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The Evolution of Chemical Sensors in Medical Diagnostics: New Materials, Modalities, and Applications

Faisal Saed Almutairi[1*], Khaled Manaja Almutairi[1], Abdullah Ali Bin Jabr[1], Abdulrahman Fahad Aldosari[1], Mohammed Marzouq T. Almutairi[2], Ahmed Nafal Alsalami[1], Raghad Mansour Binbaz[1], Hala Rajeh Alqahtani[1], Abdulrahman Abdullah Alorf[1], Yasir Ellaig Alshammari[1], Fahed Mohammed Alshammari[1], Noor Fahad Alshuraim[1], Aseel Hasson Alhasson[1], Noor Fahad Alshuraim[1]

[1] Ministry of National Guard, Saudi Arabia

[2]King Saud University, Saudi Arabia

Abstract

Medical diagnostics is being revolutionized by relentless technological progress in chemical sensing technologies. The years 2020-2024 have been especially transformative, driven by the global COVID-19 pandemic that underscored the imperative importance of rapid, sensitive, decentralized, and inexpensive diagnostic devices. This overview integrates the latest advances in chemical sensors for healthcare applications, such as the creation of biosensing platforms, integration of new nanomaterials, wearable and implantable form factor development, and the convergence of these sensors with artificial intelligence (AI) and data analytics. We begin with an overview of recognition component advances that form the basis of sensor specificity, including antibodies, aptamers, molecularly imprinted polymers (MIPs), and CRISPR-Cas systems. We then examine the transduction mechanisms—electrochemical, optical, and piezoelectric—which have been enhanced for improved sensitivity and miniaturization. A special section highlights the leading role of nanomaterials such as graphene, MXenes, metal-organic frameworks (MOFs), and quantum dots for signal amplification and new sensing modalities. The review then ventures into the breakthrough area of implantable and wearable sensors for real-time molecular monitoring of biomarkers from sweat, interstitial fluid, and tears, relocating diagnostics from the clinic to point-of-care and even the home. We also cover the emerging trend of multiplexed sensors and lab-on-a-chip platforms for full panels of biomarkers. AI and machine learning applications in data analysis, sensor calibration, and predictive diagnostics are also explored in depth. Finally, we cover existing challenges and future prospects, including regulatory hurdles, biocompatibility, long-term stability, and the path to commercial translation. This review will strive to provide a state-of-the-art overview of chemical sensors, emphasizing their unprecedented potential to revolutionize personalized medicine, remote monitoring of patients, and worldwide public health.

Keywords: Chemical sensors, public health, medical diagnostics, biomarkers, applications**.**

1. Introduction

Chemical sensors are analytical instruments that transduce chemical information, from the concentration of an individual component in a sample to total composition analysis, into an analytically useful signal (**Ramesh** et al., 2022). In clinical diagnosis, they are intended to detect specific biomarkers—proteins, nucleic acids, metabolites, ions, and gases-within complex biological matrices like blood, saliva, sweat, and breath. The ultimate aim is to unveil critical information for screening, diagnosing, predicting, and monitoring the efficacy of treatment. The global market for biosensors is growing with a vengeance, an echo of their growing irreplacability in medicine (Grand View Research, 2023).

The COVID-19 pandemic served as a humongous accelerator, speeding up innovation cycles for diagnostic devices, including rapid antigen and nucleic acid tests (Vashist, 2020). The timeframe witnessed a deluge of research on infectious diseases, but also on chronic diseases such as diabetes, cardiovascular diseases, and cancer, driven by a global shift towards preventative and personalized medicine. The most important drivers for innovation during this time have been: (1) the demand for increased sensitivity and specificity to detect low-abundance biomarkers; (2) the demand for miniaturization and cost-effectiveness to enable point-of-care testing (POCT); (3) the promise of continuous, real-time monitoring by wearable and implantable devices; and (4) the integration of smart data analytics to translate raw sensor data into clinically relevant information (**Yang** et al., 2022).

