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Early Cancer Detection Biosensors: Present Situation and Future Outlooks

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ABSTRACT Advances in biosensors have propelled the field of intelligent medicine, leading to significant innovations in the diagnosis and treatment of complex diseases, including cancer. In this context, biosensors have emerged as a promising tool for early cancer detection, offering faster, more sensitive, and more precise diagnostics. This review explores the progress in the field of electrochemical, optical, and nanotechnology-based biosensors, with a focus on detecting specific biomarkers for breast, prostate, and lung cancers. In addition, it highlights the integration of new techniques and microfluidics, which enhance the sensitivity and specificity of these devices while facilitating predictive and multiplexed analyses. This work consolidates recent developments in the field, identifies technical challenges, and proposes strategies that reinforce the use of biosensors as transformative solutions for early cancer detection, emphasizing their impact on improving clinical outcomes and global health.

INDEX TERMS Artificial intelligence (AI), biomarkers, biomedical engineering, biosensors, early cancer detection, label free, nanotechnology, point-of-care (POC) diagnostics.

I. INTRODUCTION

The development of biosensors can be traced back to the early 20th century [1], when M. Cremer, in 1906 [2], demonstrated that the concentration of hydrogen ions in a solution directly affects the electric potential across a glass membrane, establishing the principles of electrochemical (EC) sensing. Later, Søren Peder Lauritz Sørensen introduced the concept of pH in 1909, offering a systematic method for quantifying hydrogen ion concentration. Another key milestone occurred in 1922, when Hughes [3] engineered the first pH electrode, enhancing chemical analysis techniques. Around the same period, the authors in [4] and [5] pioneered enzyme immobilization on substrates, such as aluminum hydroxide and charcoal, laying the groundwork for enzyme-based biosensors. In 1956, Leland C. Clark Jr., recognized as the "father of biosensors," revolutionized the field by developing the Clark electrode for oxygen detection [6]. This breakthrough spurred the creation of subsequent biosensors, such as the amperometric enzyme electrode for glucose detection in 1962 and the potentiometric biosensor for urea detection by Guilbault and Montalvo Jr. in 1969 [7]. The commercialization of biosensors began in 1975 with the launch of the first commercially available biosensor by Yellow Spring Instruments. The emergence of the i-STAT sensor marked a new era, transforming

biosensors into a multidisciplinary domain that integrates physics, chemistry, biology, nanotechnology, electronics, and artificial intelligence (AI). These advancements have greatly enhanced the sensitivity, specificity, and overall performance of biosensors, driving continuous growth in research and applications in the field.

Currently, over 54 million people worldwide are living with cancer, reflecting the escalating global impact of the disease. In 2023, approximately ten million deaths were attributed to cancer, underscoring the urgent need for more effective diagnostic tools to reduce mortality and improve clinical outcomes [8]. Early diagnosis remains challenging, and this delay complicates therapeutic interventions, increases healthcare costs, and often limits treatment options [9]. Traditional methods of detection involve biopsies, histopathology, imaging (MRI, CT scans), and blood tests, requiring several analyses, which take days to weeks for results and may lack specificity and sensitivity. Biosensors play a key role in early cancer detection and are emerging as transformative tools in this field. These devices offer accessible, rapid, and highly sensitive capabilities, essential for improving the clinical diagnosis of various cancers and allowing for the noninvasive detection of biomarkers in body fluids, such as blood, saliva, and urine. By detecting specific biomarkers, such as human epidermal growth factor receptor 2 (HER2), prostate- specific antigen (PSA), and circulating tumor deoxyribonucleic acid (ctDNA), biosensors can identify cancers at earlier stages, significantly improving survival rates and treatment outcomes [10]. This article presents a comprehensive review of the latest biosensor technologies for cancer diagnosis, addressing the challenges associated with their development and the impact of integrating AI, nanotechnology, and microfluidic systems. It also proposes guidelines for future research to advance integrated platforms for decentralized diagnostics, highlighting opportunities to improve precision, sensitivity, and accessibility. Specifically, we address essential topics in the field, including biosensors in early detection, technological advances in biosensors, the integration of AI and microfluidics, challenges and opportunities, clinical impact, and future directions. This article covers the fundamentals and principles of biosensors, as well as biosensor attributes, the most important types of EC and optical cancer biosensors, and the new outcomes of biosensors for cancer detection.

II. FUNDAMENTALS AND PRINCIPLES OF BIOSENSORS

Biosensors are designed to interact with a multitude of biological components known as biomarkers (e.g., enzymes, antibodies, or nucleic acids), resulting in the production of detectable signals and measurable data. Modern biosensors emphasize miniaturization, portability, label-free [11], and real-time analysis [12] for medical diagnostics, environmental monitoring, and food safety applications. Their performance is defined by sensitivity, selectivity, stability, and response time. Current advances integrate nanotechnology and wireless communication for enhanced efficiency and application scope. They play an essential role in cancer research, helping scientists and speeding up the diagnostic process [10], [13], [14].

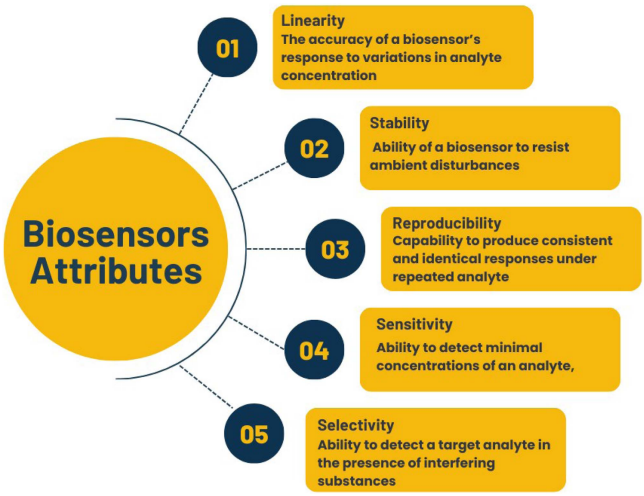

FIGURE 1. Biosensor attributes.

The attributes of biosensors are defined by performance and optimization (see Fig. 1). The first attribute is linearity, which is a parameter that characterizes the accuracy of a biosensor's response to variations in analyte concentration, typically modeled by the linear equation $y = mc$, where y represents the output signal, c denotes the analyte concentration, and m corresponds to the sensor's sensitivity [1], [15]. The linearity is linked to the biosensor's resolution and the dynamic range of analyte concentrations. The resolution of a biosensor is defined as the minimum detectable change in analyte concentration required to produce a measurable value. High-resolution capability is crucial, particularly in applications demanding qualitative detection and precise quantification of analyte concentrations. An important concept related to linearity is the linear range, which is the range of analyte concentrations where the biosensor's output remains directly proportional to the analyte concentration. This parameter is essential for ensuring the reliability and reproducibility of measurement data.

Stability is the ability of a biosensor to resist ambient disturbances that may lead to fluctuations, or bias, in its output signals [1], [15]. This bias can introduce errors in the measured analyte concentrations, thereby compromising the biosensor precision and accuracy. Stability is particularly critical in applications involving prolonged incubation periods or continuous monitoring, where consistent performance over time is essential. The stability of a biosensor can be influenced by various factors, such as temperature variations, which may disrupt signal stability. Another determinant of stability is the affinity of the bioreceptor, which reflects the strength of binding between the analyte and the bioreceptor. High-affinity bioreceptors promote robust interactions, allowing long-term stability of a biosensor.

Reproducibility refers to the capability of a biosensor to produce consistent and identical responses under repeated experimental conditions [1], [15]. This is a critical characteristic that reflects the reliability and robustness of the biosensor. Reproducibility is primarily determined by the precision and accuracy of the transducer and associated electronic components. Precision denotes the ability of the biosensor to deliver closely matching results when the same sample is measured multiple times, ensuring minimal variability between readings. Accuracy, on the other hand, represents the sensor's ability to generate a mean value that closely approximates the true value of the analyte concentration across repeated measurements. Biosensors with high reproducibility not only enhance confidence in analytical results but also support robust data interpretation, particularly in applications requiring quantitative analysis.

Sensitivity is the ability of a biosensor to detect minimal concentrations of an analyte, often quantified by its limit of detection (LOD) [1], [15], which represents the lowest concentration of an analyte that can be reliably distinguished from background noise. In various medical diagnostics and environmental monitoring applications, biosensors must exhibit exceptionally high sensitivity, being capable of detecting analyte concentrations as low as a few nanograms per milliliter (ng/mL) or even femtograms per milliliter (fg/mL). For example, in clinical diagnostics, a PSA concentration above 4 ng/mL in blood is considered a potential indicator of prostate cancer, prompting further investigation through biopsy tests. Given its role in early detection and precise quantification, sensitivity is one of the most essential performance characteristics of a biosensor, enabling accurate measurements in applications where detecting low analyte levels is crucial for timely intervention and decision-making.

Selectivity reflects the biosensor's ability to specifically detect a target analyte in the presence of interfering substances, admixtures, or contaminants [1], [15]. It ensures that the biosensor can distinguish the analyte of interest from other components in a complex sample matrix, enabling highly accurate and reliable measurements. An example of selectivity is the interaction between an antigen and its corresponding antibody. In this case, antibodies serve as bioreceptors and are immobilized on the surface of the transducer. When exposed to a solution, typically a buffered medium containing salt, the antibodies exhibit a highly specific binding affinity toward the target antigens, leaving other substances unaffected.

In recent years, smart nanomaterials responsive to biochemical signals in the tumor microenvironment (e.g., acidic pH, hypoxia, redox potential, and specific enzymatic activity) have been employed to refine selectivity in cancer biosensors, ensuring that detection occurs preferentially in malignant tissues while sparing healthy ones [16]. Carbon nanotube (CNT)-based biosensors have shown exceptional improvements in such selectivity, especially when functionalized with tumor-targeting ligands, such as folic acid, peptides, or antibodies, enabling specific recognition of cancer biomarkers, such as CA125, CA19-9, and PSA, in complex matrices [17].

