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Review

Ovarian cancer biosensors: established glycoproteins to emerging molecular biomarkers

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ABSTRACT

Ovarian cancer is one of the leading causes of death in women primarily due to late diagnosis. Consequently, there is a critical need for more accurate diagnostic technologies beyond the limited sensitivity of current methods is of great importance. This review comprehensively explores the integration of specific biomarkers with advanced biosensor platforms to revolutionize disease management. It reviews the landscape of ovarian cancer biomarkers, from established glycoproteins (CA-125, HE4) to emerging molecular markers (miRNAs, ctDNA), and reviews recent advances in optical (e.g., fluorescence, SPR), electrochemical, and point-of-care biosensors. The findings highlight the remarkable capabilities of these technologies and confirm the high sensitivity of optical biosensors with detection limits down to the fg/mL range for targets such as MUC1. On the other hand, electrochemical platforms have been shown to offer robust and portable alternatives with detection limits in the μU/mL to fg/mL range. The advent of point-of-care and microfluidic systems, the potential for rapid and multiplexed analysis, has led to synergies between an expanding biomarker panel and advanced biosensor technology, paving the way for a new diagnostic era. However, this review also critically examines the key challenges in translating these biosensors from research laboratories to clinical practice. Therefore, future efforts should focus on clinical validation and increased survival and personalized treatment through the development of integrated lab-on-a-chip devices and the translation of these innovations into robust and cost-effective tools for enabling early diagnosis.

1. Introduction

Ovarian cancer remains one of the deadliest malignancies and is therefore a major global health concern [1,2]. Its high mortality rate is attributed to non-specific symptoms such as abdominal distension and discomfort, which often result in late diagnosis when the disease has already metastasized [3]. Although current methods, such as transvaginal ultrasound and CA-125 blood tests, are valuable, their low sensitivity for early-stage detection limits their effectiveness. Consequently, there is a pressing need for more accurate and accessible detection technologies for early, more precise and accessible diagnosis of ovarian cancer [4].

Modern disease diagnostics increasingly rely on biomarkers. Today, biomarkers biological molecules found in blood, other body fluids, or tissues that are indicative of a normal or abnormal process or a disease or condition are at the forefront of modern oncology [5]. A wide range of biomarkers have been identified in ovarian cancer. These biomarkers range from well-known glycoproteins such as CA-125 and HE4 to emerging candidates such as microRNAs, autoantibodies, and circulating tumor DNA (ctDNA), which can provide a rich source of diagnostic, prognostic, and therapeutic information [6]. Multiple biomarker detection holds promise for advances in early diagnosis and disease monitoring [7].

The conversion of biomarkers into clinically applicable tools requires advanced technologies such as biosensors [5]. These technologies include analytical devices that convert a biological binding event into a measurable electronic signal by combining a biological detection element (e.g., antibody, aptamer, enzyme) with a physicochemical transducer [8]. Among the various transduction methods, optical biosensors (measuring light absorption, fluorescence, or surface plasmon resonance) and electrochemical biosensors (measuring electric current, potential, or impedance) have emerged as very powerful platforms that

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offer compelling advantages for point-of-care applications [9]. Key characteristics of these platforms include High sensitivity and specificity, rapid analysis, low cost, potential for miniaturization, and the ability to perform label-free detection are among the characteristics of this emerging technology [10]. Fig. 1 illustrates the general classifications of biosensors.

This review article examines the important relationship between these two fields. Initially, we will present a detailed summary of the key biomarkers that play a role in the development and advancement of ovarian cancer. Following that, we will explore the essential concepts and recent progress in optical and electrochemical biosensor technologies. Ultimately, we will assess and critically review the present landscape of biosensor research focused on the detection of ovarian cancer biomarkers, address the obstacles in transitioning these innovative devices from research settings to clinical application, and highlight future possibilities for transforming ovarian cancer diagnosis and enhancing patient survival rates. Fig. 2**.** General scheme of biomarker identification by biosensors.

2. Biomarkers involved in ovarian cancer

2.1. Protein biomarkers: the established and emerging players

CA125 (cancer antigen 125), the gold standard biomarker widely used in ovarian tumor detection, is a high-molecular-weight glycoprotein. Although its normal function is not well understood, it appears to play a role in cellular immunity and may inhibit natural killer (NK) cell cytotoxic responses [11,12]. CA125 expression is elevated in 90 % of patients with epithelial ovarian cancer and is used in postmenopausal women with a sensitivity of 50 % to 60 % and a specificity of 90 % [11,13]. CA125 expression is the most widely used biomarker in cancer therapy, in tissues derived from Müllerian and coelomic epithelium, thus suggesting its potential use in the early diagnosis of ovarian cancer [14]. Given that elevated CA125 levels may occur up to a year before clinical diagnosis, it can be useful in addition to early primary diagnosis, in the continuation of disease treatment, monitoring chemotherapy responses, and differentiating malignant pelvic masses from benign masses, detecting recurrence, and improving clinical trial design [15]. During chemotherapy, decreased CA125 expression can provide a favorable prognosis for the course of treatment, and serial CA125 measurements can be a good indicator for assessing disease stabilization and monitoring treatment outcomes [16]. However, factors such as the lack of CA125 expression in about 20 % of ovarian cancers and its increased concentration in some benign diseases such as liver cirrhosis, endometriosis, and peritonitis reduce its importance as an early diagnosis biomarker [17]. In addition, CA125 levels fluctuate during the menstrual cycle and pregnancy. Consequently, no screening technique recommends this biomarker for the general population [18]. However, the use of other biomarkers in addition to CA125 could be beneficial in increasing sensitivity for the early detection of the disease [12].

