays^{8,12}. For instance, sweat is typically secreted at a rate of 10–100 nl min⁻¹ cm⁻² (ref. 38), meaning that even after several minutes of on-skin collection, sample volumes often remain in the microliter or submicroliter range. Conventional LC–MS and gas chromatography (GC)–MS workflows, however, generally require tens to hundreds of microliters to achieve sufficient sensitivity and reproducibility. This disparity limits the ability to resolve short-timescale dynamics and restricts the range of biomarkers that can be translated to continuous on-body monitoring.

Sample-purity constraints. Wearable-accessible noninvasive biofluids are not sterile and typically contain epithelial debris, exogenous particulates and commensal microbiota. As a result, MS analysis of these fluids interrogates a mixed-origin molecular background in which human-derived and microbiome-derived proteins, peptides, lipids and metabolites co-occur within the same sample and analytical dataset³⁹. This introduces a downstream computational challenge in which the molecular origin of detected features must be resolved during data analysis. For mixed-origin proteomics (metaproteomics), tandem-MS spectra are commonly searched against concatenated human and microbiome databases (for example, UniProt + Human Microbiome Project) using target–decoy false discovery rate control, followed by taxonomic assignment or protein grouping as implemented in standard pipelines (for example, MetaProteomeAnalyzer, UniPept)^{40,41}. In practical workflows, proteins are extracted using either in-gel or shotgun digestion, peptides are analyzed by LC–MS/MS and spectra are mapped to both host and microbial proteomes before taxonomic grouping. For small-molecule analysis, similar ambiguity arises because several metabolite classes may originate from either host or microbiota⁴². After MS/MS-based annotation, features can be mapped onto taxonomically resolved biochemical pathway databases (for example, KEGG, BioCyc, AGORA2) or interpreted using genome-scale metabolic models, enabling tentative attribution of compounds to commensal or pathogenic microbial metabolism rather than host pathways alone.

Method-specific trade-offs. Matrix-assisted laser desorption/ionization (MALDI)–MS is well suited to ultrasmall volume samples, a clear advantage for wearable-accessible fluids. However, its reliance on organic matrices introduces high background signals at low m/z and it suffers from crystallization heterogeneity and ion suppression⁴³. These issues degrade the detectability and quantitative fidelity of small metabolites and short peptides—often the most informative species for dynamic physiological readouts. Consequently, while MALDI–MS offers rapid, low-volume profiling, it remains limited in robust, quantitative small-molecule discovery workflows.

Biofluid secretion variability and normalization. Wearable-accessible fluids exhibit time-varying secretion influenced by stress, thermoregulation, hydration, local skin physiology and anatomical location⁴⁴. The observed MS intensity is a convolution of true analyte concentration with instantaneous dilution—potentially confounding interpretation. Without correction, fluctuations may reflect secretion dynamics rather than molecular kinetics. Notably, recent sweat metabolomics studies showed that secretion-rate effects account for ~73% total variance, making rate-aware correction crucial for valid interpretation⁴⁵.

Practical normalization strategies include comeasuring flow or fluid volume, tracking surrogate dilution markers such as conductivity or osmolality, or using internal standards^{46–49}. Volumetric or total-loss microfluidic patches with evaporation barriers also prevent analyte loss and provide on-skin flow or volume readouts, allowing secretion-rate-normalized concentration estimates rather than dilution-confounded intensities⁵⁰. Embedding such normalization strategies into MS workflows is essential to prioritize biologically meaningful candidates suitable for downstream wearable translation.

In addition, validation requires demonstrating that dilution-aware normalization effectively reduces secretion-driven variance. Standard reproducibility metrics, such as prenormalization versus postnormalization coefficient of variation (CV), intraclass correlation coefficient and Bland–Altman agreement, are widely used in clinical omics to quantify residual technical and biological variability^{51,52}. Ultimately, large-scale longitudinal cohorts will be required to extend these validation frameworks to wearable-accessible biofluids and establish robust secretion-aware reference ranges.

Emerging MS technologies for noninvasive biofluids

LC–MS remains the gold standard for untargeted metabolomics and proteomics, offering broad molecular coverage and dynamic range. In large saliva cohorts, LC–MS identified colorectal cancer signatures with AUC values exceeding 0.87 across over 2,600 samples¹⁰. Similar success has been reported in tear fluid profiling of patients with chronic dacryocystitis (AUC = 0.94)¹¹ and ISF proteomic analysis using microneedle-extracted samples, which yielded >600 proteins, closely resembling plasma¹².

GC–MS complements LC–MS by profiling volatile and semi-volatile compounds, which are often poorly retained by LC. GC–MS has identified 101 exhaled breath volatile organic compounds (VOCs) predictive of acute cardiovascular diseases, achieving >80% sensitivity and specificity¹³. In saliva, it captured smoking-related metabolic changes in compounds like tyramine and adenosine, under diet-controlled conditions¹⁴.