This review will navigate the most significant developments across the entire sensor architecture. It will touch upon the development of the biorecognition elements, transduction mechanisms optimization, nanomaterials' disruptive role, appearance of wearable and implantable form factors, and the enabler's role of AI. By bringing together evidence from the latest literature, this paper aims to give a complete picture of the current state and direction of medicine's chemical sensors.

*Corresponding author e-mail ayman.mukui@gmail.com (Faisal Saed Almutairi)

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Advancement in the Recognition Elements

The specificity of a chemical sensor is defined by the recognition element, the molecule that specifically binds to the target analyte. There has been significant diversification and engineering of these elements away from typical antibodies in recent years.

Affinity Reagents and Antibodies

Monoclonal and polyclonal antibodies are the standard of choice for most high-affinity and specific immunoassays. There has been a growing focus on engineering antibody fragments (e.g., scFv, Fab) towards increased stability and easier integration into sensor platforms, particularly those requiring harsh environments (**Pirkalkhoran** et al., 2023). Additionally, non-antibody affinity reagents such as affimers and DARPins (Designed Ankyrin Repeat Proteins) are gaining popularity. These recombinant proteins offer equivalent affinity to antibodies with enhanced thermal stability and smaller size, allowing for more dense sensor surface functionalization (**Tans** et al., 2020).

Aptamers

Aptamers are in vitro-selected single-stranded DNA or RNA oligonucleotides through SELEX (Systematic Evolution of Ligands by EXponential enrichment), which have been shown to be efficient synthetic antibody alternatives. They show thermal stability, reusability, facile chemical modification, and low-cost synthesis (**Han** et al., 2020). In the period between 2020 and 2024, focus has been on developing novel SELEX strategies for generating high-affinity aptamers against challenging targets like whole cells and transmembrane proteins. Additionally, hybridization of aptamers with other nanomaterials for signal amplification has been a dominant trend, developing numerous "aptasensors" for a variety of targets ranging from small molecules like cortisol to big proteins like thrombin (**Mahmoudpour** et al., 2021).

Molecularly Imprinted Polymers (MIPs)

MIPs are synthetic polymers with specific cavities for a target molecule, or "plastic antibodies." They gained popularity due to their excellent chemical and physical stability, low cost, and long shelf life. Recently, new studies have focused on the development of novel polymerization methods for preparing MIPs for protein and macromolecule recognition, an ancient and difficult task (**Silva** et al., 2023). The development of "epitope-imprinted" polymers, imprinting a short, distinctive peptide sequence of a large protein, has been especially promising. They were successfully applied in electrochemical and optical sensors for biomarker detection in complex biological fluids to offer a stable and inexpensive recognition platform (**Saylan et al.**, 2019).

CRISPR-Cas Systems

The CRISPR-Cas systems that were discovered for gene editing have been repurposed for diagnostic sensing and have given rise to a new class of ultra-specific nucleic acid sensors. These, including Cas12, Cas13, and Cas14, possess "collateral activity" in that upon their binding to the target nucleic acid sequence, they non-specifically cleave nearby reporter molecules, producing a huge signal amplification (**Kaminski** et al., 2020). Since 2020, there has been rapid commercialization and further optimization of CRISPR-based diagnostics, led by SARS-CoV-2 diagnostic kits. Research at present is focused on multiplexing performance, development of simpler readout methods (e.g., lateral flow strips, electrochemical detection), and employing these systems to detect non-infectious disease biomarkers, such as cancer-related mutations (**Liu** et al., 2022).

Transduction Mechanism Enhancements

The very basic function of any chemical sensor is its transduction mechanism, which converts the specific biological recognition event into an analytical signal that can be quantified. Among the many techniques of transduction, electrochemical and optical transduction methods have witnessed the most impressive advances during the past few years, driven by the demands for higher sensitivity and point-of-care convenience.