HE4 (human epididymal protein 4) is a member of the WFDC (whey four-disulfide core) protein family [19]. HE4 is a protease inhibitor primarily found in the epidermis and other male reproductive organs, and it is involved in regulating the activity of proteins involved in various cell cycle processes, such as sperm maturation and fertility [20]. HE4 expression is increased in ovarian cancer and as a serum biomarker it may be promising for early detection of ovarian cancer [21]. In studies investigating the performance of HE4 as a biomarker for ovarian cancer, its measurement in combination with CA125 is more sensitive than HE4 alone [22]. HE4 as a single marker had the highest sensitivity of 72.9 % at 95 % specificity and when measured simultaneously with CA125, the sensitivity reached 76.4 % at 95 % specificity [23]. In addition, for stage I disease, HE4 had the highest sensitivity with values of 45.9 % at 95 %, which did not increase when combined with the CA125 biomarker and other biomarkers [24]. Consequently, the use of HE4 as a complement to CA125 constitutes a promising biomarker panel in improving screening and early diagnosis of ovarian cancer [24].

MSLN (Mesothelin) is a membrane glycoprotein found in mesothelial cells lining the pleura, peritoneum, and pericardium, and its overexpression in most epithelial ovarian cancers has made it a target for cancer immunotherapy [25]. Studies have shown that cancer cells in the peritoneal mesothelial epithelium undergo cell adhesion mediated by CA125 and mesothelin, and this interaction may also play a role in the peritoneal metastasis of ovarian cancer [26]. Studies have shown that mesothelin and HE4 expression are increased in older women, so age is an important predictor of mesothelin and HE4 expression [27]. In addition, cancer cells with high mesothelin expression exhibit greater migration and metastasis [27].

KLK (Kallikreins) are low molecular weight proteases (30 KD) of the human kallikrein gene family located on chromosome 19q13.4 [28]. This biomarker is composed of 15 genes that, by encoding trypsin or chymotrypsin, disrupt various types of cancer, including ovarian cancer, which can have either a favorable or unfavorable prognosis [28]. In addition to regulating many physiological processes such as smooth muscle contraction, hormonal regulation, vascular cell growth/repair, and blood pressure, KLK-related peptidases play a complex role in the pathogenesis of cancer and diabetes [29]. In other words, some KLKs, such as KLK3 (PSA), have been used as cancer biomarkers, while others are effective in the progression of diabetes [30].

PSN (Prostasin) is a serine protease that, in addition to regulating epithelial sodium channels, stimulates salivary glands and ultimately prostate function, and plays a role in regulating insulin secretion by pancreatic beta cells [31]. PSN expression is increased in epithelial ovarian cancer and is produced at a higher level than in healthy controls

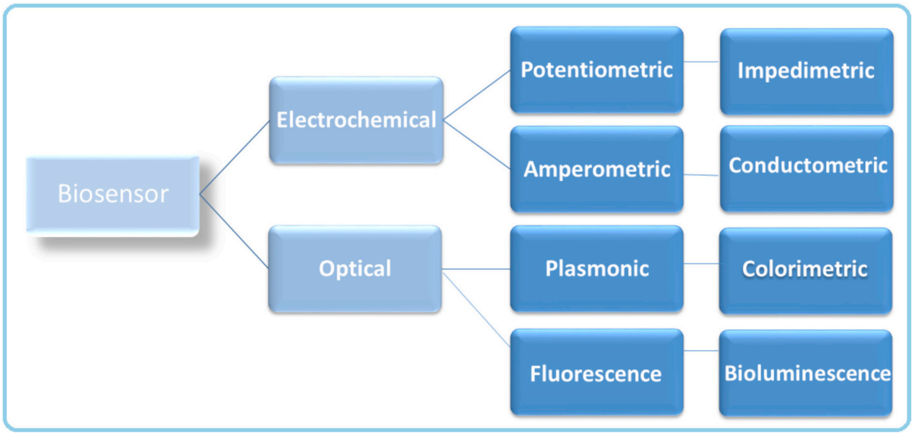

Fig. 1. Biosensor classification diagram.