TABLE 1. Comprehensive List of Cancer, Biomarkers, and Biosensors

Cancer Type	Biomarkers	Biosensors
Bladder	BAT, FDP, NMP22, HA-Hase, BLCA-4, CYFRA 21-1, FGFR3, TERT mutations, miRNA-126	EC, Optical, LSPR, Immunosensors
Breast	CA15-3, CA125, CA27.29, CEABRCA1, BRCA2, MUC-1, CEA, NY-BR-1, ING-1, HER2, PIK3CA mutations, ESR1	EC, Optical, SPR, Fluorescence-based, Photonic crystal biosensors
Colon and Pancreatic	CEA, CA19-9, CAA24-2, p53, KRAS mutations, APC, SMAD4, ctDNA, miRNA-21	EC, Optical, Microfluidic-based sensors, Raman-based optical sensors
Esophagus Carcinoma	SCC, VEGF, p16, TP53	Optical, EC, Fluorescence-based biosensors
Gastric Carcinoma	CA72-4, CEA, CA19-9, HER2, FGFR2, EBV-associated markers	EC, SPR, ELISA-based sensors, LSPR biosensors
Leukemia	Chromosomal abnormalities, NPM1, FLT3, IDH1/2, TET2, RUNX1	Microfluidics, DNA-based sensor, Optical biosensors
Liver	AFP, CEA, DCP (des-gamma-carboxy prothrombin), GP73, miRNA-122	EC, Optical, Immunosensors, SPR, Fluorescence-based biosensors
Lung	NY-ESO-1, CEA, CA19-9, SCC, CYFRA21-1, NSE, ALK fusions, EGFR mutations, KRAS mutations, PD-L1	EC, Optical, Nanoparticle-based sensors, Raman biosensors, Photonic biosensors
Melanoma	Tyrosinase, NY-ESO-1, TMB, BRAF mutations, NRAS mutations, PD-L1	EC, Optical, Nanosensors, LSPR-based optical
Ovarian	CA125, AFP, hCG, p53, CEA, HE4, BRCA1/2 mutations, miRNA-200 family	EC, SPR, Immunosensors
Prostate	PSA, PAP, PCA3, TMPRSS2-ERG fusion, miRNA-375, PTEN deletions	EC, Optical, DNA-based sensors
Testicular	AFP, β-hCG, CAGE-1, ESO-1, LDH	EC, Optical, Immunosensors
Colorectal	CEA, CA19-9, ctDNA, KRAS, BRAF mutations, PIK3CA, MSI, miRNA-92a	EC, Optical, Microfluidic-based, Fluorescence and Photonic biosensors

Biomarkers also act as analytes and are used as indicators of physiological, pathological, or biological processes. Table 1 summarizes the most common types of cancer, the biomarkers responsible for their detection, and the types of biosensors.

Transducers are critical components in biosensor systems, converting physical parameters into electrical signals, often in digital form. The transducer can be EC, optical, calorimetric, mass-sensitive, or magnetic, each employing distinct detection principles [18]. EC transducers, operating based on amperometry, potentiometry, or con- ductimetry/impedimetry, remain the most used due to their simplicity, cost-effectiveness, and high sensitivity. However, optical systems are rapidly gaining space due to their versatility and capability to expand practical applications [19], [20], [21], [22], [23]. Optical systems rely on detection of changes in

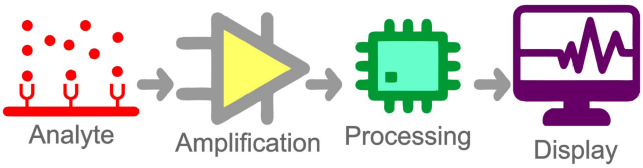

FIGURE 2. Biosensor components diagram. It shows the biosensor working flow, from the bioreceptors through signal amplification and data processing to display.

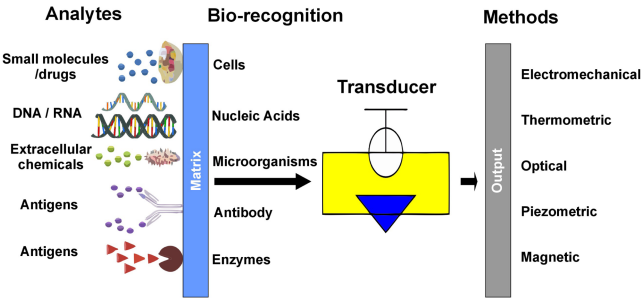

FIGURE 3. Workflow of biosensor technology, illustrating analyte recognition, signal transduction, and output generation.

color, fluorescence, luminescence, or interference patterns to signal molecular interactions, removing the need for reporter molecules or enzyme labels, typically required in electrochemical assays. Recent advances in optical systems include plasmonic biosensors that utilize surface plasmon resonance (SPR) and localized SPR (LSPR) for highly sensitive and label-free detection of cancer biomarkers [22], [23], [24].

A. COMPONENTS OF A BIOSENSOR

A biosensor is made of several parts, each serving a specific function in detecting and measuring a target analyte. Bioreceptors are responsible for recognizing and binding to the analyte through highly specific interactions, such as those involving enzymes, antibodies, or DNA probes. Once the analyte is detected, the transducer converts this interaction into a measurable signal, which is amplified and processed by the signal processor, including electronic circuits or microcontrollers to enhance accuracy and remove noise. The results are then displayed through the output unit as a text display or a graphical interface (see Fig. 2).

The utility of biosensors in oncology has been extensively reviewed, underscoring their critical role in enhancing diagnostic capabilities and improving clinical outcomes. Fig. 3 shows the functioning of a transducer biosensor system [25], illustrating the correlation among analytes, biorecognition components, transducer, and output methods. Analytes (e.g., drugs, DNA/RNA, chemicals, and antigens) interact with biorecognition elements (e.g., cells, nucleic acids, antibodies, and enzymes) in the matrix. The transducer (yellow block) converts this biochemical interaction into a measurable signal (electrical, optical, or mechanical), which is then analyzed through various output methods, including electromechanical, thermometric, optical, piezoelectric, or magnetic.

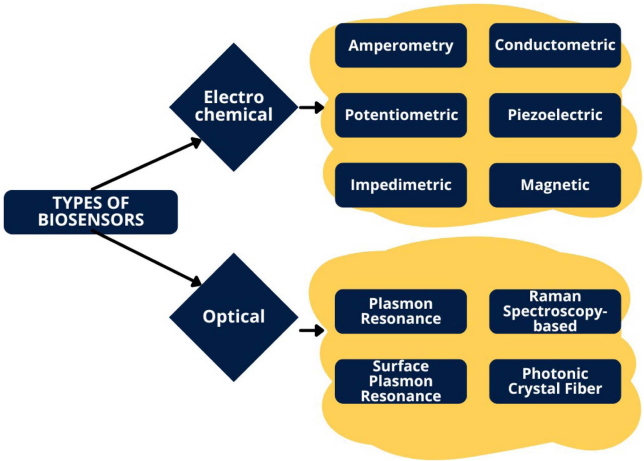

FIGURE 4. Types of biosensors and their subtypes.

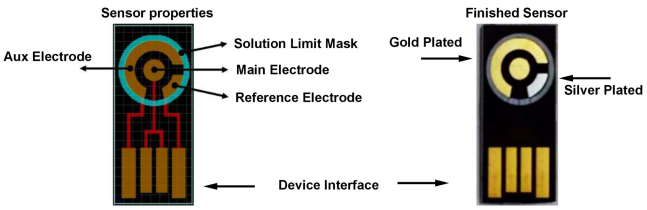

FIGURE 5. Example of an EC sensor with a three-electrode system [30].

Types of biosensors: The most widely used biosensors for cancer detection are divided into two groups: EC and optical and their subtypes (see Fig. 4).

III. EC BIOSENSORS

These biosensors are analytical devices that combine a biological recognition element with an EC transducer to detect specific analytes by measuring electrical signals resulting from biochemical interactions. Their sensitivity, specificity, rapid response, and potential for miniaturization make them suitable for various applications in medical diagnostics, including cancer detection. EC biosensors are divided into subtypes: potentiometric, conductometric, piezoelectric, magnetic, amperometric, and impedimetric [26], [27], [28], [29].

Fig. 5 shows a potentiometric sensor to detect the hepatitis C virus. This sensor is made with a copper printed circuit board modified through electroplating to change the surface to gold and silver [30], where the specific voltage variation through the analyte determines the presence of hepatitis C in the solution. While this specific platform was designed for HCV detection, the underlying technology, EC biosensors, has been extensively explored for cancer diagnostics, such as prostate, breast, colorectan, and lung. These biosensors offer advantages, such as high sensitivity, portability, rapid response times, and the capability for miniaturization, making them suitable for point-of-care (POC) applications. Conductometric biosensors are widely used for detecting analytes, such as blood glucose and lactic acid, by measuring changes

in electrical conductivity between two electrodes. Ionic components in the sample, such as Na^+, Cl^-, and H^+, cause variations in conductivity, enabling quantitative measurements. This principle has been adapted for detecting biomarkers, such as apolipoprotein A1 (APOA1), a recognized biomarker for bladder cancer [31]. The detection of APOA1 using conductometric biosensors is achieved with silicon nanowire sensors, which operate on the conductometric principle. Changes in the conductance of the silicon nanowires indicate the presence of the target protein. The device is fabricated using a bottom–up approach, where silicon nanowires are positioned between nickel electrodes through dielectrophoretic forces. This process creates a nickel/nanowire/nickel sandwich structure that minimizes contact resistance, enhancing signal stability and enabling the sensor to function effectively in wet environments, such as biological fluids. Key performance indicators for silicon nanowire-based conductometric biosensors used in APOA1 detection include a sensitivity of 2.4 μA/(μg/mL), a specificity exceeding 95%, an LOD of 0.25 μg/mL, and a response time of less than 5 min [25].