Despite their analytical capabilities, LC–MS and GC–MS require multistep sample preparation (for example, extraction and derivatization) and relatively large sample volumes (typically 5–200 μ l for LC–MS and 100–500 μ l for GC–MS), limiting their suitability for rapid or low-volume analysis. This has spurred interest in direct ionization technique⁵³ and in miniaturized MS workflows tailored to microscale biofluids. Recent advances, including microsampling, nanoflow LC columns and online solid-phase extraction/trap preconcentration, have enabled minute-scale temporal resolution from submicroliter samples, making it possible to capture participant-specific pharmacokinetics and metabolic trajectories at volumes compatible with wearable-accessible fluids^{54–56}. For example, fingertip-sweat LC–MS has been used to track minute-by-minute changes in caffeine and its metabolites after coffee or capsule ingestion, resolving individual uptake, metabolism and clearance kinetics from microliter-scale samples⁸, highlighting the value of dynamic biomarkers that reflect temporal trajectories rather than static snapshots.

LDI–MS, including matrix-assisted format, MALDI, bypasses the need for chromatography and enables label-free analysis from minute sample volumes. When paired with engineered nanomaterials,

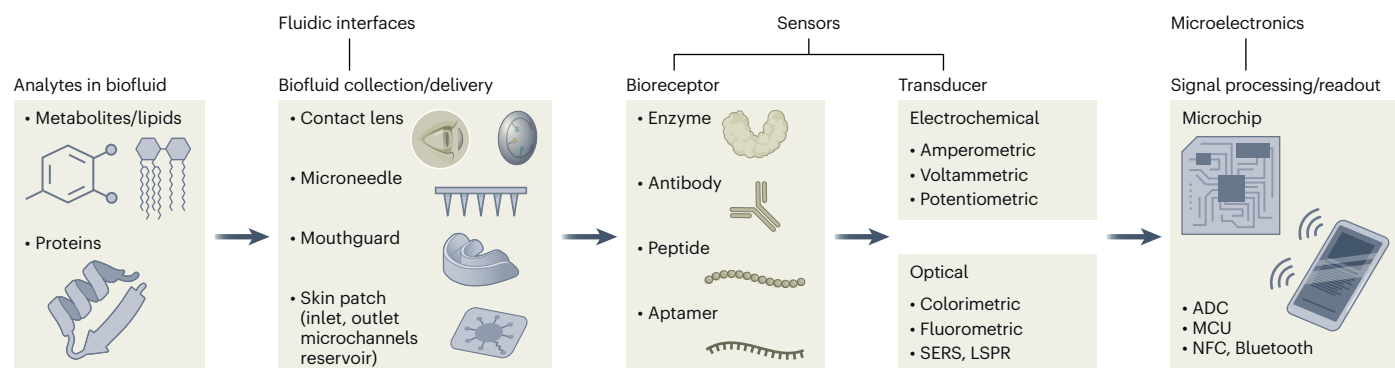


Fig. 3 | General architecture of wearable chemical biosensors. Analytes (for example, metabolites/lipids and proteins) are accessed through biofluids collected through skin-interfaced systems such as contact lenses, microneedles, mouthguards or skin patches. Biofluids interface with bioreceptors (enzymes, antibodies, peptides or aptamers) that confer target specificity. Signals are

transduced and processed by electronic modules for on-device or wireless readout. Figure created in BioRender; Kim, M. J. <https://BioRender.com/0zsn92d> (2026). SERS, surface-enhanced Raman scattering; LSPR, localized surface plasmon resonance; ADC, analog-to-digital converter; MCU, microcontroller unit; NFC, near-field communication.

LDI-MS benefits from enhanced ionization through photothermal, plasmonic or electronic effects⁵⁷. Nanomaterial-enhanced LDI-MS addresses the low-*m/z* matrix background by using nanostructured substrates as desorption/ionization enhancers. This directly tackles ultralow-volume analysis and has yielded compelling diagnostic results. For example, Au/Ag nanoparticle-assisted LDI-MS distinguished bladder cancer from 0.3 μ l of urine (AUCs > 0.82)¹⁵, ferric-oxide nanoparticle-assisted LDI-MS profiled 10 nl of tear fluid for glaucoma biomarkers (AUC = 0.827–0.891)¹⁶ and similar analysis of 10-nl saliva identified Parkinson's disease signatures (AUC = 0.85)¹⁷. In practice, LC-MS excels at capturing temporal dynamics from microliter samples, while nanomaterial-enhanced LDI-MS enables disease discrimination at nanomicroliter to submicroliter scales—offering practical pathways for biomarker selection and sampling strategies in future wearable systems.

These advances address sensitivity and volume constraints, but real-world deployment is still limited by throughput and per-sample cost. Recent high-throughput LC-MS pipelines address this by pairing 96-well (or higher-density) automation with sub-30-min gradients, allowing a single instrument to process tens to hundreds of samples per day while retaining quantitative rigor (often <10% CV in quality control series)⁵⁸. Because extraction, aliquoting and plate handling are automated, labor requirements per sample are reduced relative to manual LC-MS workflows. Shorter gradients also increase daily sample capacity, reducing instrument time allocated per sample and thereby lowering effective cost in high-volume studies^{59–61}.