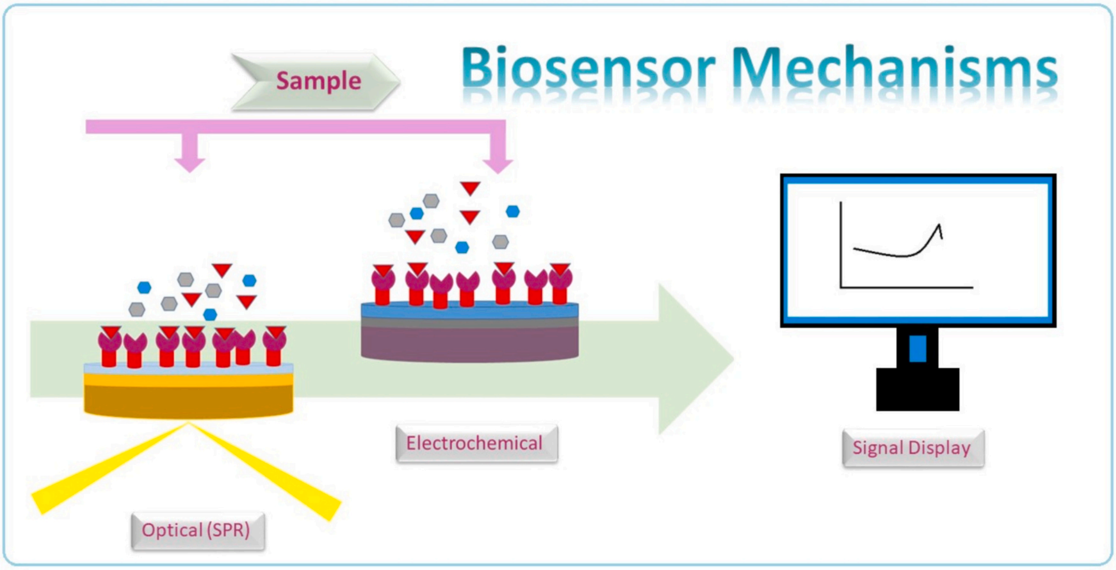

Fig. 2. General scheme of biomarker identification by biosensors.

[25]. This biomarker, either alone or in combination with CA125, can be used for the early detection of ovarian cancer and improve the sensitivity and specificity of cancer detection [32].

MUC1, a membrane mucin glycoprotein encoded by MUC1, forms a protective barrier in various tissues, including the airways, gastrointestinal tract, and reproductive tract [33]. MUC1 prevents the entry of pathogens and degrading enzymes by lubricating and hydrating cell surfaces [34]. MUC1 is overexpressed in most epithelial cell adenocarcinomas of the ovary and breast, and releases large amounts of the protein into the blood [35]. In cancer, this protein becomes hyperglycosylated and affects cell signaling, cancer growth, and metastasis. Therefore, identifying and quantifying MUC1 has promising results [36].

2.2. *Nucleic acid and cellular biomarkers: the molecular frontier*

miRNAs are short RNA molecules of 20 to 25 nucleotides in length that do not code for proteins [37]. These RNAs are naturally present in eukaryotes and can be easily isolated from cells, tissues, and various body fluids such as urine, blood, etc. [38]. Their role in regulating biological processes, such as gene expression by degrading or blocking the translation of specific target mRNAs, can be described as disrupted in various cancers [39]. By interacting with mRNAs, miRNAs can target and regulate the target mRNA by affecting the expression of different genes [40]. Studies have shown that miRNAs play a particular role in the development of diseases [41]. Furthermore, they are involved in various biological processes associated with cancer, such as tumor development, cell proliferation, differentiation, apoptosis, blood vessel formation, invasion and dissemination of cancer cells, treatment resistance, transformation of cell types, and forecasting disease prognosis [42].

Epigenetic changes include changes and modifications made to histone proteins or DNA methylation. This change does not affect the coding sequence but affects the structure and stability of DNA [43]. Epigenetic changes, due to their significant impact on cancer progression, can be applied as prognostic and diagnostic biomarkers [44]. On the other hand, biomarkers can be utilized to accurately track response to treatment [45]. Among the early events of cancer development is increased DNA methylation in promoter regions. Therefore, methylation in ctDNA was identified and introduced as a biomarker for ovarian cancer [46].

CTCs (Circulating tumor cells) are cancer cells that shed from the primary tumor and circulate in the bloodstream [47]. They are believed to play a key role in metastasis [48]. CTCs can help track the disease by becoming a source of neoplastic material, in addition to having the potential to be used for molecular and phenotypic analysis [49]. Although CTCs are limited in quantity, they can be isolated by a variety of new technological methods [50]. Table 1 summarizes the biomarkers and their characteristics.

3. Optical biosensor

3.1. *Fundamental principles of optical biosensing*

Optical biosensors convert the binding event into a measurable signal, thereby leading to the detection of biomolecular interactions [51]. This approach involves light-based techniques for quantitative analyte measurement, such as fluorescence (FL), absorption, or surface plasmon resonance (SPR), to quantify the analyte [52,53]. In these biosensors, a bioreceptor, such as an antibody, enzyme, or receptor, is immobilized on the sensor surface to capture the analyte through a specific interaction [54]. The binding of the analyte results in a change in one of the properties of light, such as a change in refractive index or light intensity. For example, in fluorescence, the light emitted by the labeled analyte is measured, or in absorption, the binding of the analyte results in a change in the absorption of light at a specific wavelength [55]. SPR is a new technique that has attracted much attention. It measures the analyte based on the change in the refractive index of light, whereby the analyte bound to a receptor on the surface of a gold chip causes changes in the surface [56]. The difference in angle created by the incident laser light before and after the analyte is bound is measured [56]. In another technique based on evanescent waves, the binding of an analyte changes the properties of a decaying electromagnetic wave near the sensor surface. The altered light signature is converted by a transducer into a measurable signal proportional to the analyte concentration [57–59].