Recent advancements in conductometric biosensors include the use of advanced nanomaterials, such as graphene, carbon nanotubes, and hybrid composites, to further improve sensitivity, reduce noise, and enhance biocompatibility. In addition, miniaturization and integration with microfluidic systems have enabled the development of portable, high-throughput devices capable of detecting multiple biomarkers simultaneously. These improvements have expanded the applications of conductometric sensors beyond bladder cancer to include other biomarkers, such as carcinoembryonic antigen (CEA) for colorectal cancer and HER2 for breast cancer. For instance, a graphene-based conductometric sensor for CEA detection demonstrated a sensitivity of 0.42 μA/(ng mL^{-1}), an LOD of 0.1 ng/mL, and a response time under 60 s [32]. Similarly, a CNT-based biosensor for HER2 detection exhibited an LOD of 0.05 ng/mL and high specificity exceeding 97%, with a total response time of 90 s [33]. These biosensor platforms demonstrate faster response times and comparable or superior sensitivity to the ELISA technique, which is the gold standard detection method. Therefore, while conductometric biosensors offer rapid, label-free, and miniaturized alternatives ideal for POC settings, they may require further calibration and validation for widespread clinical deployment [34].

Piezoelectric biosensors operate based on the piezoelectric effect, where mechanical stress generates an electrical signal, or an applied electrical signal induces mechanical vibrations. Biosensors use piezoelectric materials, such as quartz crystals, to detect mass variations, making them ideal for label-free, real-time detection of molecular interactions. The principle relies on changes in the resonant frequency of the crystal, functionalized with bioreceptors, such as antibodies, enzymes, or nucleic acids. When target analytes bind to the bioreceptor layer, the added mass alters the oscillation frequency, enabling quantitative analysis based on the frequency shift (see Fig. 6). For example, they are used to detect tumor biomarkers by monitoring antibody–antigen binding or

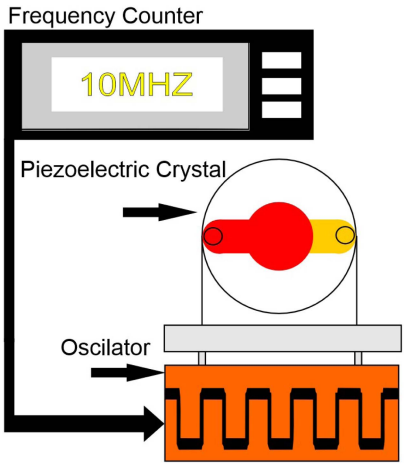

FIGURE 6. Working principle of a piezoelectric biosensor.

studying DNA hybridization to identify genetic mutations. Their label-free detection simplifies workflows, maintains analyte integrity, and allows detection of low concentrations, often in the nanogram to femtogram range [35], [36], [37]. Reported performance indicators of piezoelectric biosensors include a sensitivity of 5 Hz/ng for CEA, specificity over 98%, and an LOD as low as 0.25 ng/mL. The typical response time ranges from 2 to 12 min, depending on the analyte and device configuration [38]. Compared to ELISA, which typically has an LOD of approximately 0.5–1.0 ng/mL for CEA and requires 2–4 h for analysis, piezoelectric biosensors offer significant advantages in response time and do not require labeling or multiple washing steps [37].

Magnetic biosensors use magnetic materials to detect biological interactions, offering significant advantages in cancer diagnostics due to their high sensitivity, specificity, and ability to perform label-free detection. These biosensors typically employ magnetic nanoparticles (MNPs) functionalized with bioreceptors, such as antibodies or nucleic acids, to specifically bind target cancer biomarkers. Upon binding, the magnetic properties of the nanoparticles change and can be detected and quantified using various techniques, including magnetoresistive sensors and superconducting quantum interference devices [39], [40], [41], [42], [43]. One notable application is in the detection of ctDNA and microRNAs (miRNAs) in liquid biopsies. MNPs can be engineered to capture these nucleic acids from blood samples, and their magnetic properties facilitate the separation and detection of these biomarkers, enabling early cancer diagnosis and monitoring. Recent studies report that MNP-based magnetic biosensors for miRNA detection achieve a sensitivity of 1.39 fM, an LOD of 0.98 fM, specificity over 96%, and a response time of less than 10 min for clinical samples [42], [43]. For ctDNA detection, sensors demonstrate LODs as low as 10 fg/mL with comparable response times and high reproducibility [39]. In comparison, qPCR, the current standard for ctDNA and miRNA detection, offers a similar detection

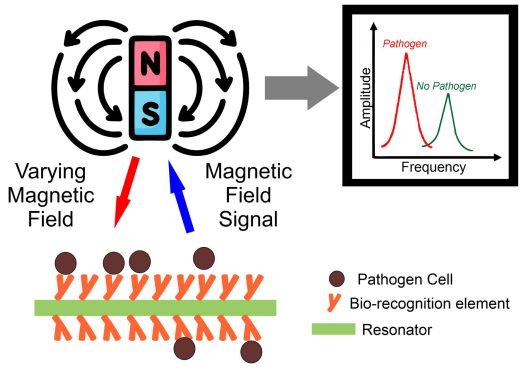

FIGURE 7. Schematic of a CV setup used for EC analysis of a cancer-related biomarker. The system includes an EC cell containing an electrolyte solution to ensure ionic conductivity. A three-electrode configuration is employed: a working electrode modified with a biorecognition element for specific interaction with the cancer biomarker, a counter electrode (CE) to complete the circuit, and a reference electrode to provide a stable potential. The CV method measures current response as the potential is swept, providing redox profiles indicative of biomarker presence and concentration.

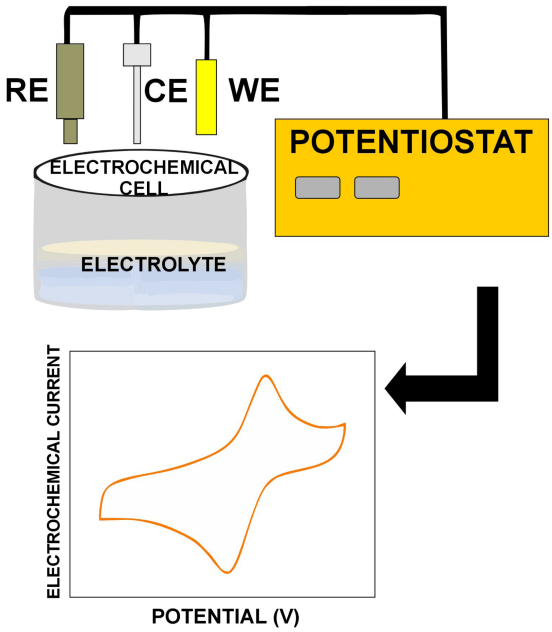

FIGURE 8. Setup of a CV method.

limit in the low femtomolar range but typically requires 2–6 h of sample preparation, amplification, and analysis time. ELISA lacks the sensitivity and specificity required for reliable nucleic acid biomarker quantification, with LODs often above 100 pg/mL. Thus, magnetic biosensors provide faster, label-free detection and simplified workflows ideal for POC applications [44]. Fig. 7 shows the working principle of a magnetic biosensor used for detecting pathogens. The system consists of a resonator coated with biorecognition elements that specifically bind to pathogen cells. When a varying magnetic field is applied, it interacts with the resonator, creating a magnetic field signal that can be measured. The presence of pathogen cells bound to the biorecognition elements alters the magnetic properties of the system, which changes the frequency response of the resonator. These changes are detected and analyzed, producing a signal that distinguishes between the presence and absence of pathogens.

Cyclic voltammetry (CV) is an EC biosensor method that uses differential pulse voltammetry (DPV) and electrochemical impedance spectroscopy (EIS). CV analyzes redox reactions occurring at the electrode surface, providing detailed information about the EC behavior of the system. DPV enhances sensitivity by measuring current changes at specific potential intervals, allowing the detection of subtle biomarker signals. EIS evaluates charge transfer resistance and impedance changes, offering insights into the binding interactions and the surface properties of the sensor. Together, these methods improve the sensitivity and specificity of biomarker detection, facilitating early diagnosis and monitoring of cancer. The working electrode is functionalized with biomolecules, such as antibodies or DNA probes, designed to specifically bind to cancer biomarkers present in the sample. The reference electrode provides a stable potential to monitor and control the voltage applied to the working electrode, while the counter electrode maintains the flow of current in the system. A potentiostat regulates the potential between the working and reference electrodes and measures the resulting EC current generated by the interaction between the cancer biomarkers and the functionalized surface of the working electrode. The output is displayed as a cyclic voltammogram, which is a graph of current versus potential (see Fig. 8). Characteristic peaks in the voltammogram indicate oxidation or reduction reactions associated with the biomolecular interactions, providing valuable information about the presence and concentration of cancer markers. This technique is highly sensitive and is often employed for early cancer detection, monitoring disease progression, and evaluating therapeutic responses. Compared to ELISA, which typically detects biomarkers in the nanomolar to picomolar range with analysis times of several hours, CV-based biosensors offer detection down to the femtomolar scale and response times under 10 min. CV biosensors enable label-free, multiplexed, and rapid detection without amplification, reducing sample preparation complexity. Nonetheless, qPCR and ELISA are more extensively validated for clinical use, whereas CV biosensors still face regulatory and standardization challenges for widespread deployment [45].

IV. OPTICAL BIOSENSORS

Optical biosensors are devices that utilize light to detect biological changes, offering high sensitivity, specificity, and real-time monitoring capabilities. They operate based on the interaction between analyte and light, with changes in optical properties, such as absorbance, fluorescence, or refractive index, serving as indicators of molecular binding events. Optical biosensors are widely applied in cancer diagnostics, particularly in detecting circulating tumor cells (CTCs), miRNAs,

and exosomes in biological samples. Their ability to analyze these biomarkers noninvasively has revolutionized cancer detection, enabling the early diagnosis and monitoring of disease progression [35], [36]. Recent advances in silicon photonic biosensors, SPR, and LSPR systems have yielded compact, label-free, and highly integrated platforms for sensitive detection of cancer-related biomarkers. Among these, optical fiber biosensors have emerged as highly promising due to their flexibility, miniaturization potential, and suitability for in vivo and POC diagnostics. These biosensors typically employ photonic crystal fibers (PCFs), tapered fibers, or fiber Bragg gratings, often functionalized with plasmonic coatings or aptamers to enhance specificity. For example, photonic crystal fiber-based SPR sensors integrated with graphene or gold coatings have achieved detection limits as low as 0.005 RIU and sensitivities exceeding 10 000 nm/RIU for breast and colorectal cancer biomarkers. Another design, employing Ag–ZnO–WS_2 multilayers in a fiber-optic SPR architecture, demonstrated an exceptional sensitivity of 7000 nm/RIU and a figure of merit of 80 RIU^{-1} in colorectal cancer detection. In addition, tapered multicore optical fibers functionalized with DOX-specific aptamers have been used to monitor chemotherapeutic drug levels in real time, with detection limits of 0.42 μM and high specificity.