Cohort-scale feasibility has already been demonstrated in noninvasive matrices—a 96-well hydrophilic interaction LC–data-independent acquisition workflow, for example, processed 842 urine samples with controlled variability⁵⁸, and μ LC-MS/MS platforms running 15–25-min gradients have delivered 50–70 injections per day continuously over multiyear studies (>38,000 samples)⁵⁹. Beyond workflow automation, chemical multiplexing strategies such as tandem mass tag (TMT) and TMTpro isobaric labeling further increase throughput by allowing 10-plex and 16-plex sample analysis, respectively, within a single LC-MS/MS run⁶². For example, TMT-based multiplexed MS with MS3 quantification has been used to profile serum proteins across discovery, validation and multicenter cohorts for early diagnosis of drug-induced liver injury biomarker identification⁶³.

In parallel, MALDI-MS eliminates the need for LC, removing both column and solvent consumable costs. In clinical workflows, this enables subhour sample preparation and per-spectrum acquisition times on the order of seconds, making it amenable to clinical decision support and rapid screening⁶⁴. Accordingly, MS enables large-scale discovery and analytical validation of biomarker panels, after which

those targets are translated into wearable sensors for population-level, real-time monitoring.

Collectively, these advances broaden the use of MS for untargeted profiling in diverse noninvasive biofluids. By supporting broad, discovery-driven analysis at small volumes and large cohorts, they unlock molecular insights across clinical contexts. The power of untargeted omics lies in its agnostic nature—eschewing assumptions in favor of broad molecular exploration. Unlike targeted assays that test predefined hypotheses, untargeted metabolomics and proteomics aim to discover what is present, responsive and mechanistically relevant. This openness requires rigorously structured workflows from sample preparation through computational analysis (Fig. 2b, Supplementary Note 1 and Supplementary Fig. 1). At the instrument level, analyzers such as the Orbitrap–Astral and timsTOF Pro 2 extend throughput and sensitivity, combining high-efficiency ion transmission and rapid MS/MS duty cycles (up to ~200 Hz) with quantitative reproducibility (<10% CV), enabling deep, low-volume, cohort-scale analyses^{65–67}. Ultimately, MS's value lies not merely in data acquisition, but also in processing and interpreting spectra to uncover biologically meaningful insights.

Wearable biosensors from bench to body

Real-time molecular sensing on the body

While untargeted MS offers unparalleled capabilities for discovering mechanistically rich biomarkers, its static, laboratory-based nature limits accessibility and temporal resolution. In contrast, wearable and ingestible biochemical sensors have the potential to transform how molecular information is monitored and used. Rather than static snapshots, these systems generate continuous, real-time data streams that capture dynamic changes within localized tissues or across the body in situ. Such functionality enables high-resolution, longitudinal insights into health status and therapeutic response, offering potential for managing chronic diseases and transient events such as stress, infection or acute metabolic fluctuations.

These integrated systems can sensitively detect biomarkers from accessible biofluids such as sweat⁶⁸, ISF⁶⁹, saliva⁷⁰, tears⁷¹, exhaled breath condensate (EBC)⁶, wound exudate^{72–74}, gastrointestinal fluids^{75,76}, sebum and cerumen, which contain abundant clinically relevant information. For each biofluid, unique technological considerations arise across three essential domains that shape platform design to achieve widespread adoption—fluidic interface for biofluid extraction and transport, sensing elements that transduce molecular recognition into measurable signals and electronics systems for data processing and wireless communication (Fig. 3 and Supplementary Fig. 2)⁷.

Materials and form factors for wearability

Translating rigid laboratory devices to wearable systems requires mechanical compliance with soft tissues. Stretchable substrates, soft hydrogels and bio-integrated polymers provide conformal skin contact, while microfluidics regulate fluid flow. Elastomers such as polydimethylsiloxane or styrene–ethylene–butylene–styrene offer tunable elasticity, and ultrathin polyimide films provide low bending stiffness^{77–79}. Natural textiles such as cotton, silk and chitin deliver compliance and breathability and can be functionalized by printing or dip-coating^{79–81}.

Electronic integration is achieved through the incorporation of conductive materials such as carbon nanomaterials, metal–carbon nanocomposites and metallic nanomaterials. State-of-the-art conductors include gold and silver nanowire meshes, graphene and carbon nanotube inks, and MXene coatings that maintain high conductivity under strain. Structural layouts such as serpentine, fractal or kirigami patterns distribute strain, while liquid-metal designs based on eutectic gallium–indium sustain large deformations^{82–86}. To ensure robust tissue–device interfaces, hydrogel or bioadhesive interlayers reduce impedance and enhance long-term adhesion, while breathable, anti-fouling encapsulants improve comfort and wearability⁷⁸.

Toward autonomous multiplexed sensing

Despite recent progress, most wearable biosensors remain limited to measuring a single analyte or a small panel of analytes, thereby restricting their clinical utility. Achieving autonomous multiplexed, high-resolution sensing requires concurrent advances in microfluidics, recognition chemistry and signal processing. On the fluidic side, interfaces that leverage low-volume, highly efficient fluid collection structures can help standardize the collection and analysis of biofluids by minimizing the dilution, lag and evaporation effects^{7,47}. On the biosensing side, multiplexed sensing platforms that simultaneously track multiple analytes can yield deeper metabolic and physiological insights. In practice, multiplexing is realized by assigning distinct recognition chemistries (for example, enzymes, aptamers/antibodies, ion-selective membranes) to parallel electrodes, while microfluidics partitions the fluid streams. Together, these strategies enable selective, simultaneous detection of multiple analytes on a single wearable patch.