3.2. *Optical biosensors for biomarker detection*

Developing simple and sensitive methods for detecting CA-125, the primary ovarian cancer biomarker, is crucial. In 2021, Mona N. Abou-Omar et al. designed an optical nanobiosensor consisting of gold nanoparticles (AuNPs) embedded with a Schiff base ligand in a thin sol-gel film of nanogold surface [60]. After irradiation with a wavelength of 340 nm, it is excited and emits a central fluorescence band at a

Table 1
Summary of biomarkers and their characteristics.

Biomarker	Molecular Type	Function	Association with Ovarian Cancer	Sensitivity/Specificity	Limitations
CA125	High molecular weight glycoprotein	Cellular immunity, possibility of inhibiting NK cell responses	Increase in 90 % of epithelial ovarian cancers; useful for monitoring treatment and diagnosis recurrence	Sensitivity: 50–60 % (postmenopausal); Specificity: 90 %	False positives in benign conditions (endometriosis, cirrhosis); not expressed in 20 % of ovarian cancers
HE4	WFDC family protease inhibitor	Sperm maturation, fertility, protein regulation	Overexpression in ovarian cancer; used for better diagnosis, usually in combination with CA125	Sensitivity: 72.9 % (single), 76.4 % (with CA125); Specificity: 95 %	Low sensitivity for Stage I (45.9 %); age-dependent expression
MSLN	Membrane glycoprotein	Cell adhesion (binds to CA125), peritoneal metastasis	Overexpression in ovarian cancer; a target for immunotherapy	N/A	Age-dependent expression; its role in metastasis makes it more prognostic than diagnostic
KLK	Proteases (kallikrein family)	Smooth muscle contraction, hormone regulation, cancer progression	Use of KLK3 (PSA) as a biomarker; other markers are associated with ovarian cancer prognosis	Varies by subtype (e.g., KLK5–7 associated with poor prognosis)	Complex roles (both pro- and anti-tumor effects)
PSN	Serine protease	Regulation of epithelial sodium channels, insulin secretion	Overexpressed in epithelial ovarian cancer	Improves sensitivity/specificity when combined with CA125	Limited standalone data
MUC1	Membrane mucin glycoprotein	Forming protective barriers; lubricating cell surfaces	Hyperglycosylation in ovarian/breast cancers; release into blood	N/A	Non-specific (elevated in other adenocarcinomas)
miRNAs	Non-coding RNAs (20–25 nt)	Regulating gene expression by targeting mRNAs	Dysregulated in ovarian cancer; impact on tumor growth, metastasis, and treatment resistance	High tissue/fluid specificity (e.g., miR-200 family)	Complex profiling; requires validation
Epigenetic	DNA methylation/ histone changes	Changing gene expression, without changing the DNA sequence	Promoter methylation (e.g., BRCA1) in ctDNA as an early diagnostic biomarker	N/A	Requires advanced detection methods
CTCs	Circulating tumor cells	Metastasis: A resource for molecular analysis	Separate from ovarian tumors; useful for tracking progress	Isolation challenges (rare in blood)	Technically demanding to isolate/ analyze

wavelength of 423 nm. To detect CA-125, the fluorescence signal must be quenched. In this study, samples from patients with ovarian cancer were evaluated in comparison to healthy women to determine the sensitivity and specificity of the device for the detection of CA-125. The findings showed that the present biosensor, with a sensitivity of 97.35 % and specificity of 94.29 % can detect biomarkers in a wide linear range between 2.0 and 127.0 units/mL for CA-125 with a detection limit (LOD) of 1.45 units/mL. Due to the interference of CA-125 with CEA, CA 15–3, and CA 19–9 in real samples, CA-125 was first incubated with CA-125 antibody, then after antigen-antibody separation, the biomarker