The most widely used optical biosensors remain SPR-based systems, which detect changes in the refractive index near a sensor surface when biomolecules bind to immobilized receptors. SPR systems, such as the widely adopted Biacore biosensor chip (Cytiva, USA), have demonstrated exceptional effectiveness in detecting cancer biomarkers, offering high sensitivity, specificity, and real-time analysis capabilities for applications ranging from basic research to clinical diagnostics. SPR biosensors for CEA detection have reported sensitivities up to 0.1 Hz/(ng mL^{-1}), an LOD of 0.1 ng/mL, a specificity exceeding 98%, and a response time of approximately 5–10 min [46]. LSPR biosensors for HER2 detection demonstrate LODs as low as 0.05 pg/mL, with sensitivities in the range of 100%–200% signal shift per pg/mL, specificity above 97%, and response times under 10 min [47]. LSPR biosensors are being explored for POC diagnostics, particularly in oncology, where early detection of biomarkers, such as HER2 and CEA, is critical [48], [49], [50], [51], [52], [53], [54], [55]. Compared to ELISA, SPR and LSPR optical biosensors offer superior sensitivity (down to the picogram or even femtogram level) and real-time, label-free detection. Likewise, qPCR is more suited for nucleic acid detection with high amplification fidelity, but lacks the label-free and rapid kinetic monitoring capacity of optical sensors. Hence, optical biosensors provide an advantage in detecting subtle biomolecular interactions in real time and are well suited for early cancer detection and therapeutic monitoring, especially in decentralized or resource-limited settings [36], [43], [51].

SPR technology's ability to detect small biomolecular interactions in real time makes it invaluable in cancer diagnostics. SPR sensors rely on surface plasmons, which are waves traveling along the boundary between a metal, typically gold, and

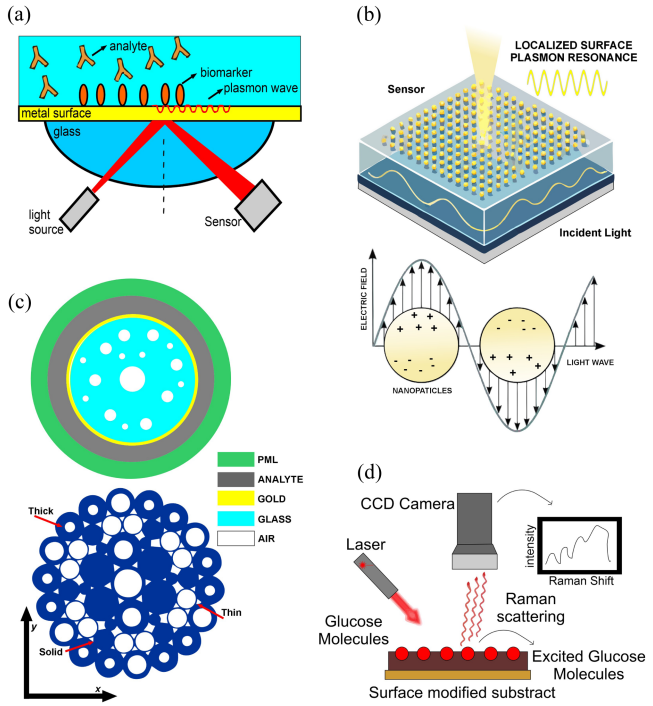

FIGURE 9. **(a) Working principle of an SPR biosensor. (b) Upper schematic of an LSPR sensor, showing metallic nanoparticles on a substrate and the excitation of surface plasmons by incident light, creating a localized electromagnetic field sensitive to environmental changes and lower illustration of the physical mechanism behind LSPR, depicting electron oscillations within metallic nanoparticles and the formation of dipoles under an external electric field. (c) Upper nanocavity-integrated PCF biosensor: a cross-sectional structure highlighting layered design, and also lower spectral shifts for cancerous and normal cells based on refractive index variations. (d) Working principle of a Raman scattering biosensor.**

a dielectric, often glass. When light of varying wavelengths hits the metal surface, it excites the surface plasmons, creating a resonance effect. This resonance is affected by changes in the refractive index caused by the binding of cancer biomarkers to receptors on the sensor surface. These changes are detected as shifts in reflected light, which are analyzed to determine the presence and concentration of cancer markers [56]. Their ability to target a wide range of biomarkers, combined with advancements in materials, such as graphene and gold nanoparticles (AuNP), highlights their growing potential for early detection, treatment monitoring, and precision diagnostics in oncology. For PSA detection, SPR biosensors have demonstrated a sensitivity of 1.3 10^4 RU/(ng mL^{-1}), a specificity greater than 97%, and an LOD as low as 6.28 pg/mL, with a response time of less than 10 min [57]. Fig. 9(a) describes an SPR biosensor, where a light source directs a beam onto the gold surface at a specific angle, creating a plasmon wave, a collective oscillation of electrons highly sensitive to changes in the surrounding environment. Biomarkers (orange ovals) are immobilized above the metal surface to capture specific analytes (yellow Y-shaped molecules). When an analyte binds to a biomarker, the refractive index near the metal surface changes, affecting the plasmon wave and altering the

angle or intensity of the reflected light, which is detected by the sensor. SPR sensors are widely used for studying molecular binding events, such as antigen–antibody interactions.

A novel SPR biosensor chip employing microcontact imprinting has been developed for the detection of PSA. This method utilizes methacrylic acid as the functional monomer, providing distinct advantages, such as low production costs, ease of fabrication, reusability, and strong binding affinity, comparable to natural biomolecules. Cross-linking agents, such as ethylene glycol dimethacrylate and α, α-azoisobutyronitrile, further enhance the stability of the recognition layer, reducing activity loss over time and ensuring prolonged usability [58]. For exosome detection, SPR biosensors have shown LODs as low as 2.110^3 exosomes/μL, with specific detection of prostate cancer-derived exosomes via PSA and CD63 markers, specificity above 95%, and response times under 8 min [53], [59], [60]. Exosomes, which are abundant in blood samples from various cancers (approximately 10^9 exosomes/mL), have also emerged as a promising diagnostic target. An SPR-based aptasensor, incorporating a gold film and AuNPs, has been developed to detect exosomes released by MCF7 breast cancer cells and MCF-10A normal cells. This sensor achieved a relative standard deviation (RSD) of 3.3%, demonstrating its sensitivity, precision, and reliability for cancer diagnostics [61]. Such aptasensors have achieved detection limits as low as 1.610^3 exosomes/μL, with specificity exceeding 96% and response times under 10 min [62].

A graphene-coated SPR fiber-optic biosensor has been designed for the detection of 916delTT and 6174delT mutations associated with the BRCA1 and BRCA2 genes in breast cancer. This innovative sensor integrates a high-index prism with a gold-coated fiber core, followed by a graphene monolayer and an analyte layer, collectively enhancing detection sensitivity and specificity. For HER2 detection, optical fiber-based SPR biosensors utilizing aptamers achieve LODs down to 0.1 ng/mL, with specificity of 97%–99% and rapid response times of approximately 5 min [63]. A recent design by Salah et al. [64] demonstrated a colorectal cancer-specific optical fiber SPR sensor employing Ag–ZnO–WS_2 multilayers, achieving an exceptional sensitivity of 7000 nm/RIU and a figure of merit of 80 RIU^{-1} using wavelength interrogation methods. Such highly engineered multilayer systems mark significant progress toward clinically viable fiber-optic diagnostics.

LSPR biosensors employing graphene oxide (GO)-AuNP hybrids have demonstrated high efficiency in detecting deregulated miRNAs associated with cancers, such as prostate carcinoma, hepatocellular carcinoma, colon cancer, and cervical cancer in preclinical studies [65]. These LSPR aptasensors for miRNA detection exhibit LODs in the range of 0.8–1.4 fM, with response times under 15 min and specificity exceeding 95% [66]. The hybridization of gold nanorods with oligonucleotide aptamers has further enabled the development of LSPR aptasensors capable of detecting Mucin-1, a protein overexpressed in several cancers, with high specificity and sensitivity [67]. Reported LODs for Mucin-1 range between 0.1–0.5 ng/mL, with an average sensitivity of 0.42 μA/(ng mL^{-1}) and a typical response time under 10 min [68]. The integration of porous metal-organic frameworks (MOFs) with LSPR and EC assays marks a significant advancement in cancer detection methodologies. A zirconium-based MOF, UiO-66, functionalized with silver nanoclusters, has been utilized for detecting CEA. This approach provides high thermal stability and a large surface area, and achieves an RSD of less than 5% [69]. Optical fiber-based LSPR sensors, paired with microfluidic channels, have been developed for PSA detection, showcasing enhanced sensitivity and multiplexing capabilities [70]. For lung cancer detection, a metal–insulator–metal nanodisk-based LSPR sensor has been designed to measure A549 cancer cells. This configuration employs a 60-nm SiO_2 layer sandwiched between 50-nm Au films, supported by a polydimethylsiloxane substrate, achieving high transparency, acid resistance, and bioinert properties. In the EC domain, an AuNP-based SPR EC aptasensor incorporating a 2-D nanocomposite of graphitic carbon nitride and MoS_2 quantum dots has been employed for PSA detection. This sensor exhibits remarkable plasmonic properties, high specificity, and a low RSD of 2.38% [71]. In addition, a novel switchable linker-based AuNP sensor has been developed for detecting prostate and breast cancers. The switchable linkers amplify visual signals by clustering nanoparticles, offering significantly improved sensitivity [72]. Fig. 9(b) exemplifies an LSPR biosensor.