Electrochemical Transduction

Electrochemical sensors remain the workhorse of medical diagnosis due to their high sensitivity, low cost, inherent portability, and excellent miniaturization suitability. The recent improvements have aimed at increasing the signal-to-noise ratio and permitting multiplex detection of a single sample. Potentiometric sensors, which quantify the accumulation of a charge potential at an electrode surface, have been significantly advanced through the development of solid-contact ion-selective electrodes (SC-ISEs). These employ stable, hydrophobic conducting films such as poly(3-octylthiophene) or carbon nanotubes to create robust, consistent sensors to detect critical electrolytes such as potassium (K^+), sodium (Na^+), and calcium (Ca^{2+}) in biofluids such as sweat and blood (**Sempionatto** et al., 2022). Meanwhile, amperometric and voltammetric sensors, in which current from redox reaction is measured, have been revolutionized with nanomaterial-modified electrodes. These nanomaterials greatly increase the electroactive surface area and facilitate electron transfer, leading to enhanced sensitivity.

Glucose sensing is optimized, while this idea has been successfully extended to a wide array of other metabolites, including lactate, uric acid, and cholesterol (Rahman et al., 2022). One key milestone within this area is the creation of reagentless, third-generation biosensors, whereby the enzyme enjoys direct contact with the electrode, thereby minimizing interfering reactions and improving overall operation stability. In addition to these are impedimetric sensors based on Electrochemical Impedance Spectroscopy (EIS), which is a high-performance label-free method for the detection of biorecognition events, such as antibody-antigen or aptamer-protein bindings, by means of the measurement of alterations in the electrical impedance at the electrode interface (**Wang, 2006**). New research focuses on simplifying the complicated data analysis of EIS and designing low-cost, portable impedance analyzers for facilitating this labile method to be used in point-of-care diagnostics.

Optical Transduction

Optical transduction mechanisms that rely on the detection of a change in properties of the light are a versatile and sensitive alternative. Fluorophore-based sensors, which are highly sensitive, have seen performance enhancements through the development of new fluorophores like carbon dots and upconversion nanoparticles. Such materials possess superior resistance to photobleaching and large Stokes shifts, and their use in ratiometric sensing schemes, where the ratio of intensity at two emission wavelengths is measured, provides an internal reference that minimizes instrumental or environmental variation-induced error (Li et al., 2022). Surface Plasmon Resonance (SPR) is yet another powerful optical technique that detects a change in refractive index at the surface of a metal upon the binding of molecules. Although traditional SPR systems are benchtop, there is a highly dominant trend towards miniaturization, and fiber-optic SPR probes have been developed for handheld sensing (**Lee et al.**, 2021).

Localized Surface Plasmon Resonance (LSPR), which exploits metallic nanoparticle characteristics, is by definition more readily miniaturizable and has been extensively used in low-cost colorimetric assays, where analyte-induced nanoparticle aggregation results in a visible colorimetric response. Colorimetric sensors, in turn, underpin low-resource diagnostics, and during the period from 2020 to 2024, have seen a spate of smartphone-based colorimetric analysis. This approach utilizes the ubiquitous smartphone camera, computing power, and connectivity to provide quantitative readout for applications ranging from quantifying lateral flow assays to pH and ion sensing, and thereby democratizing access to advanced diagnostics (**Qian et al., 2022**). Figure 1 shows the core architecture of a chemical sensor, emphasizing recognition elements and signal transduction.