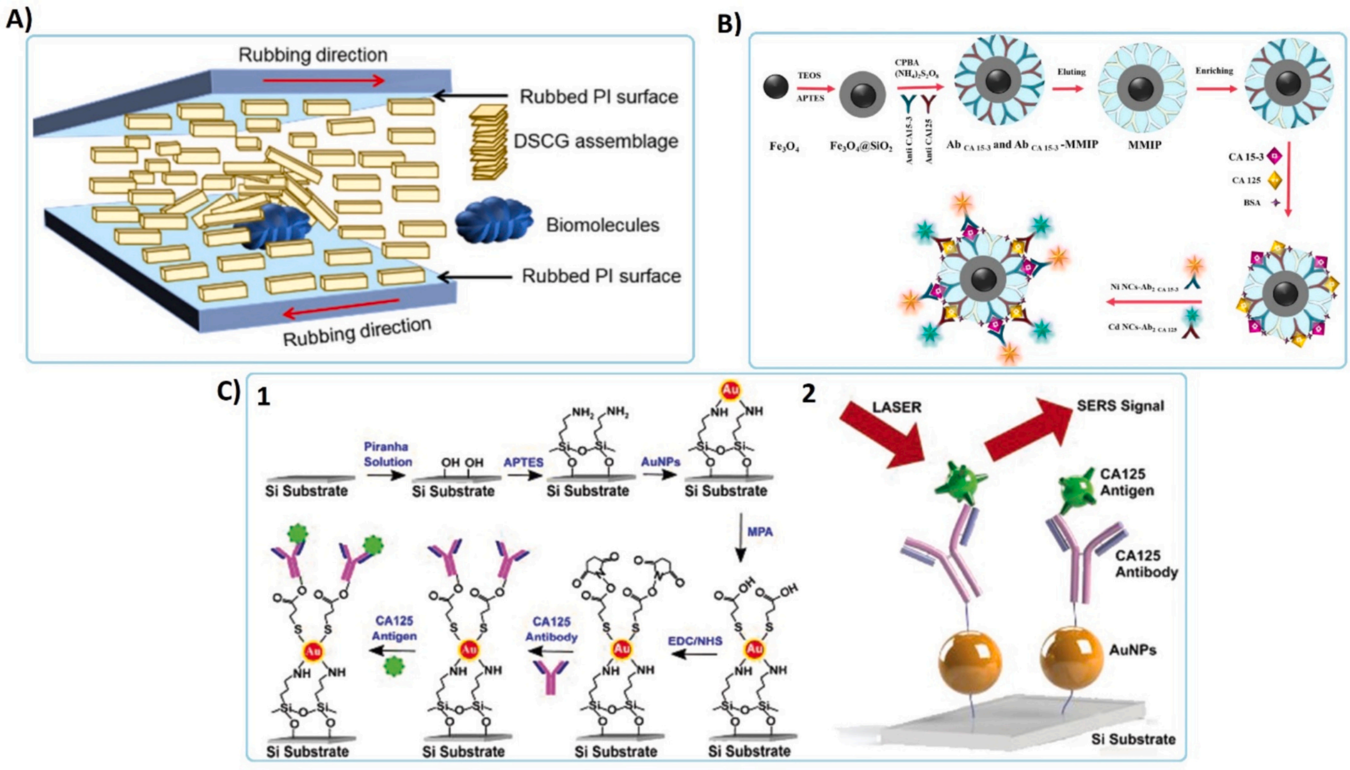

Fig. 3. A- Disruption of DSCG columnar structures by biomolecules [61], B- Schematic representation of the multiplex MIP-FL sandwich immunoassay designed for the concurrent detection of CA 125 and CA 15–3. [62], C (1)- The steps for depositing CA125 antibody and antigen onto self-assembled AuNPs are outlined, (2) Description of the chemical processes involved in label-free SERS detection of the CA125 cancer antigen, which generates Raman spectra from the AuNPs film [63].

was measured with the nanosensor.

In various studies on the biosensing potential of liquid crystals, although lyotropic chromonic liquid crystals (LCLC) are more biocompatible than thermotropic liquid crystals (LC), less attention has been paid to LCLCs. In a 2021 paper by Hassanin Shaban et al., a sensing mesogen in an LCLC-based biosensor with a nematic phase, a common mesophase between thermotropic LCs and LCLCs, was developed from disodium chromoglycate (DSCG) [61]. The platform was designed to be homogeneously aligned by the planar anchoring power of the polyamide. This planar alignment was disrupted in the presence of proteins such as bovine serum albumin (BSA) or the cancer biomarker CA125 captured by an anti-CA125 antibody, generating an optical signal. The wavelength and optical signal dependent on the analyte concentration were investigated using transmission spectroscopy in the visible spectrum using parallel or crossed polarizers. The measurement of CA125 was performed by immobilizing 10–10 g of CA125 antibody, with an LOD of 1.1 × 10–10 g/mL. Fig. 3A shows the disruption of platform alignment in the presence of proteins such as bovine serum albumin (BSA) or the cancer biomarker CA125.

To avoid false detection of tumors, it may be desirable to use two biomarkers in clinical diagnosis. In 2021, Delnia Bahari et al. designed a specific and sensitive FL detection method based on molecularly imprinted polymers for the simultaneous measurement of tumor markers CA125 and CA15–3 [62]. Nickel nanoclusters (Ni NCs) and noble cadmium nanoclusters (Cd NCs) were used as emitting surfaces in this biosensor due to their economical and efficient nature, then magnetic graphene oxide (GO-Fe3O4) was added as a support for molecularly imprinted polymers. FL emission at wavelengths 330 and 500 nm, with the same excitation wavelength, can be produced in a single experiment for both Ni NCs and Cd NCs. Nanocomposites exhibit high photoluminescence efficiency, strong stability, and outstanding biocompatibility, and because they are cost-effective, they can serve as alternatives to costly fluorescent emitters for effective simultaneous analysis. The measurement of biomarkers CA 125 and CA 15–3 in the prepared solution was achieved with a very low detection limit of 50 μ units/mL. On the other hand, satisfactory results were obtained in the measurement of biomarkers in blood sera compared to ELISA. The multiplex MIP FL sandwich immunoassay for the simultaneous detection of CA 125 and CA 15–3 is shown in Fig. 3B.

In recent years, imaging of biomolecules using surface-enhanced Raman spectroscopy (SERS) has garnered considerable attention as an analytical tool due to its label-free approach. This technique Surface-enhanced Raman spectroscopy (SERS) has gained significant attention as a label-free analytical tool for biomolecule imaging. In a study conducted by Ilknur Tunç et al. in 2020, a self-assembled monolayer of gold nanoparticles was utilized on the SERS platform for the detection of the CA125 antibody-antigen complex [63]. In this method, hot spot structures are created around gold AuNPs by creating highly enhanced electromagnetic fields due to the spatial distribution of SERS enhancement on CA125 proteins at the nM concentration level. Despite the observation of blinking behavior, time-resolved SERS mapping of CA125 antibody-antigen pairs was recorded repeatedly. Therefore, it was concluded that the blinking behaviors are related to single-molecule recognition. Fig. 3C shows the steps of antibody and antigen deposition on self-assembled AuNPs and the chemical processes for label-free SERS detection of cancer antigen CA125 to generate Raman spectra of gold nanoparticle films.