PCF-based sensors, which employ microscopic air hole structures and guide light via mechanisms, such as evanescent fields and SPR, have emerged as a compelling alternative due to their capacity for real-time, highly sensitive cancer detection in clinical settings. Recent reviews emphasize their adaptability in integrating SPR and interferometric detection for malignancy-associated biomarkers [73]. Li et al. [74] developed a biophotonic sensor based on antitaper and direct-taper structures integrated with seven-core and four-core fibers. This probe, functionalized with DOX-specific aptamers and nanomaterials, such as MWCNTs and CeO_2-NRs, achieved a detection limit of 0.42 μM, enabling precise real-time monitoring of chemotherapeutic drugs during cancer treatment. In oncology diagnostics, PCFs have demonstrated unparalleled sensitivity and specificity. Functionalization with bioreceptors or infilling with cancer-specific biomarkers enhances their ability to detect minute changes in refractive index or fluorescence indicative of malignancy. PCF-based SPR biosensors report sensitivity levels as high as 10 200 nm/RIU, specificity above 98%, an LOD down to 0.005 RIU, and rapid response times of under 3 min for detecting breast, lung, and colorectal cancer markers [75]. For CEA detection, PCF sensors offer ultra-low LODs of 0.08 ng/mL, specificity above 97%, and real-time response under 6 min [54]. Moreover, twin-core refractive index sensors within PCFs can differentiate cancerous cells from noncancerous cells by analyzing coupling length and transmitted spectra variations. This is achieved through precise tailoring of cladding air hole dimensions, which critically influences the fiber's sensitivity and optical response.

These twin-core PCF biosensors demonstrated a detection accuracy of 96%, LOD in the range of 10^{-3}–10^{-4} RIU, and sub-5-min detection times across various cancer biomarkers [76]. A notable advancement includes a bowl-shaped monocoque SPR sensor with a 35-nm titanium coating, designed to exploit the plasmonic bandgap for efficient cancer cell detection. The sensor successfully detects multiple cancer types, including blood cancer, cervical cancer, adrenal gland cancer, breast cancer, and skin cancer, directly comparing cancerous and normal cells, improving diagnostic accuracy, and achieving resolution ranges from 1.510^{-2} to $9.33\ 10^{-3}$ RIU, which is superior to prior models [77]. This bowl-shaped C-grooved dual-core PCF SPR sensor exhibited a sensitivity of 13 200 nm/RIU, specificity over 97%, and an LOD of 6.510^{-4} RIU with a response time under 3 min [78]. Fig. 9(c) demonstrates a cross-sectional view of a PCF sensor, illustrating its layered structure. At the center is the core, made of glass, where light is guided through the fiber. Surrounding the core are small circular air holes, which are crucial for manipulating how light travels through the fiber by creating a photonic bandgap or supporting total internal reflection. Around these air holes is a gold coating, which is used to enhance sensitivity by enabling SPR. The next layer represents the analyte. Changes in the analyte's properties, such as its refractive index, cause shifts in the light spectrum, allowing detection. Finally, the outermost green layer is a perfectly matched layer designed to absorb unwanted light and prevent reflections, ensuring the sensor works accurately. The air holes are arranged in a structured pattern, with variations in size. Larger air holes, labeled "thick," help control light confinement, while smaller air holes, labeled "thin," fine-tune the sensor's properties. At the center, the solid core is free of air holes, enabling light to be guided effectively. This carefully designed lattice of air holes is essential for defining the fiber's optical properties, such as its ability to guide specific wavelengths of light and interact with the analyte for sensing applications.

Raman spectroscopy-based biosensors rely on inelastic scattering of light to produce a molecular fingerprint of the analyte [see Fig. 9(d)]. A laser source directs a focused beam of light onto a surface-modified substrate, which in this case contains glucose molecules. When the laser light interacts with these molecules, it excites them, causing some of the scattered light to undergo a shift in energy due to interactions with molecular vibrations. This shifted light, known as Raman scattering, is collected and analyzed by a charge-coupled device camera. The resulting data are displayed as a spectrum showing intensity versus Raman shift, where specific peaks correspond to vibrational modes of the molecules. These peaks provide information about the chemical structure, bonding, and com- position of the sample. Surface-enhanced Raman spectroscopy (SERS)-based biosensors for CEA and HER2 have shown LODs as low as 1–10 pg/mL, specificity of 96%–99%, and typical response times of 3–8 min [52], [53].

Advances in nanophotonic biosensors, which integrate nanoscale light manipulation, are also paving the way for highly sensitive platforms capable of multiplex detection. Whispering gallery mode (WGM) resonators and PCFs, for example, provide ultra-high sensitivity and are under active investigation for applications in cancer biomarker detection and single-molecule analysis. Recent studies have reported that WGM-based biosensors for PSA detection achieve LODs as low as 10 fg/mL, with sensitivities of up to 0.1 nm/(pg mm^{-2}) and specificity over 98% [54]. Recent innovations include metasurface-based sensors, which manipulate light at subwavelength scales, enabling compact and highly sensitive platforms for label-free detection. These metasurfaces have shown promise in detecting low-abundance cancer biomarkers, such as PSA and alpha-fetoprotein (AFP) [55]. Metasurface biosensors for AFP detection have demonstrated LODs down to 0.2 ng/mL, response time under 6 min, and specificity exceeding 96% [79]. Despite these advances, optical biosensors face challenges in adapting to POC devices, particularly for onsite analysis. However, portable SPR systems and smartphone-integrated detection platforms are actively being developed to fill this gap. For instance, smartphone-based SPR systems now offer high-performance biomarker detection in resource-limited settings [80]. In addition, integrated photonic chips, which combine optical sensing components on a single microchip, are emerging as a transformative technology. These chips provide compact, cost-efficient solutions for real-time, label-free detection across diverse environments, including clinical and POC settings. With advancements in nanofabrication and AI integration, these systems are expected to further enhance the accessibility and diagnostic capabilities of optical biosensors [50]. AFP EC biosensors with nanostructured gold electrodes achieve a sensitivity limit of 0.5 ng/mL. However, when both AFP and CEA are targeted, through a dual-mode system that combines EC and photoelectrochemical detection, sensitivity is significantly improved, with a detection limit of 0.2 ng/mL. CEA can also be detected using WGM optical biosensors, providing an ultra-sensitive detection limit of 0.02 ng/mL. In the case of ferritin, which can be indicative of certain cancers, a mass-sensitive SPR-based microfluidic biosensor is employed, with a detection limit of 0.1 ng/mL. For human chorionic gonadotropin (hCG), a biomarker relevant in certain cancers, fluorescence-based biosensors using quantum dots achieve a detection limit of 25 U/mL. CA15-3 is a common breast cancer biomarker, which is detected using an optical biosensor based on SPR with plasmonic AuNP. This advanced platform achieves a detection limit as low as 0.1 U/mL. Similarly, CA125, another ovarian cancer biomarker, is detected using nanoparticle-enhanced electrochemical biosensors with a detection sensitivity of 0.6 U/mL. CA19-9, a pancreatic cancer biomarker, is detected using a mass-sensitive quartz crystal microbalance immunosensor, offering a detection limit of 0.05 U/mL. Finally, PSA, a crucial biomarker for prostate cancer, may be detected using EC biosensors modified with graphene, achieving a detection limit of 0.1 ng/mL. Table 2 provides an overview of the latest biosensor technologies used for detecting cancer biomarkers, focusing on the principle, assay mechanism, and detection limit.

TABLE 2. Cancer Biomarkers Detected Using Various Biosensor Platforms, Their Assay Mechanisms, and Detection Limits

Cancer Marker	Biosensor Principle	Assay Mechanism	Detection Limit	Ref
AFP	EC	Immunosensor with nanostructured gold electrodes	0.5 ng/mL	[81]
AFP and CEA	EC	Dual-mode EC and photoelectrochemical detection	0.2 ng/mL	[24]
CA125	EC	Nanoparticle-enhanced immunosensor	0.6 U/mL	[82]
PSA	EC	Graphene-modified immunosensor	0.1 ng/mL	[83]
CA19-9	Mass Sensitive	Quartz crystal microbalance immunosensor	0.05 U/mL	[84]
Ferritin	Mass Sensitive	Microfluidic SPR-based biosensor	0.1 ng/mL	[71]
CA15-3	Optical	SPR biosensor using plasmonic AuNPs	0.1 U/mL	[85]
CEA	Optical	WGM biosensor	0.02 ng/mL	[86]
hCG	Optical	Fluorescence biosensor with quantum dots	25 U/mL	[87]