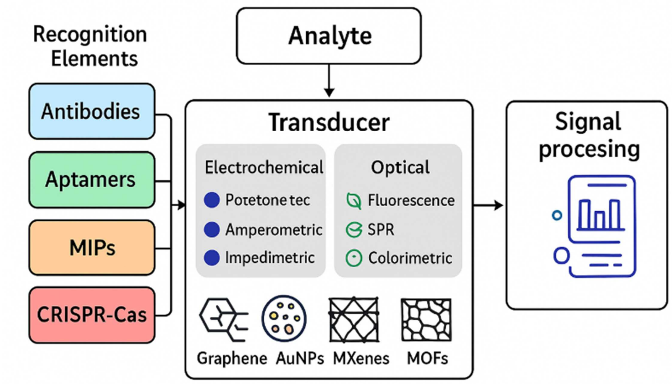

Figure 1: Architecture and Transduction Mechanisms of Modern Chemical Sensors

The Critical Role of Nanomaterials

The phenomenal progress in mechanisms of transduction has been tremendously promoted by the strategic use of nanomaterials that have been central to pushing the boundaries of sensor performance. Their high surface-to-volume ratio, unique electrical and optical characteristics, and amenability to functionalization make them notably ideal for signal amplification as well as transduction. Carbon nanomaterials such as graphene, its derivatives, and CNTs are still the most prevalent to employ. Their superior electrical conductivity makes them perfect for maximizing electron transfer kinetics in electrochemical sensors, while their excellent fluorescence quenching capability is priceless in optical "on-off" assays (**Pandikumar & Rameshkumar, 2018**). Metal nanoparticles, particularly gold (AuNPs) and silver (AgNPs), are the first choice for optical sensing due to their strong localized surface plasmon resonance (LSPR) effects, the signature component in hundreds of millions of lateral flow immunoassays and colorimetric sensors. Their application is also extended to electrochemical platforms, where they act as efficient electron transfer conduits (**Si** et al., 2021).

MXenes (e.g., $Ti_3C_2T_x$) have also become a novel generation of 2D materials that have been of specific interest due to their metallic conductivity, hydrophilic nature, and versatile surface chemistry. They have proved to shown excellent promise not only as active sensing materials for gas, small molecule, and protein detection but also as electrodes for electrochemical capacitors (supercapacitors) for energy storage in self-powered sensor systems (**Sinha** et al., 2020). Metal-Organic Frameworks (MOFs), due to their ultra-high porosity and tunable pore size, are basically high-capacity hosts for immobilizing enzymes and other recognition units, providing their bioactivity a shelter. Notably, certain MOFs also exhibit inherent catalytic or photoluminescent activity, and thus they can act as direct signal reporters (**Liu** et al., 2024). Finally, semiconductor quantum dots (QDs) have also proven to be better fluorescent labels compared to typical organic dyes because of their size-controllable photoluminescence and high quantum yield. Their application is particularly efficient in multiplex sensing, where differently colored QDs will capture multiple analytes simultaneously, which is a major area of research in complex diagnostic panels (**Rousserie** et al., 2010). Table 1 provides an overview of significant nanomaterials and applications in chemical sensors.

Table 1: Overview of Significant Nanomaterials and Applications in Chemical Sensors

Nanomaterial	Key Properties	Role in Sensor	Example Application
Graphene/CNTs	High electrical conductivity, large surface area, and good mechanical strength	Electrode modifier for enhanced electron transfer, fluorescence quencher	Electrochemical aptasensor for cortisol (Zubarev et al., 2022)
Gold Nanoparticles (AuNPs)	Strong LSPR, biocompatibility, and facile functionalization	Colorimetric reporter, electrochemical label, signal amplifier	Lateral flow immunoassay for SARS-CoV-2 (Ardekani & Thulstrup, 2022)
MXenes (e.g., $Ti_3C_2T_x$)	Metallic conductivity, hydrophilicity, tunable surface	Active sensing layer, electrode material for	Electrochemical sensor for dopamine (Riazi et al., 2022)

	chemistry	supercapacitors	
Metal-Organic Frameworks (MOFs)	Ultra-high porosity, tunable pore size, and catalytic activity	Immobilization matrix for enzymes, signal generator (luminescence)	MOF-based immunosensor for carcinoembryonic antigen (Zhang et al., 2021)
Carbon Dots (CDs)	Tunable photoluminescence, low toxicity, and photostability	Fluorescent probe, enzyme mimic (nanozyme)	Ratiometric fluorescence sensor for pH in sweat (Ji et al., 2022)

The Era of Wearable and Implantable Sensors

Perhaps the most paradigm-shifting development has been the shift from in vitro diagnostics to real-time, continuous in vivo monitoring using wearable and implantable chemical sensors. These sensors can potentially revolutionize chronic disease treatment through dynamic, real-time physiological feedback.