Examples include the Stressomic patch integrating iontophoresis, burst-valve microfluidics and nanostructured electrodes to concurrently quantify cortisol, epinephrine and norepinephrine, capturing dynamic hypothalamic–pituitary–adrenal–sympathetic nervous system activity in humans⁸⁷, and a multimodal electronic skin that tracks six sweat biomarkers alongside three vital signs with an ML-based discrimination of stressors and accurate classification of state anxiety levels¹⁹. Combining amperometric, voltammetric and potentiometric approaches, as well as incorporating complementary modalities (for example, optical and electrochemical, physical and chemical), improves calibration robustness, accuracy and overall information density and quality⁴.

On the analytics side, AI is poised to transform heterogeneous sensor outputs into stable, calibrated and clinically meaningful signals. By fusing analyte-specific data streams with contextual reference inputs such as fluid rate, temperature and pH, AI models could suppress errors resulting from motion artifacts and dilution in real time. Sequence-aware filters could further compensate for transport delays, ensuring that rapid physiological changes are captured. Learned calibration maps have enabled alignment with blood or clinical values, with transferability across devices and users, while online drift modeling can preserve accuracy over hours to days. In addition, AI-driven frameworks could detect failing or contaminated channels, impute short gaps and dynamically adjust sampling rates or measurement ranges—ensuring that computational and power resources are allocated to the most informative signals (reviewed in ref. 88).

Fluidic interfaces and molecular access

Noninvasive and minimally invasive biofluids for health monitoring

As biomolecular profiling technologies advance, increasing emphasis has been directed toward leveraging noninvasive biofluids for health monitoring. These biofluids (Box 1) carry rich biochemical information and have emerged as central targets for wearable and ingestible sensing platforms^{5,89}. Compared with blood, they can be accessed with minimal pain and lower risk, enabling frequent or even continuous sampling in daily life and supporting personalized health management.

However, each fluid exhibits distinct secretion dynamics, molecular composition, sample volumes and contamination risks, necessitating fluid-specific strategies for sampling, stabilization and transport (Supplementary Fig. 3 and Box 1). Molecular analysis systems must therefore use tailored interfaces that preserve physicochemical integrity while ensuring user comfort and biosafety. Notably, the sampling step itself is critical for untargeted MS-based molecular profiling, as sample accessibility and integrity directly determine whether molecular signatures can be reliably translated into real-time biosensing metrics⁹⁰. Consequently, fluidic interface design should be regarded as the foundational conduit linking internal physiology to external readouts.

Engineering fluid interfaces for real-world deployment

Reliable fluid sampling is a core requirement for wearable microfluidic platforms. Conventional one-time sampling approaches often suffer from analyte dilution, degradation or cross-contamination, whereas self-refreshing microfluidic architectures—such as capillary-driven channels²³, porous interfaces⁶⁸ and unidirectional valves⁹¹—enable stable, continuous flow during biofluid collection. These designs ensure that fresh fluid is continuously introduced into the detection zone, while residual and potentially contaminated samples are promptly removed. Such strategies preserve sample fidelity and support real-time molecular monitoring over extended durations without reliance on terminal or batch-based sampling.

At the detection level, fluidic interface design critically dictates sensitivity and signal reliability. Because many biomarkers exist at low concentrations within complex biofluids, elective filtering and enrichment mechanisms must be incorporated into fluidic pathways. For instance, microstructured surfaces⁹² and selective membranes⁹³ can suppress nonspecific adsorption and enrich target analytes during transport. Real-time multiparameter calibration (for example, temperature or pH compensation) enhances accuracy⁴. In addition, antifouling coatings⁹⁴ and self-regeneration surfaces⁹⁵ mitigate protein adsorption and microbial adhesion, thereby limiting signal drift during long-term operation.

User comfort and mechanical compliance are equally important. Materials such as stretchable elastomers⁹⁶, ultrathin polymer films⁹⁷ and hydrogels⁹⁸ primarily function as mechanical substrate layers rather than as sensing interfaces, imparting tissue-like mechanics to the device and enabling stable adhesion to the skin or mucosa under stretching, bending and friction, while minimizing irritation through breathability and softness. Textile-based substrates and porous architectures confer enhanced breathability and lightweight features, rendering the devices nearly imperceptible during daily use⁹⁹. Miniaturization and lightweight designs reduce the wearing burden and ensure stable function under motion or routine activities¹⁰⁰. Such ‘invisible’ and ‘imperceptible’ user experiences are pivotal for advancing wearable platforms from laboratory prototypes toward real-world adoption¹⁰¹.