V. TECHNOLOGICAL ADVANCES IN BIOSENSORS FOR CANCER

EC biosensors remain pivotal in cancer biomarker detection due to their portability, simplicity, cost-effectiveness, and rapid diagnostic capabilities at the POC. Their small, disposable designs make them suitable for home use and clinical settings, with glucose biosensors being a widely recognized example of their utility. These sensors, often based on screen-printed amperometric electrodes, facilitate onsite analysis, revolutionizing diagnostics for chronic diseases. For example, handheld devices, such as the i-STAT clinical analyzer, which integrates multiple EC biosensors on a single chip, demonstrate the versatility of this technology by enabling the simultaneous detection of various electrolytes, metabolites, and biomarkers in clinical samples. In addition, enzyme-free EC biosensors using nanozymes and molecularly imprinted polymers (MIPs) have shown promise for cancer diagnostics due to their stability and ease of fabrication [88], [89]. Recent EC biosensors integrating microfluidics and nanomaterials have achieved sensitivity up to 92.5 μA cm^{-2} ng^{-1}, LODs as low as 10 fM, and specificity over 97%, with response times ranging from 3 to 8 min [90]. The integration of microfluidics with EC biosensors has further expanded their applicability, enabling multiplexed biomarker detection on a single platform. This innovation is particularly valuable in oncology, where simultaneous detection of multiple biomarkers is crucial for early diagnosis and treatment monitoring. Moreover, the incorporation of AI and data analytics with EC biosensor data is revolutionizing diagnostics by enhancing predictive accuracy and enabling real-time monitoring of disease progression [91]. EC devices for cancer diagnostics are increasingly focusing on detecting genetic mutations and protein biomarkers. DNA-based biosensors, for instance, involve immobilizing single-stranded DNA sequences on an electrode surface to detect mutations through hybridization. Detection methods include guanine oxidation (label-free), enzyme or redox labeling, and conductivity or capacitance changes caused by the formation of DNA duplexes on the electrode surface. Wang and Kawde [91] demonstrated label-free guanine oxidation to detect mutations in breast cancer genes BRCA1 and BRCA2, while Tansil et al. [92] reported detecting breast cancer marker genes via guanine catalytic oxidation. Modern CRISPR-Cas-integrated EC DNA biosensors for BRCA and EGFR mutations have reported LODs between 10–30 fM, specificity above 98%, and detection times under 10 min using EIS [93]. Recent advances in CRISPR-Cas technology have further enhanced DNA-based biosensors by enabling highly specific detection of oncogenes and mutations associated with cancers, such as lung and breast cancer [94]. EC biosensors are also widely employed for protein biomarker analysis. In these systems, antibodies or antigens are labeled with enzymes, such as horseradish peroxidase or alkaline phosphatase, which catalyze substrates to produce electroactive species detectable by the transducer. In addition, impedance and capacitance changes on the sensor surface caused by antibody–antigen interactions offer label-free detection methods. Label-free impedance-based protein biosensors have reported specificity above 96%, LODs as low as 0.1 ng/mL, and average response times of 6–10 min [95]. Multiarray working electrodes, fabricated using screen-printing or semiconductor chip technologies with macro/microarray patterns, allow simultaneous profiling of multiple proteins on a single chip, enhancing the throughput and efficiency of biomarker detection.

Despite these advancements, challenges in commercializing EC biosensors for cancer diagnostics persist. Issues, such as high background signals, nonspecific binding, and variability in antigen–antibody interactions, remain significant hurdles. Recent innovations in nanomaterials, including graphene, CNTs, and metallic nanoparticles, have shown promise in enhancing signal amplification, reducing noise, and improving sensitivity and reproducibility [96]. Comprehensive reviews of CNT-based EC biosensors highlight their superior electrical properties and adaptability through surface functionalization, enabling heightened selectivity and POC readiness for various cancer biomarkers [97]. Surface modification techniques, such as the use of self-assembled monolayers and MIPs, are being actively pursued to improve specificity and stability [98]. Furthermore, the integration of microfluidics with EC biosensors has facilitated automated and multiplexed analysis of biomarkers in small sample volumes. This is complemented by advancements in wearable and portable biosensor devices, which are becoming increasingly feasible for POC applications [99]. Such developments

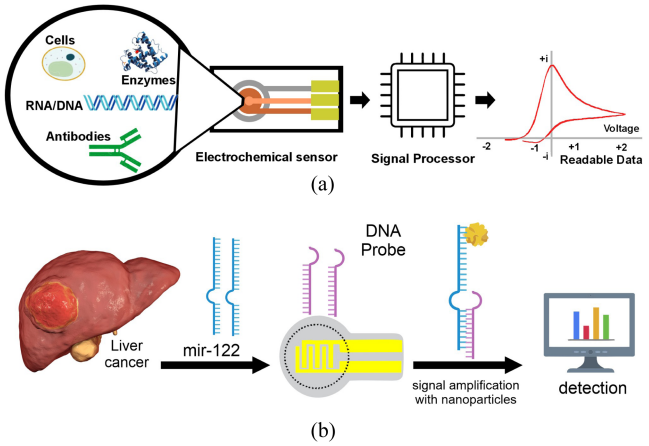

FIGURE 10. **(a) Representation of the EC analysis system. (b) EC biosensor components to detect liver cancer using miRNA.**

are paving the way for more robust, cost-effective, and practical biosensor platforms, bringing cancer diagnostics closer to real-world clinical implementation. Fig. 10(a) shows the structure of an EC sensor designed to detect substances and convert that detection into readable data. Various biological recognition elements (cells, enzymes, RNA/DNA, and antibodies) serve as detection agents for specific targets, such as molecules, ions, or pathogens. The EC sensor contains electrodes that generate an electrical signal upon interaction with target substances. This signal, indicative of the presence and concentration of the target, is transmitted to a signal processor (microchip), which amplifies, filters, and processes it. The processed signal is then translated into a readable format, such as a graph or numerical data, with typical output shown as a current versus voltage graph indicating the levels of detected substance.

A notable application of EC biosensors is in the detection of miRNA for the diagnosis of liver cancer [100]. miRNAs, which play a crucial role in gene regulation, are implicated in liver cancer progression, with miR-122 and miR-21 identified as key indicators of the disease when detected in blood or tissue. For miR-122 detection, an AuNP-dotted reduced graphene oxide (rGO/Au) nanocomposite is used as the probe material. DNA probes are immobilized onto the rGO/Au composite via a thiol linker, enabling specific binding to target miRNA-122. Upon binding, a bioreaction generates an EC signal. An electroactive electrode, incorporating AuNPs and Prussian blue nanocomposite, enhances the sensitivity of miRNA-122 detection. This biosensor configuration achieves an LOD as low as 0.34 fM, with a dynamic detection range from 1 fM to 1 nM, a sensitivity of 97%, and a specificity of 95%–98%. Response times are typically within 3–6 min [101], [102]. The generated signal is measured using DPV and EIS. DPV detects the inherent oxidation signal of guanine bases from the miRNA hybridization, while EIS measures charge transfer resistance, reflecting the binding interactions at the sensor's surface. These methods together provide a highly sensitive platform for detecting miRNA-122 and diagnosing liver cancer. Fig. 10(b) displays the operation of an electromechanical biosensor for detecting miRNA from liver cancer samples. The process begins with the extraction of miRNA molecules, which serve as biomarkers. The biosensor uses specific probes immobilized on its surface that are complementary to the target miRNA sequence, allowing selective binding. When the miRNA binds to the probe, a hybridization event occurs, generating a measurable electromechanical signal due to changes in the sensor's physical or electrical properties. This signal is transmitted to a data processing system and visualized on a computer, typically as a graph quantifying the miRNA detected, providing critical diagnostic or monitoring information for liver-related conditions.

Bacterial nanocellulose (BNC)-based EC biosensors offer significant potential for cancer detection through innovative material design and functionalization techniques. BNC, a biopolymer synthesized by bacteria, possesses exceptional structural and chemical properties, including high porosity, hydrophilicity, and mechanical strength. These characteristics make it an ideal platform for immobilizing biomolecules, such as antibodies, enzymes, and DNA aptamers, enhancing the sensitivity and specificity of biosensors for cancer diagnostics. These biomolecules are critical for recognizing and binding to specific cancer biomarkers, such as tumor-associated antigens, ctDNA, and cancer-related proteins. Recent studies report that BNC-based biosensors functionalized with AuNP and carbon nanomaterials have achieved sensitivities up to 78.2 μA cm^{-2} ng^{-1}, LOD as low as 0.23 μM or 12.6 pg/mL, and specificity values exceeding 95%, with rapid detection times under 5 min [103], [104]. This functionalization enables precise electron transfer processes and amplifies signal detection, facilitating the identification of biomarkers at ultra-low concentrations, which is crucial for early cancer diagnosis [105], [106]. Fig. 11 illustrates the biosynthesis and structural organization of BNC. It begins with the production of cellulose by bacteria, shown inside a bioreactor or culture medium where bacteria synthesize cellulose chains. These chains are extruded by the bacteria and self-assembled into microfibrils, which further aggregate to form cellulose fibers. These fibers exhibit a hierarchical structure consisting of crystalline and amorphous regions. The crystalline regions, highlighted in the structural zoom-in, provide mechanical strength and rigidity, while the amorphous regions contribute to flexibility and porosity. The bottom-right section of the diagram depicts the molecular structure of cellulose, which consists of repeating glucose units linked by β-14-glycosidic bonds. This arrangement forms a stable, hydrogen-bonded network that contributes to the material's high tensile strength and biocompatibility. The inset at the top shows a BNC membrane harvested from the culture medium, emphasizing its practical usability. Functionalization of nanocellulose with specific biomarkers enables highly sensitive and selective identification of cancer-associated molecular indicators, facilitating the detection of molecular events at the earliest stages of disease progression. Assis et al. [105] provided a comprehensive

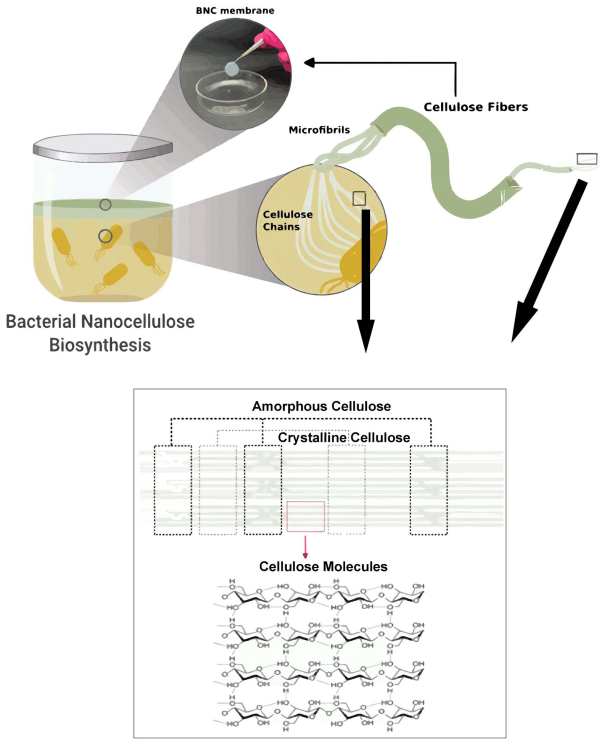

FIGURE 11. Structure of BNC.