Wearable Sensors

Wearable chemical sensors represent a new frontier in non-invasive medical diagnosis, which are being engineered to test for large numbers of biomarkers in simply accessed biofluids such as sweat, interstitial fluid (ISF), tears, and saliva. Among these, sweat has proved to be a very rich and informative matrix, containing electrolytes like sodium (Na^+), potassium (K^+), and chloride (Cl^-), metabolites like glucose, lactate, and urea, and even hormones like cortisol. The technology has also progressed from simple sensing devices to full wearable patches. The sophisticated systems incorporate microfluidic networks for controlled sampling of sweat, sensor arrays for multiplex detection of analytes, and flexible electronics allowing wireless transmission of data to a smartphone to analyze in real-time (Gao et al., 2016). These combined systems are presently being heavily validated across a range of uses, from sports performance optimization in sports science and chloride concentration monitoring to treat cystic fibrosis, through to hydration status assessment.

At the same time that sweat sensing has been revolutionized, monitoring biomarkers in interstitial fluid (ISF) has itself been revolutionized through the commercial success of continuous glucose monitoring (CGMs). Although currently mainstream for diabetes care, ongoing research continues to work toward making them more precise, longer lasting in terms of functionality lifespan, and more biocompatible. The largest challenge remains the foreign body response (FBR), a natural immune response that leads to the growth of biofilms and sensor fouling, ultimately compromising performance. Some of the novel strategies to reverse this response include the use of anti-inflammatory coatings, the inclusion of nitric oxide-releasing membranes that inhibit bacterial adhesion, and the development of biomimetic materials that camouflage the sensor against the immune system (Zhang et al., 2021).

The sensing range of ISF is also expanding beyond glucose, with the continued development of sensors for biomarkers like lactate for monitoring tissue oxygenation in critical care and for antibiotics to enable personalized therapeutic drug monitoring. Specialty wearable platforms are also being explored with other biofluids. For instance, intelligent contact lenses with micro-sensors for glucose and intraocular pressure have come on the cutting edge of development to offer a non-invasive window into physiological status (Jang et al., 2021). Similarly, the oral cavity is also being explored as a sensing site with mouthguards and dental patches designed to monitor salivary biomarkers such as uric acid in gout therapy and cortisol in stress monitoring, completing a diverse arsenal of wearable biochemical monitoring.

Implantable Sensors

Implantable sensors are appropriate for long-term indwelling use and are capable of monitoring deep tissue. The primary challenges are achieving long-term stability, biocompatibility, and a reliable power source. Recent advances are focused on degradable sensors that dissolve at the conclusion of an effective lifespan, eliminating the need for surgical extraction (Chen & Ahn, 2020). These are envisioned for short-term postoperative monitoring of parameters like pH or temperature to track for infection. Moreover, the development of self-sustaining sensors, which harvest energy from the physiological environment (e.g., glucose biofuel cells), is a crucial advance towards fully autonomous implants (Jeerapan et al., 2020).

Multiplexing, Microfluidics, and Lab-on-a-Chip

Human physiology often entails the simultaneous measurement of two or more biomarkers for accurate diagnosis. Accordingly, multiplexed sensors that can identify two or more analytes in a single test are of particular interest.