Ultimately, true deployability requires system-level integration. Beyond fluid sampling and target detection, *in situ* microfluidic platforms usually accommodate power management, circuit control and wireless communication within constrained form factors. Seamless coupling of fluidic modules with wireless units such as Bluetooth¹⁰² or near-field communication¹⁰³, combined with onboard recording and

BOX 1

Overview of noninvasive body fluids, sampling and stability/storage considerations for biomolecular profiling

Noninvasive and minimally invasive body fluids offer unique windows into systemic and localized physiological processes. Rich in diverse biomolecular content, these fluids support a wide range of clinical and translational applications, including diagnosis, monitoring, treatment evaluation, prognosis and personalized health management. Their effective use depends on fluid accessibility, biomarker composition and sampling strategy.

ISF

ISF resides between cells and reflects dynamic exchange with blood capillaries. It contains glucose, lactate, amino acids, electrolytes and other small molecules, with reduced macromolecular content compared to plasma. ISF supports continuous glucose monitoring and emerging applications in lactate tracking and drug pharmacokinetics. It can be accessed through microneedles, reverse iontophoresis, microdialysis or ultrafiltration, enabling minimally invasive real-time biochemical monitoring. Collection typically proceeds on ice with eluates archived at -80°C for molecular assays; dried microneedle/patch formats show stable storage when fully desiccated and sealed, whereas liquid extracts are kept cold to avoid freeze–thaw cycles.

Sweat

Secreted by eccrine and apocrine glands for thermoregulation and waste elimination, sweat contains electrolytes (Na^+ , Cl^- , K^+), metabolites, hormones (cortisol, estradiol), amino acids, vitamins, drug metabolites and other biomarkers. Sweat can be collected with absorbent patches, microfluidic devices or iontophoretic systems. It enables noninvasive assessment of hydration status, electrolyte balance, exercise metabolism, stress response, drug adherence, cystic fibrosis screening and various physiological states. Samples are commonly capped immediately to prevent evaporation, cooled and stored at -80°C for mass spectrometric analyses.

Tears

Tears lubricate and protect the ocular surface, containing glucose, lactate, electrolytes, antimicrobial proteins, immunoglobulins, inflammatory mediators and other bioactive molecules. Tear biomarkers have been linked to diabetes mellitus, dry eye syndrome and systemic inflammatory conditions. Sample collection can be achieved through Schirmer strips, glass capillaries or smart contact lenses. Although sample volumes are limited, tear fluid supports low-invasive ocular and systemic monitoring. Tears are typically cooled immediately and stored at -80°C . Protease inhibitors are commonly added for proteomics, and drying of Schirmer strips before freezing improves archival stability; thus, repeated freeze–thaw cycles are avoided.

Saliva

Produced continuously in the oral cavity, saliva has roles in digestion, immunity and homeostasis. It contains digestive enzymes, hormones, immunoglobulins, glucose, lactate, urea, viral nucleic acids, bacterial DNA, drug metabolites, oral microbiome components and numerous other biomolecules. Sampling is straightforward via passive drooling, stimulated collection or swab-based sampling. Saliva is widely used in infectious disease screening, pharmacokinetics, stress response, hormone monitoring, cancer diagnostics and general health assessments. Samples are cooled immediately, aliquoted when possible and stored at -80°C ; 4°C holds are used for near-term analysis, and freeze–thaw events are minimized.

EBC

EBC arises from aerosolization of airway lining fluid and water vapor condensation. It contains pH indicators, VOCs, oxidative stress markers, inflammatory mediators (NO_2^-), ions (NH_4^+), proteins and other biomarkers. Collected with specialized condensers or mask-based collection systems, EBC supports noninvasive monitoring of asthma, chronic obstructive pulmonary disease, lung infections, metabolic disorders and various health conditions through breath analysis. Rapid processing onto inert surfaces and -80°C storage preserve pH-sensitive and volatile components; sample volume/time and avoidance of repeated thawing are essential.

Gastrointestinal fluids

Gastrointestinal fluids encompass secretions such as gastric juice, bile, pancreatic juice and intestinal contents. They contain digestive enzymes, bile salts, short-chain fatty acids, amino acids, microbial metabolites, neurotransmitters and inflammatory markers. Sampled through ingestible capsules, wireless motility capsules, tethered probes, endoscopic procedures and gastrointestinal fluids enable investigation of inflammatory bowel disease, colorectal cancer, celiac disease, irritable bowel syndrome, microbiota-related metabolic diseases and various gastrointestinal disorders. Due to high enzymatic and microbial activity, samples are rapidly chilled and stored at -80°C ; acidification, antioxidants or protease inhibitors are used based on the analyte class.

Wound exudate

Wound fluid reflects the biochemical state-of-the local wound environment. It contains albumin, cytokines, matrix metalloproteinases, bacterial metabolites and other markers of inflammation and infection. Sampling is achieved through wound swabs, absorbent dressings or integrated smart bandages. Wound exudate is used for infection diagnosis, chronic wound assessment, healing progression monitoring and guiding personalized wound care strategies. Samples are cooled immediately, often treated with protease inhibitors for proteomics, and stored at -80°C while minimizing freeze–thaw cycles.