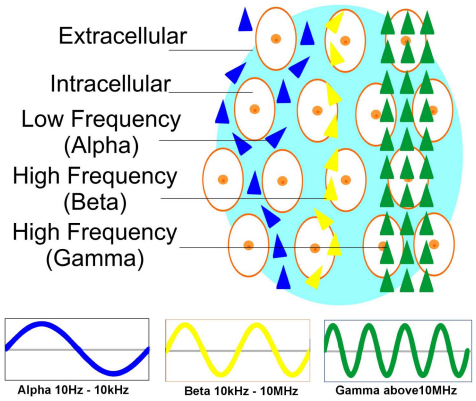

FIGURE 12. Behavior of a bioimpedance signal.

review of BNC-based EC biosensors, focusing on their functionalization, challenges, and future perspectives.

Impedance spectroscopy is a powerful, label-free analytical technique used in cancer research to study the electrical properties of biological tissues and cells. It evaluates the linear electrical response of a material, including the influence of electrode interfaces, through small-signal perturbations. This approach facilitates the extraction of critical information regarding the physicochemical properties and underlying mechanisms governing the system. Bioelectrical impedance spectroscopy (BIS), often referred to as bioimpedance, represents the opposition of biological tissues to the flow of an external electrical current or the way a living organism interacts with such currents. This measurement involves the application of electrical signals and the subsequent evaluation of voltage responses generated by tissue impedance via electrodes. The bioimpedance frequency response is highly dependent on the physiological and biochemical conditions of cells and tissues, exhibiting variability across individuals. This technique provides valuable insights into cell structure, composition, and physiological states, making it particularly useful for cancer detection, classification, and monitoring. Recent studies report that BIS can detect malignancies with sensitivity levels ranging from 89% to 96%, specificity between 90% and 95%, and LOD in the micromolar to nanomolar range, depending on the target cancer type. Response times for BIS measurements are typically within 2–10 min [107], [108].

BIS evaluates two components of electrical impedance: resistance and reactance across different frequencies. At low frequencies, the current primarily passes through extracellular spaces, while at higher frequencies, it penetrates cell membranes and interacts with intracellular components. This frequency-dependent behavior helps to distinguish healthy cells from cancerous ones, as cancer cells often exhibit altered membrane properties, cytoplasmic composition, and tissue architecture [109], [110]. The electrical properties of cells vary with the frequency of the applied electric current, exhibiting distinct dispersion regions classified as alpha, beta, and gamma. Alpha dispersion, occurring at low frequencies between 10 Hz and 10 kHz, is influenced by the ionic composition surrounding the cells. Beta dispersion, observed within the frequency range of 10 kHz to 10 MHz, reflects structural relaxation processes. Gamma dispersion, which emerges at higher frequencies, is primarily associated with the behavior of water molecules. At low frequencies, cell membranes exhibit high bioimpedance, causing the applied electric current to flow predominantly through the narrow extracellular pathways within tissues, resulting in elevated bioimpedance (see Fig. 12). The use of BIS has gained significant attraction in the medical field. Currently, BIS is routinely incorporated into clinical practice, particularly in intensive care units and nutritional therapy, where it aids in evaluating fluid volumes, fluid balance, and body composition to guide nutritional interventions. In recent years, growing medical interest and research have focused on investigating BIS variations across different types of malignancies.

Surface plasmon resonance imaging (SPRi) is an advanced optical sensing technique, enhancing detection capabilities by capturing spatially resolved changes in refractive index across a surface and enabling simultaneous monitoring of multiple interactions in an array format. An SPRi biosensor was developed for detecting laminin-5, a potential cancer biomarker, particularly in the bladder, and the results were compared to the ELISA.

The SPRi biosensor was able to detect degraded fragments of laminin-5, which ELISA failed to recognize. It presented a detection limit of 4 pg/mL with a dynamic response range of 0.014–0.1 ng/mL [111]. State-of-the-art SPRi devices now enable the detection of up to eight biomarkers

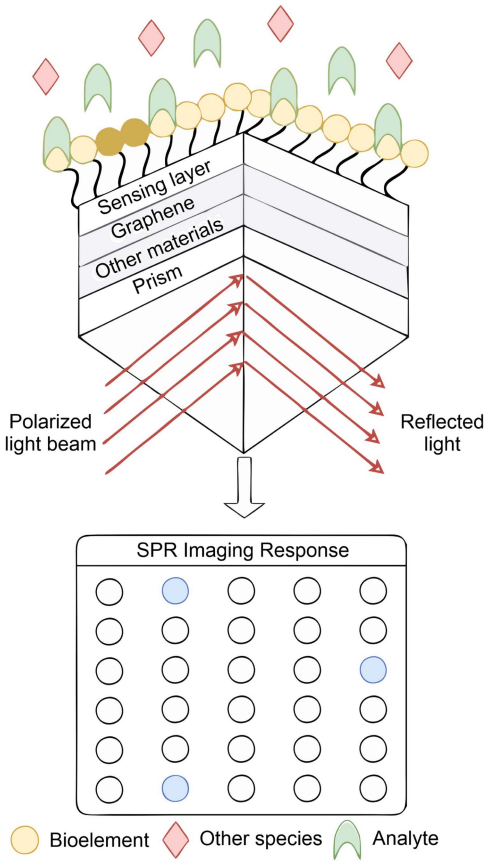

FIGURE 13. SPRi with hybrid physical construction to improve selectivity.

simultaneously with negligible cross-reactivity, achieving detection limits down to 0.05 pg/mL [112]. Hybrid physical constructions, such as graphene and titanium dioxide layers, further improve SPR selectivity and LOD performance (see Fig. 13). Multiplexing in SPR biosensors has emerged as a powerful technique for the simultaneous detection of multiple analytes in a single assay. An AuNP-based LSPR biosensor was tested for three biomarkers: AFP, CEA, and PSA. The biosensor demonstrated simultaneous, label-free detection with no cross-reactivity and LODs below 0.1 ng/mL [46]. Researchers also integrated SERS biosensor technology with machine learning (ML) algorithms, such as support vector machines (SVM), enabling label-free identification of exosomes from different cancer types. This approach was able to detect exosomes derived from the TIMP-1 protein with 85.7% classification accuracy, differentiating lung and colon cancer exosomes at the single-vesicle level [113].

VI. APPLICATIONS, CHALLENGES, AND FUTURE OUTLOOKS

A. INTEGRATION OF BIOSENSORS AND AI

Advancements in AI allow a more integrated and fast approach to improve biosensing through data analysis, significantly enhancing the efficiency and performance of biosensors, optimizing detection methods, and enabling real-time monitoring. The use of ML algorithms enables the processing of complex datasets generated by biosensor data, identifying patterns and correlations that traditional analysis methods might miss. AI models can also enhance signal processing by filtering noise and amplifying relevant signals, identifying new patterns, and revealing new information, leading to higher sensitivity and accuracy.

In addition, AI enables biosensors to perform predictive modeling, allowing early detection of diseases or pathogens by recognizing subtle changes in the biosensor's output. It can also optimize biosensor designs by simulating and predicting performance under different conditions, reducing development time and costs. SVMs have demonstrated high specificity in classifying biosensor responses for cancer biomarker detection, even in the presence of noisy signals or overlapping features, by constructing optimal decision boundaries. Ensemble models, such as gradient boosting machines, have also been used to aggregate predictions from multiple biosensor features, achieving improved diagnostic accuracy in detecting infectious diseases and metabolic disorders [114].

AI-driven biosensors can also be integrated into Internet of Things systems for remote monitoring, enabling continuous health tracking and rapid response in critical situations [115], [116]. However, as biosensors process patient-specific health data, integrating AI raises critical concerns regarding data privacy, security, and ethical use. Compliance with regulations, such as the Health Insurance Portability and Accountability Act in the U.S. and the General Data Protection Regulation in the EU, is essential. These frameworks mandate that personal health data must be securely stored, anonymized when necessary, and only accessible to authorized personnel, ensuring that AI-enabled diagnostics do not compromise patient confidentiality [117], [118].

AI, particularly ML algorithms, can be used to process and analyze the raw data generated by the biosensor. AI algorithms are trained to recognize patterns and distinguish between healthy and cancerous profiles based on subtle variations in signal patterns. For example, deep learning models, such as convolutional neural networks (CNNs), have been trained on spectroelectrochemical biosensor data to achieve over 95% classification accuracy in distinguishing cancerous from noncancerous samples, outperforming traditional statistical approaches. Random forest models have also been employed for their robustness and interpretability in identifying influential biomarkers from multivariate biosensor outputs, enhancing clinical decision support. Moreover, hybrid AI systems combining CNNs for feature extraction and SVMs for classification have achieved high-performance metrics across multiple biosensor platforms, including EC, optical, and piezoelectric devices [119].

Regarding signal preprocessing, AI can filter out noise and correct baseline drift in the data to ensure accurate readings. Concerning feature extraction, it can identify key features, such as peak intensities, current changes, or reaction rates, which are most relevant to detect cancer markers. In terms of classification models, AI algorithms, such as SVMs or

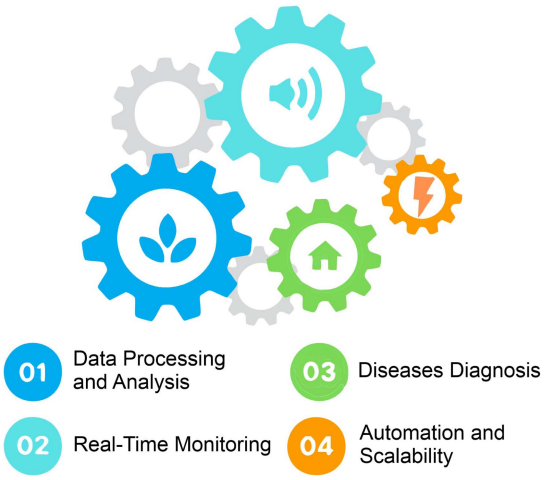

FIGURE 14. Applications of AI in the context of biosensors.

artificial neural networks, can be used to classify data into positive or negative cancer categories, or predict the likelihood of cancer through a quantitative probability assessment, helping clinicians to make informed decisions quickly. Therefore, AI-enhanced biosensors have the potential to offer faster, more accurate, and highly sensitive detection, even at extremely low concentrations of biomarkers, enabling early diagnosis, better treatment monitoring, and personalized medicine approaches [119].