Multiplexed Sensor Arrays

By placing multiple discrete recognition elements (e.g., different antibodies or aptamers) on the same substrate, sensors are able to generate a fingerprint response to a target disease state. Electrochemical platforms may achieve this via individually addressable microelectrode arrays, and optical platforms via spatial encoding (unique spots on a chip) or spectral encoding (unique colored fluorescent tags) (Reyes-De-Corcuera et al., 2021). This is extremely beneficial in differential diagnosis, e.g., distinguishing between bacterial and viral infections from inflammatory biomarker panels.

Microfluidic integration

Microfluidics, which manipulates very small amounts of liquid in microscopic fluidic channels, is perfect for POC sensors. Microfluidics enables automatic sample preparation, including mixing, separation, and reagent delivery, all on a miniaturized "lab-on-a-chip" (LOC) device. Coupling sensors with paper-based microfluidics (e.g., µPADs) has been highly successful in creating cheap, disposable diagnostic tests (Tian et al., 2018). More advanced systems using polymer-based chips can perform high-level assays like cell disruption, nucleic acid amplification (PCR, LAMP), and detection in an entirely miniaturized and automated process (Table 2).

Table 2: Comparison of Significant Sensor Platforms for Point-of-Care Diagnostics

Platform	Key Advantages	Key Limitations	Example (2020-2024)
Lateral Flow Assay (LFA)	Low cost, rapid, user-friendly, no instrument needed (for qualitative)	Lower sensitivity than lab tests, mostly qualitative/semi-quantitative, limited multiplexing	SARS-CoV-2 rapid antigen tests; Multiplex LFA for sepsis biomarkers (Ardekani & Thulstrup, 2022)
Electrochemical Strip	High sensitivity, quantitative, portable, low sample volume	Requires a reader, can suffer from biofouling, and calibration can drift	Commercial glucose strips; Electrochemical sensor for miRNA in cancer (Meng et al., 2020)
Wearable Patch	Continuous monitoring, real-time data, non-invasive/mildly invasive	Calibration challenges, signal drift due to biofouling, limited analyte portfolio	Multiplexed sweat sensor for lactate and glucose (Gao et al., 2016)
Smartphone-Based Optical Sensor	Ubiquitous platform, powerful processing, connectivity, colorimetric/fluorimetric detection	Dependent on phone hardware, ambient light interference requires an accessory	Smartphone-based ELISA for Zika virus; pH sensor for wound monitoring (Qian et al., 2022)
Lab-on-a-Chip (LOC)	Full automation, complex assay integration, small sample/reagent volumes	Higher cost per device, fabrication complexity, can clog	Microfluidic PCR chip for pathogen identification; Organ-on-a-chip for drug toxicity screening (Lapizco-Encinas & Zhang, 2023)

The Convergence of Artificial Intelligence and Data Analytics

The dissemination of continuous and multiplexed sensor arrays creates huge, complex data sets beyond the capabilities of conventional human intuition, necessitating artificial intelligence (AI) and machine learning (ML) as key instruments within the contemporary diagnostic landscape. AI encompasses the entire data life cycle, beginning with sophisticated data analysis and calibration. ML algorithms can eliminate physiological and environmental noise, correct baseline drift, and deconvolute a specific analytical signal from the complex background of biological samples very effectively. This is particularly important for wearable sensors, where AI enables the development of dynamic personalized calibration models that include inter- and intra-individual variation, thereby immensely enhancing measurement accuracy (Hanitra et al., 2021).