MSLN, a biomarker overexpressed by ovarian tumor cells, interacts with CA-125 to promote metastatic progression. Therefore, early detection of both biomarkers could help in the diagnosis and treatment of premetastatic disease. In this regard, Erenildo Ferreira de Macedo et al. (2024) designed a biosensor based on the surface plasmon resonance imaging (SPRi) technique enhanced with AuNPs [64]. To obtain the LOD of CA-125 and MSLN, sequential injections were performed in the analytical range of 9 to 120 nm, and the results were 3.03 nm and 13.62 nm, respectively. Chip functionalization and protein addition were performed using a sciFLEXARRAYER (scienion) staining robot, which is capable of producing multiple spots in a single column with a volume of approximately 100 nanoliters/ drop. The staining solutions included CA-125, MSLN, and the corresponding antibodies, anti-CA-125, and anti- MSLN.

In 2025, Bo Wang et al. conducted a study to design a biosensor made of a tapered fiber coated with PDMS combustion product and graphene oxide (PGTF) for highly sensitive detection of MUC1 [65]. Since the PDMS combustion product has a rough surface texture, it significantly increases the specific surface area of the fiber structure. In addition, the integration of the PDMS combustion product with the fiber coating material facilitates the light leakage from the core. This eliminates the need to thin the tapered fiber waist by creating a strong transient field and interference effect, ultimately improving the mechanical strength and sensitivity of the biosensor. Graphene oxide was applied to the surface of the PDMS combustion product-coated tapered fiber using a layer-by-layer self-assembly technique, and its surface was modified with MUC1 antibody. Graphene oxide, with its numerous oxygen-containing functional groups and wrinkled surface structure, serves as a binding site for biomolecules. According to the results, the PGFT biosensor has a low LOD (0.11 pM), excellent specificity, and reusability, making it suitable for applications in disease marker detection and medical diagnosis.

In a separate study, Na Li et al. developed a dual-mode SERS colorimetric aptasensor aimed at detecting MUC1 [66]. This research combined SERS probes with magnetic separation to leverage their distinctive benefits for quick and effective detection of MUC1. This dual-mode aptasensor facilitates quick diagnosis with colorimetric indicators visible to the naked eye, enabling faster screening. Additionally, SERS-based identification enhanced the sensitivity of the analysis to a LOD of 0.1 units /mL. The integration of SERS and colorimetric methods boosts the efficiency of MUC1 detection while preserving the benefits of both techniques. In this study, magnetic nanobeads were functionalized with aptamers specific to MUC1 to isolate MUC1 from intricate biological samples, while gold-silver core-shell nanoparticles, modified with Raman reporters and complementary sequences for MUC1, serve as signal markers that can simultaneously generate SERS signals and colorimetric changes. Consequently, this approach provides an effective detection range.

Another study details a novel label-free aptasensor that exploits the orientational properties of nematic liquid crystals (LCs) for MUC1 detection [67]. The sensor is constructed using amine-functionalized aptamers that are attached to the surface, with the LCs acting as the responsive components. When MUC1 interacts with the bound aptamers, a complex is formed that changes the orientation of the LCs, shifting them from a homotropic state to a random configuration. This variation in the orientation of the LCs can be easily observed through polarized light microscopy, where the optical appearance of the LCs shifts from dark to bright. The sensing system exhibits a high sensitivity with a LOD of 5 fg/ mL, and it demonstrates remarkable specificity in identifying MUC1 without requiring any additional labeling or amplification steps.

Aptamer-linked gold nanostars (AuNSs) represent a promising strategy for targeted biomarker detection by combining specific molecular recognition with unique plasmonic properties. Tozivepi Aaron Munyayi et al. (2024) developed a colorimetric biosensor for the detection of MUC1, in which AuNSs were linked to the S2.2 aptamer [68]. Given the high colorimetric presence of the MUC1 protein on the surface of cancer cells, the detection mechanism was designed based on the specific interaction of the S2.2 aptamer with the MUC1 protein. Upon binding of the S2.2 aptamer to MUC1, concentration-dependent aggregation of AuNSs was observed as a color change. This biosensor LOD of 450 cells/ well in both aqueous and serum media. A summary of optical biosensors is summarized in Table 2.

Table 2
Types of optical biosensors for ovarian cancer detection.