Sebum

Sebum is a lipid-rich secretion from sebaceous glands that spreads across the skin surface¹²¹. It contains triacylglycerols, wax esters, squalene, free fatty acids and cholesterol/cholesteryl esters, with profiles influenced by skin physiology and microbiota. Collected noninvasively using Sebutape, D-squame, swabs or medical gauze, sebum supports LC–MS and shotgun lipidomics for dermatologic conditions (for example, acne) and neurological disease studies (for example, Parkinson's disease)^{118,119}. Light and oxygen exposure are minimized, and samples are stored and sealed at -20°C (short term) or -80°C (long term) to limit oxidation.

Cerumen

Cerumen comprises desquamated epithelial cells mixed with lipids from ceruminous and sebaceous glands¹²². It contains long-chain lipids (for example, fatty acids, ceramides, wax and cholesteryl esters, squalene) and VOCs detectable by headspace GC–MS. Samples are collected with swabs or curettes and remain stable at ambient conditions. For VOC analyses, headspace vials are sealed and stored chilled or frozen (-20°C to -80°C) to help retain volatiles¹²³; for nonvolatile lipidomics, drying followed by dark, sealed, cold storage—preferably at -80°C —supports stability.

calculating, enables real-time networking and interuser consistency. Meanwhile, strategies such as duty-cycled operation, event-triggered sensing and energy collecting ensure low-power consumption and long-term autonomous operation^{104,105}. Modular design further enhances serviceability and scalability, exemplified by interchangeable ‘wet-end’ units coupled with reusable ‘dry-end’ components, which reduce consumable costs and improve reproducibility⁶. A further determinant of whether MS-derived biomarkers can be translated into wearable sensors is the extent to which plasma molecular signatures are preserved in noninvasive biofluids. As small molecules, hormones, cytokines and metabolites transit into biofluids, they experience diffusion, epithelial filtering, dilution and secretion-driven modulation. As a result, only certain classes retain reconstructable relationships with blood. A detailed analysis of these plasma-to-biofluid transformations—including partitioning behavior, attenuation ranges, diffusion-driven lag and class-specific reconstruction fidelity—is provided in Supplementary Note 3.

Integrating discovery and sensing

Achieving sensor readiness through viable target selection

MS can reveal thousands of molecular features across metabolomic and proteomic landscapes, but only a fraction can be feasibly monitored by wearable sensors. Many exist at trace levels, degrade rapidly or possess chemistries incompatible with on-body detection. Translational progress begins with identifying sensor-ready biomarkers whose biological relevance aligns with the operational constraints of wearable platforms. The following practical criteria should be considered.

Detectability in microliter-scale samples. Noninvasive fluids such as sweat, saliva and ISF are typically available only in microliter or submicroliter quantities over short time frames. Viable biomarkers should be measurable at these volumes with analytically defensible performance. In practice, this implies clear limit of detection (LOD) and limit of quantification (LOQ; for example, $LOD \approx S/N \geq 3$, $LOQ \approx S/N \geq 10$) and replicate precision at or near the LOQ^{106,107}. These requirements reduce false positives and ensure that targets can be detected using compact low-volume sensors.

Responsiveness on physiological timescales. Because wearable sensing aims to capture dynamic processes, biomarkers should show reproducible, interpretable fluctuations on minute-to-hour timescales under standardized perturbations (for example, exercise, thermal stress or pharmacological challenge)^{8,108,109}. Ideal candidates demonstrate effect sizes that exceed baseline variability and display rise/decay kinetics consistent with meaningful physiological processes.

Stability under short collection and handling intervals. Many biofluids are chemically unstable under ambient conditions, subject to degradation through solvent loss, pH shifts, oxidation, hydrolysis or enzymatic activity^{110,111}. Targets must maintain integrity over minutes to tens-of-minutes, or be amenable to stabilization through buffering, antioxidants, enzyme inhibitors or low-bind surfaces.

Robustness to secretion variability. Concentrations in wearable-accessible fluids are confounded by fluctuating secretion rates. To mitigate this, viable biomarkers should retain interpretability after normalization. Ratiometric, internal standards or pathway-linked metrics (for example, product-to-precursor ratios or coregulated analyte pairs), and secretion-aware modeling using concurrent fluid flow or surrogate markers like conductivity or osmolality can help cancel dilution effects^{46,47,112,113}.

Compatibility with practical transduction. A good candidate must map onto realistic sensing mechanisms. Targets that are redox-active or enzyme-coupled can be addressed electrochemically; optically

responsive molecules are amenable to photonic platforms; and affinity-based detection can leverage aptamers, antibodies or molecularly imprinted polymers to enhance selective binding before signal transduction. Concentration ranges and dynamics should match sensor linearity and calibration/drift management constraints.

Together, these criteria define what constitutes a sensor-ready biomarker from untargeted MS—detectable at low volume, dynamically informative, chemically stable, dilution-aware and transducible. Applying these principles enables the informed selection of analyte panels suitable for wearable translation.