Fig. 14 illustrates how the integration of AI with biosensors creates a powerful system for enhancing healthcare and environmental monitoring. AI algorithms can process and analyze the vast data generated by biosensors, enabling real-time monitoring and precise disease diagnosis. This synergy allows for the automation of tasks, scalability in applications, and the development of efficient, intelligent systems for predicting and managing health conditions or environmental changes. The collaboration enhances biosensor capabilities, providing advanced, actionable insights for improved outcomes.

B. REGULATORY PROCESS: FOOD AND DRUG ADMINISTRATION (FDA) AND CE

Biosensor certification is an essential part of development. Devices intended for clinical use must undergo stringent regulatory evaluation before receiving market approval. In the United States, the regulatory pathway is governed by the FDA, which classifies biosensors under the broader category of medical devices. The FDA categorizes these devices into three classes according to their risk level: Class I (low risk), Class II (moderate risk), and Class III (high risk). Most biosensors, particularly those intended for diagnostic purposes, fall into Class II. To obtain FDA clearance for Class II devices, manufacturers typically submit a 510(k) premarket notification, demonstrating that the device is substantially equivalent to an existing, legally marketed device. However, if a biosensor is deemed high-risk, such as implantable sensors or those used for critical health monitoring, a more rigorous premarket approval process is required. This route involves comprehensive clinical testing, analytical validation, and detailed documentation of safety and efficacy [120], [121].

An essential early stage in the FDA approval process involves a presubmission interaction, where sponsors meet with the FDA to clarify the regulatory classification and testing requirements. If clinical tests are needed, an investigational device exemption must be obtained to conduct human trials. In addition, compliance with the quality system regulation, codified in 21 CFR Part 820, is mandatory to ensure robust manufacturing and quality control practices [122].

In contrast, in the European Union, biosensor regulation falls under the medical device regulation or in vitro diagnostic regulation, depending on the specific use. These frameworks require CE (Conformite' Europe'enne) stamps, a symbol that informs conformity with health, safety, and environmental protection standards. CE classification is based on risk levels ranging from Class A to Class D, with biosensors usually falling into Class B or C. Devices in these classes must undergo conformity assessment by a notified body, including a review of technical documentation and a clinical performance evaluation [123], [124].

A critical component of biosensor approval in both the U.S. and Europe involves clinical tests. This typically progresses through multiple phases. Initially, analytical validation is performed to assess metrics, such as accuracy, precision, sensitivity, and specificity, under laboratory conditions. Once analytical validation is established, clinical validation evaluates the biosensor's performance in real-world or clinical environments [125].

For devices requiring human tests, trials generally follow the classical clinical trial phases. Phase 0 or Phase I trials focus on basic safety and dosage or exposure response in a small group of volunteers or patients. Phase II trials assess the biosensor's efficacy in a larger group while monitoring for side effects. Phase III trials involve large-scale testing across multiple sites to confirm clinical effectiveness, evaluate side effects, and compare the device to standard treatments or diagnostics. Finally, Phase IV, or postmarketing surveillance, continues once the biosensor is on the market, aiming to detect any long-term or rare adverse effects and ensure continued safety [126], [127].

With the emergence of digital and wearable biosensors, both FDA and European regulators have increasingly embraced hybrid and decentralized clinical trial designs. These approaches leverage digital health technologies to collect data from participants in nontraditional settings, which is especially valuable for remote patient monitoring devices [123], [127].

Furthermore, biosensors that incorporate ML or AI present novel regulatory challenges. For such devices, additional scrutiny is applied to software validation, cybersecurity, and real-time learning algorithms, which are not typically present in conventional medical devices [120].

A notable challenge in the approval process lies in demonstrating not just technical performance but also clinical utility. Regulatory agencies now expect evidence that a biosensor will significantly influence clinical decision-making or patient outcomes. Moreover, for home-use or wearable biosensors, human factor studies are required to ensure that users can operate the device correctly and safely [124], [127].

Regulatory approval for biosensors is a multidisciplinary effort that combines engineering, clinical science, and regulatory strategy. Successfully navigating these pathways requires early planning, transparent communication with regulatory bodies, and robust clinical evidence to demonstrate both safety and efficacy.

C. MANUFACTURING AND REPRODUCIBILITY

Scaling biosensor fabrication for industrial deployment presents substantial engineering bottlenecks, notably reproducibility, throughput, cost-effectiveness, and integration with miniaturized electronics. Traditional microfabrication techniques, such as photolithography and etching, although precise, are constrained by complex process flows, high material wastage, and limited flexibility in substrate compatibility, all of which hinder their utility in mass production and reduce batch-to-batch consistency [128]. The result is significant variability in biosensor performance, signal drift, and challenges in regulatory standardization.

Recent strategies have increasingly focused on transitioning to additive, high-throughput manufacturing methods, particularly roll-to-roll (R2R) printing and wafer-level processing (WLP). R2R printing, which includes gravure, flexographic, screen, inkjet, and nanoimprint lithography, has emerged as a compelling route due to its continuous processing capabilities, reduced material consumption, and compatibility with flexible substrates, such as polyethylene terephthalate, polyimide, or paper [129], [130]. By enabling deposition of conductive inks, biomolecule layers, and dielectric patterns in a layered, digitally controlled manner, R2R systems support modular production while achieving micrometer-scale feature sizes [131]. However, the implementation of R2R presents challenges in ink formulation and rheology, surface tension mismatches between ink and substrate, registration errors across layers, and mechanical instabilities, such as stretching or wrinkling during reel processing [132]. Moreover, print-based biosensors are often sensitive to environmental fluctuations during manufacturing, which can introduce noise or drift in the sensor response. Strategies to address these issues include incorporating real-time optical alignment, UV/thermal curing stabilization, and plasma or corona treatment to increase surface energy for improved adhesion [133].

In contrast, wafer-level packaging, a process, inherited from the semiconductor industry, allows for the simultaneous fabrication of hundreds of sensors on a single substrate with submicron accuracy. Wafer bonding, chemical mechanical planarization, and deep reactive ion etching enable integration of biosensing elements with complementary circuitry at nanoscale resolution. This process supports miniaturization, automation, and parallelism, crucial for ensuring uniformity and high reproducibility [134]. Notably, the ability to perform wafer-level packaging (WLP) allows encapsulation, electrode formation, and surface functionalization to occur prior to die separation, thereby improving sensor yield and stability [135].

Hybrid manufacturing platforms that combine the scalability of R2R with the precision of wafer-level lithography are emerging as next-generation solutions. For instance, R2R nanoimprint lithography can standardize large- area nanostructures with high fidelity, followed by wafer-level integration of microfluidic or MEMS components for enhanced specificity and multiplexing capabilities [136]. Such integration supports the development of biosensor arrays with uniform response characteristics across devices, critical for applications, such as disease biomarker detection or environmental pollutant monitoring.

Moreover, R2R-compatible nanomaterials, such as graphene, CNTs, or MXenes, have been engineered for printable biosensors with high electrical conductivity and large surface-to-volume ratios, further enhancing sensitivity and reducing power consumption [137]. These materials can be functionalized via inkjet or aerosol jet techniques for site-specific biomolecular interactions. Combined with wafer-scale passivation and encapsulation, the resulting systems achieve both robustness and biochemical selectivity, essential for clinical reliability. Standardization efforts are vital to overcome reproducibility challenges across manufacturing sites and laboratories. Efforts by institutions, such as the ISO/TC 229 committee, and initiatives in microfluidics standardization are driving alignment in materials, testing protocols, and interface formats. Standardization ensures compatibility across devices and platforms, facilitating regulatory approval and adoption in healthcare systems [138].

VII. CONCLUSION

The advancements in biosensor technology outlined in this article underscore their transformative potential in revolutionizing cancer diagnosis. The unique combination of sensitivity, specificity, and rapid detection capabilities offered by biosensors addresses one of the most critical challenges in oncology: detecting cancers at their earliest and most treatable stages, thereby significantly improving patient outcomes. The integration of nanotechnology has markedly enhanced the sensitivity of biosensors, allowing for the detection of minute changes in biomarker concentrations. Innovations in biosensor design, including EC, optical, and conductometric platforms, each tailored to detect specific cancer biomarkers, have also been pivotal. Molecular recognition elements, such as antibodies, aptamers, and peptides, provide the means to specifically target cancer-associated biomarkers, such as HER2, PSA, and ctDNA. Advanced transducers, such as SPR and LSPR, enable real-time, label-free monitoring of biomolecular interactions, improving the accuracy of early detection and streamlining diagnostic workflows. The integration of wearable biosensors and POC diagnostic devices

further enhances the potential for real-time, continuous monitoring of cancer biomarkers, allowing for earlier intervention and more personalized treatment strategies. Looking into the future, the field of biosensors for early cancer diagnosis stands to benefit greatly from the latest advancements in whole genome sequencing, next-generation sequencing, spatial profiling technology, and single-cell sequencing. These technologies will expand the list of detectable biomarkers, allowing for a more comprehensive and precise assessment of an individual's cancer risk and progression. Diseases can be influenced by various biomarkers, and future biosensors must be designed to accommodate a wider range of biomarkers. Moreover, the rapid advancements in AI and ML hold the promise of further enhancing the capabilities of nanobiosensors. AI algorithms can analyze complex datasets, offering predictive analytics for disease progression and response to therapy. The integration of AI and ML with the biosensor technology will push the field toward more accurate, efficient, and personalized cancer diagnostics, creating models that can effectively analyze complex patterns in large amounts of spectral data. The continuous evolution of biosensors has the potential to improve early detection and democratize access to cutting-edge diagnostic technology, particularly in resource-limited settings. Innovations, such as microfluidic integration and multiplexing capabilities, reduce diagnostic time and cost, making these technologies more accessible. Portable and miniaturized biosensors equipped with AI and data analytics are expanding access to diagnostics and enabling timely interventions. In summary, biosensors represent a pivotal advance in the early identification of cancers. By combining high sensitivity, specificity, and real- time analysis with cutting-edge sequencing technologies and AI, biosensors will become indispensable tools in personalized oncology. These innovations will significantly improve clinical outcomes and reduce the global burden of cancer, bringing about a new era of precision medicine.

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