Besides basic data polishing, AI drives prediction diagnosis, which can pick out weak, pre-symptomatic signals in longitudinal data streams. For instance, algorithms are being trained to forecast glycemic excursions for diabetes, hypotensive episodes for intensive care units, and even the onset of viral infection through tracking deviations in resting heart rate and other physiological signals captured by wearables (Natarajan et al., 2020). Moreover, the role of AI is now increasingly extending further upstream into the sensor design process itself, where machine learning algorithms are capable of rapidly traversing vast chemical and material spaces to predict binding affinity of new aptamer sequences or performance of new nanomaterial composites, greatly accelerating future sensing platform development cycle and optimization (Leong et al., 2022). Figure 2 shows how modern diagnostic ecosystems integrate wearable, implantable, and AI-driven sensors

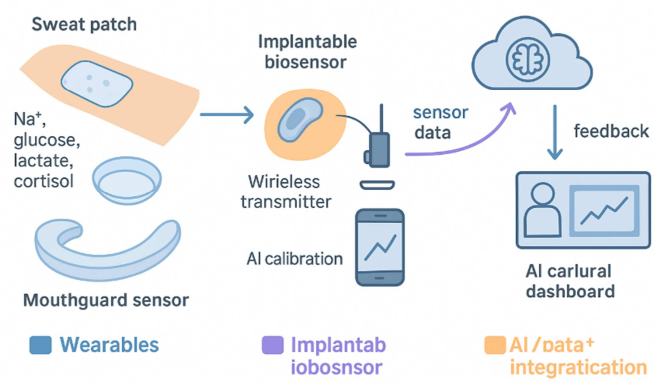

Figure 2: Next-Generation Diagnostic Platforms — From Wearables to AI-Integrated Systems

Challenges and Future Perspectives

Despite the tremendous advances, the broad clinical acceptances of these sensitive chemical sensors are in many ways dependent on the surmounting of several major challenges. One of the main challenges is achieving biocompatibility and avoiding biofouling since the foreign body response, featuring protein corona formation and cellular encapsulation, inevitably compromises the performance of any indwelling sensor in the long run. Future research should thus target the synthesis of "stealth" coatings and biomimetic interfaces designed to elude the host immune system (Zhang et al., 2021).

Simultaneously, long-term stability and calibration reliability a significant challenge, especially for denaturation-vulnerable enzyme-based sensors. This encourages the need for more potent synthetic recognition devices, e.g., molecularly imprinted polymers (MIPs) and constructed aptamers, and the search for self-calibrating or calibration-free sensor structures.

The path from a laboratory prototype to a clinically cleared device is also replete with regulatory hurdles and commercial translation challenges. The marriage of emerging nanomaterials and "black box" AI methods introduces additional regulatory challenges with which they need to deal, needing close collaboration among academia, industry, and regulatory bodies at the earliest stages of research (Lang et al., 2020). In addition, the lack of standard fabrications and validation procedures slows cross-group reproducibility and comparative outcomes, highlighting the necessity of large-scale clinical trials in comparison to gold-standard methods. Finally, practical problems with stable, long-term sources of power and secure, dependable wireless connectivity for fully implantable sensors call for continued advances in energy harvesting and low-power electronics. In the future, chemical sensors for medical diagnostics wait in the wings to be exciting. We can anticipate the emergence of mature closed-loop "sense-act" systems, such as a fully autonomous artificial pancreas, and consolidation of chemical, physical, and electrical sensing modalities onto a single wearable to provide an integrated view of an individual's health. Ultimately, the democratization of diagnostics by low-cost, smartphone-interfaced sensors could potentially address health disparities and allow a worldwide community to engage in active, personalized health management.

Conclusion

The period from 2020 to 2024 has been a showcase for the dynamic, multidisciplinary character of chemical sensor science. Stimulated by advances in materials science, nanotechnology, microengineering, and data science, the field has proceeded stoutly toward the construction of extremely sensitive, selective, and user-friendly diagnostic devices. Transitions from one-shot, benchtop assays to continuous, wearable, and intelligent sensing systems are a sea change in the philosophy of medical diagnosis. Although significant problems of biocompatibility, stability, and regulatory clearance persist, direction has been established. Chemical sensors will soon be integrated into our daily lives and clinical practice, enabling an age of predictive, personalized, and participatory medicine more efficient, accessible, and proactive than ever before.

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