Translating MS outputs into on-body sensing requirements

Beyond identifying which molecules merit monitoring, MS also defines the engineering constraints for sensing those molecules on-body. The physiological concentrations measured by MS establish the calibration span that wearable devices must maintain, while variance analyses reveal that much of the fluctuation in noninvasive biofluids arises from dilution or changes in secretion rate rather than biochemical shifts. This directly motivates incorporating a normalization channel—such as flow, conductivity or osmolality—so that wearables can report corrected, ratiometric outputs. Perturbation-based MS time courses further provide experimentally validated kinetics (rise, decay and recovery profiles) that specify the temporal resolution needed for accurate monitoring, indicating when devices must sample rapidly to capture fast transients versus when longer averaging windows suffice.

These MS-derived insights become concrete engineering specifications for wearable platforms. The translation follows a reproducible workflow—(1) MS profiling determines which analytes are detectable in noninvasive biofluids and their physiological concentrations. (2) These concentrations define the calibration window and linear-response span that a wearable must maintain. (3) Variance decomposition across MS datasets identifies dilution-driven fluctuations, informing the choice of a built-in normalization channel (for example, flow, conductivity, osmolality). (4) Perturbation-based MS time courses provide rise, decay and recovery kinetics that set the temporal sampling frequency required for accurate on-body tracking. (5) These molecular and kinetic parameters are then mapped directly to engineering specifications—LOD, dynamic range, normalization architecture and sampling interval—that the wearable must satisfy for reliable in situ sensing.

Translating MS-discovered panels into practical wearables requires platforms that deliver the following methods.

High sensitivity to low-abundance targets. MS often identifies biomarkers present at nanomolar or picomolar levels. To match this, wearable sensors must enhance both sensitivity and linear range to reliably capture such low-abundance analytes during continuous monitoring. This can be achieved through high-surface-area transducers (for example, nanostructured electrodes or photonic interfaces), enzyme-coupled amplification and low-noise electronics with environmental compensation. For example, catecholamines such as norepinephrine and epinephrine are present in sweat at subnanomolar concentrations, historically undetectable by conventional in situ sensors. Recent advances in high-affinity immunorecognition and nanostructured transducers (for example, gold nanodendrite-decorated graphene electrodes⁸⁷) now enable picomolar detection, broadening the scope of sensor-compatible targets.

Signal stability. Candidate analytes must yield stable, low-drift signals during continuous monitoring. Signal stability reflects both hardware drift and noise susceptibility under motion, temperature or humidity fluctuations. As an operational check, baseline drift and signal-to-noise ratio should be quantified over hours of operation, with acceptable variance thresholds specified to ensure reliable panel-level interpretation.

Multiplexing capacity. Because MS-derived specificity often relies on multi-analyte patterns, wearable platforms must support simultaneous measurement of multiple analytes with minimal crosstalk. This can be achieved through parallelized transduction sites, spectrally separated optical channels and microfluidic sample partitioning^{4,78}.

Secretion-aware normalization. Accurate interpretation of biomarker concentrations often requires normalization against fluid secretion rates or dilution surrogates. Wearable systems should incorporate real-time flow or volume sensors, or surrogate measures such as conductivity or osmolality, to deliver secretion-normalized outputs.

High-fidelity fluidics. To maintain analyte integrity, the fluidic interface must minimize evaporation, back-diffusion and sample contamination. Key design features include high-barrier laminates, anti-reflux microfluidic geometries, antifouling and low-adsorption surfaces, and skin-conforming mechanical structures to ensure a robust, comfortable seal during extended wear^{38,50,78,114}.

Calibration and drift management. For continuous operation, wearable sensors require in situ calibration and strategies to mitigate drift and environmental interference. Techniques such as ratiometric referencing (electrochemical or optical), on-chip calibration standards, differential/reference electrode configurations and automated quality control mechanisms—including compensation for temperature, ionic strength and pH—are increasingly being incorporated to address signal instability and biofouling^{24,115,116}.

Despite these advances in wearable sensor design, some barriers remain. First, expanding multiplex capacity introduces risks of cross-reactivity, signal crosstalk and environmental interference, limiting the robustness of panel-level sensing outside controlled settings. In addition, secretion-aware normalization—although conceptually validated in MS studies—remains technically challenging to implement continuously in compact devices; flow and osmolality channels can drift with motion, temperature or site-to-site variability, often requiring per-user calibration. Long-term wear can also lead to practical obstacles, including biofouling, evaporation or clogging of microfluidics, degradation of adhesives and skin irritation, all of which reduce durability and user compliance. Finally, constraints of energy budget, wireless data transmission and privacy/regulatory oversight slow translation from proof of concept to clinically deployable systems. Beyond device-level engineering, the next step is to validate whether candidate biomarkers and sensing strategies maintain stability, accuracy and clinical relevance in real-world, longitudinal use cases outside of controlled laboratory settings.