Bio-sensing Method	Detected biomarker	Signal Transducers	Immobilized molecules	LOD	Sample	Ref.
nanobiosensor	CA-125	AuNPs	coated with Schiff base	1.45 units/mL	CA-125 solution	[60]
Immunosensor	CA-125	LCLCs	Ab to CA-125	1.1 × 10–10 g/mL	CA-125 solution	[61]
Immunosensor	CA125 and CA15–3	Ni NCs and Cd NCs	Imprinting polymer, Ni NCs, Cd NCs and GO-Fe3O4	50 µ units/mL	CA125 and CA15–3 solution	[62]
Immunosensor	CA125	AuNP	Ab to CA-125	–	CA-125 solution	[63]
Immunosensor	CA-125 and MSLN	AuNPs	Ab to CA-125, and MSLN	3.03 nm and 13.62 nm	CA-125 and MSLN solution	[64]
Immunosensor	MUC1	PGTF	Ab to MUC1	0.11pM	MUC1 solution	[65]
Aptasensor	MUC1	Au NPs and Ag-cDNA	Aptamer to MUC1	0.1 units/mL	MUC1 solution	[66]
Aptasensor	MUC1	Nematic LC	Aptamer to MUC1	5 fg/mL	MUC1 solution	[67]
Aptasensor	MUC1	AuNSs	Aptamer	450 cells/ well	solution of MUC1and human serum	[68]

4. Electrochemical biosensors for ovarian cancer biomarkers

4.1. *Fundamental principles of electrochemical biosensing*

The general structure of electrochemical biosensors for ovarian cancer detection typically comprises three fundamental components: (1) **bioreceptor layer**, responsible for the specific recognition and binding of ovarian cancer biomarkers; (2) **electrode surface**, which serves as the interface where the biomolecular interaction occurs; and (3) the **detection system**, which converts the biological recognition event into a measurable electrical signal [69,70]. Electrochemical biosensors function through a series of selective recognition and signal transduction steps, transforming a biological interaction into an electrical response that can be quantitatively analyzed. The process begins with the immobilization of a biorecognition element such as an antibody, aptamer, or nucleic acid probe onto the electrode surface, enabling selective and sensitive detection [53,71]. A general classification of biosensors and a summary of their mechanism of action are given in Fig. 4. **Immunosensors** are a type of electrochemical biosensor that rely on the high specificity of antigen–antibody interactions to detect ovarian