Climbing the validation ladder from bench to body

Even sensor-ready analytes require staged validation to ensure that laboratory performance translates to reliable on-body sensing. Initial *in vitro* testing defines sensitivity, detection limits, dynamic range and robustness against pH, temperature or interferents, with benchmarks typically assessing calibration linearity and signal-to-noise ratio performance. Then, *ex vivo*, authentic biofluids are used to assess accuracy and precision in complex matrices. Regulatory standards typically require accuracy within 85–115% of nominal concentration and CV <15%¹⁰⁷. Enzyme-based sensors may degrade in biofluids due to proteases, whereas ion-selective sensors may drift in low-salt conditions, necessitating appropriate stabilization strategies before deployment. Next, wearables are tested short-term on-body alongside reference methods (same biofluid or related fluids like plasma analyzed by MS or commercial assay kits) to capture variables not fully replicated *ex vivo*, such as surface contamination, secretion variability, and physiological pH and temperature fluctuations. This direct comparison quantifies real-world accuracy, identifies sources of deviations and informs calibration strategies. Finally, broader trials in independent

cohorts assess generalizability across populations, environments and clinical conditions, revealing variations by age, sex, hydration status or comorbidities.

Iterative feedback between stages refines both sensor chemistry and analyte selection. ML can optimize translation by integrating molecular descriptors, validation outcomes and real-time sensor data to reprioritize candidates dynamically.

Redefining biomarkers through fusion analytics

Integrating MS and wearable sensing goes beyond validation—it redefines biomarkers themselves. MS offers molecular identity, structural annotation and pathway mapping, while wearables provide continuous, context-rich temporal data. Together, they transform static concentration values into dynamic biomarker profiles capturing rates of change, recovery kinetics, and circadian or ultradian rhythms¹⁰⁹. MS-derived priors can guide wearable data analysis, highlighting biologically meaningful patterns such as co-fluctuation of pathway-linked metabolites. Temporal alignment and multivariate feature extraction can fuse both data streams into hybrid biomarker models that integrate molecular identity, secretion dynamics and environmental context for more robust diagnostics^{9,117}.

As outlined above, MS datasets not only identify which biomarkers are measurable in noninvasive fluids but also define the calibration range, dilution-handling strategy and temporal resolution required for reliable on-body sensing. In the opposite direction, real-time wearable outputs can prompt targeted MS reassessment, allowing iterative refinement of biomarker panels, sensing strategies and interpretation models.

A concrete example illustrates how this loop could operate in practice. For instance, if a lactate-sensing wearable reports a sudden fourfold increase while the wearer is sedentary—and internal quality control channels (for example, temperature, impedance, sweat rate) indicate normal device function—the anomaly can trigger MS verification using stored or newly collected samples. If MS confirms no corresponding change in lactate, the deviation is attributed to a sensing artifact (for example, cosmetic interference or membrane fouling), prompting adjustment of filtering or cross-reactivity handling. If MS instead verifies a true biochemical rise, the update flows in the opposite direction—the wearable may shift from absolute to ratiometric reporting, widen its calibration range or incorporate lactate into a broader multi-analyte panel.

In this integrated, bidirectional model, MS functions first as a discovery and design engine, and later as a validation layer that periodically recalibrates the sensing framework. Wearables, in turn, serve as continuous monitors that reveal unexpected physiological changes and trigger targeted MS reassessment when anomalies arise. Rather than a linear handoff, the two systems operate as complementary subsystems within a unified closed-loop architecture, informing and updating one another across different temporal and analytical scales. This co-adaptive structure establishes a foundation for platforms capable not only of sensing molecular changes but also of predicting and responding to them dynamically.

Outlook and future directions

To translate MS–wearable integration from laboratory demonstrations to routine clinical use, we must address more than just analytical performance. The following four domains are critical: standardization, clinical validation, data infrastructure and equitable deployment. Together, these define the path from proof of concept to scalable, routine use in personalized healthcare.

Standardized, reproducible biofluid sampling is essential for comparing results across devices, sites and studies. Protocols for sweat, saliva, tears and ISF must be resilient to environmental and physiological variability, such as hydration-dependent changes in sweat electrolyte composition. Harmonized, consensus-based guidelines

for collection, calibration and reporting will support both cross-study interoperability and regulatory approval.

Clinical translation will depend on longitudinal studies that connect temporal biomarker patterns to actionable health outcomes. These trials should evaluate both agreement with reference methods and predictive value for relevant conditions, such as metabolic instability or inflammatory flare. Embedding molecular monitoring into existing care pathways will help establish intervention thresholds and demonstrate impact on patient management.

As continuous molecular profiles enter personal health records, secure and interoperable data architectures will be needed to safeguard privacy while enabling multi-institutional analyses. Governance models must also address equity to ensure that the benefits of real-time biochemical monitoring are accessible across populations and healthcare systems.

Beyond translation, these platforms will open new avenues for discovery—mapping short-term coupling between systemic physiology and local biochemical changes, detecting presymptomatic molecular shifts and tracking resilience trajectories over extended periods. Addressing these translational, regulatory and ethical dimensions alongside technical refinement will be essential to establish MS—wearable integration as a reliable, scalable capability for personalized, real-time healthcare. Concrete applications include identifying presymptomatic molecular deviations, guiding individualized intervention timing using on-body trends and monitoring recovery dynamics and resilience trajectories over weeks to months.

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Author contributions

M.-J.K. and W.G. conceived the study and designed the outline and scope. M.-J.K., J.A.L.R., W.H. and W.G. wrote the manuscript.

Competing interests

W.G. is a cofounder and advisor at Persperity Health. The other authors declare no competing interests.

Additional information

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