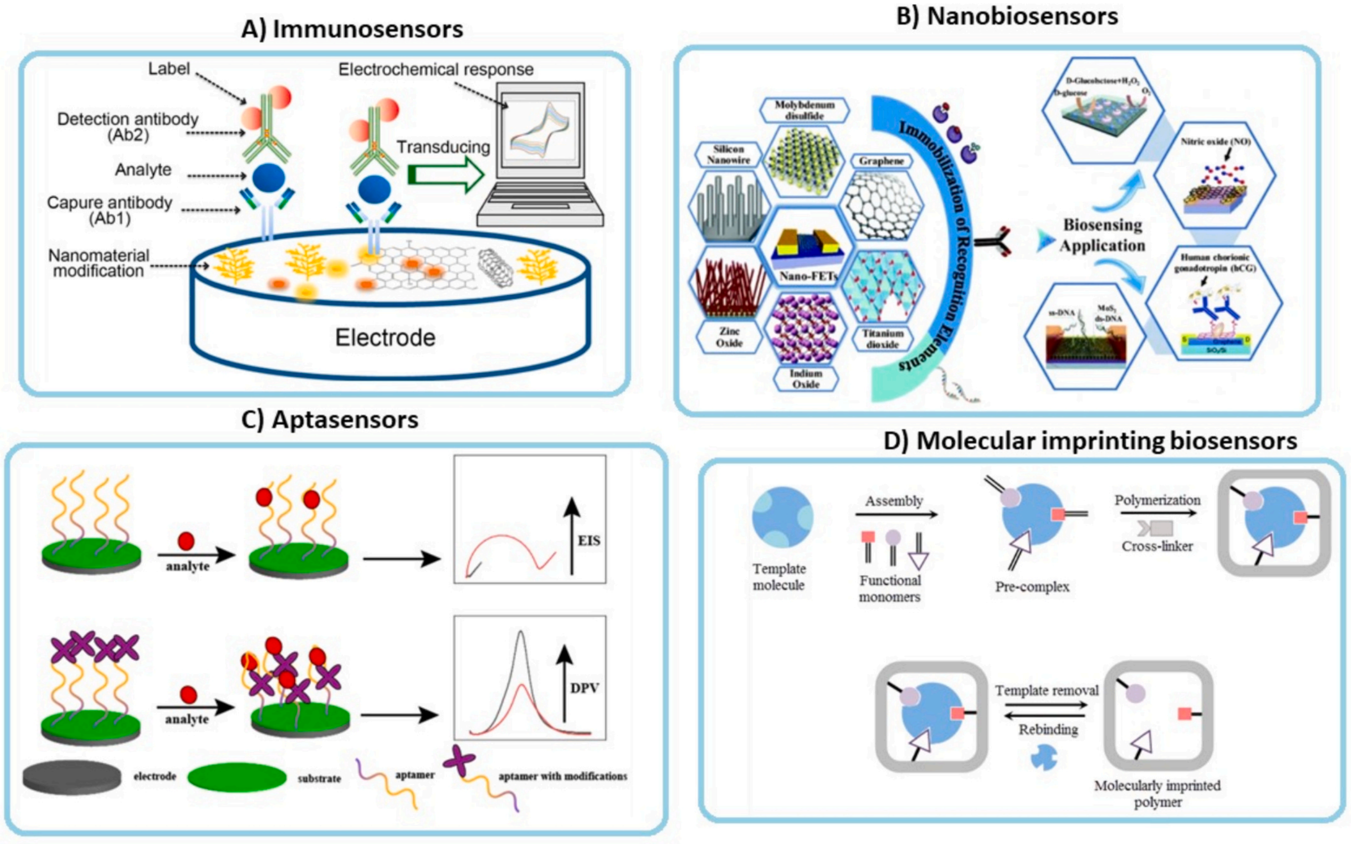

Fig. 4. Schematic classification of biosensors based on their recognition and transduction mechanisms. Biosensors are classified into four main types: A) Immunobiosensors, which utilize antigen–antibody interactions for highly specific detection of biomolecules [75]; B) nanobiosensors, which incorporate nanomaterials such as nanoparticles, nanotubes, or quantum dots to enhance sensitivity and signal transduction [76]; C) Aptasensors, which employ synthetic oligonucleotide aptamers as biorecognition elements offering high affinity, stability, and reusability [77]; and D) Molecularly imprinted biosensors, which rely on molecular imprinting polymers that create selective recognition sites complementary to target molecules in shape and functionality [78].

cancer biomarkers. Immunosensors leverage antibody–antigen specificity to sensitively detect target proteins, making them particularly well-suited for ovarian cancer biomarkers such as CA-125 and HE4. CA-125 and HE4 are clinically established markers in ovarian cancer (often evaluated together via the ROMA risk algorithm), so immunosensor platforms have been developed to quantify both analytes concurrently with high precision.

4.2. Electrochemical biosensors for biomarker detection

Samadi Pakchin et al. in 2020 designed a novel sandwich-type electrochemical immunosensor for the ovarian cancer biomarker CA125 (MUC16). They modified a glassy carbon electrode with three-dimensional reduced graphene oxide–multiwalled carbon nanotube (3DrGO-MWCNT) composites and incorporated polyamidoamine/gold nanoparticles (PAMAM/AuNPs) to enhance conductivity and antibody loading. An O-succinyl-chitosan–magnetic nanoparticle carrying toluidine blue acted as a tracer label. Under optimized conditions, this sensor achieved an extremely low detection limit (~6 μU/mL) over a very wide linear range (0.0005–75 Units/mL) for CA125 [72]. More recently, Cotchim et al. in 2023 reported a portable, label-free CA125 immunosensor based on hierarchical microporous carbon derived from waste coffee grounds. Their screen-printed electrode was coated with this carbon and decorated with AuNPs to capture anti-CA125 antibodies using a smartphone-connected potentiostat, they detected CA125 in human serum with a limit of detection of 0.4 U/mL and linear range of 0.5 to 50.0 U/mL ($R^2 = 0.9995$) [73]. In other study, Krathumkhet et al. (2023) developed a CA125 immunosensor using a carbon-ink/carbon-dot/ZnO composite electrode on ITO and silver@polypyrrole (Ag@PPy)–labeled antibodies for signal amplification. This sensor delivered an ultralow LOD (~0.1 fg/mL) and covered an astonishing linear range from 1 attogram/mL to 100 ng/mL for CA125, reflecting the synergistic conductivity of the nanocomposite and redox activity of the Ag@PPy label [74].

Kamaç et al. in 2023 introduced a disposable, label-free dual electrochemical immunosensor on bifurcated screen-printed carbon electrodes for simultaneous detection of CA125 and HE4. The electrodes were modified with reduced graphene oxide, polythionine and AuNPs, and individual antibodies for CA125 and HE4 were immobilized on separate sensing spots. By using differential pulse and square-wave voltammetry, this platform achieved sensitive, high-selectivity measurement of both markers in overlapping concentration ranges (approx. 1–100 pg/mL for one and 1–50 ng/mL for the other) [79] Fig. 4A, shows the steps of manufacturing the CA125-HE4 dual immunosensor. Finally, Xu et al. in 2024 reported a sandwich-format immunosensor specifically for HE4. They employed Prussian Blue (PB) as a covalently bound electrochemical label and a functionalized titanium-based metal–organic framework (TiMOF) nanocomposite (TiMOF–Ketjen black–AuNPs) to amplify the signal. In this design, PB-conjugated secondary antibodies provided intense redox currents, while the TiMOF nanocomposite enhanced electron transfer and antibody immobilization. This sensor achieved a broad linear detection range from 0.1 to 80 ng/mL and an exceptionally low LOD (0.02 ng/mL) for HE4, demonstrating strong potential for clinical ovarian cancer diagnostics [80]. Of course, in most of the studies described, nanoparticles have been used in the immunosensor structure to improve sensitivity and conductivity and can also be introduced as nanobiosensors. In fact, nanomaterials have become integral to electrochemical biosensors for ovarian cancer biomarkers because their unique properties dramatically enhance sensor performance. For example, carbon-based nanostructures like multi-walled carbon nanotubes (MWCNTs) and graphene quantum dots (GQDs) provide very large surface areas for antibody or probe immobilization and excellent electron conductivity, so that target binding produces amplified electrochemical signals [81,82]. CNT/AuNP hybrid electrodes have detected cancer-related nucleic acids at sub-picomolar levels (e.g. an Multi-Walled Carbon Nano Tubes/AuNP sensor gave a miR-223 LOD of ~0.73 pM, in linear dynamic response ranging from 1pM to 10 nM) in the result, significantly improved sensitivity and detection limits. Likewise, noble-metal nanoparticles (especially AuNPs) are routinely employed as labels or electrode modifiers: their biocompatibility and surface plasmon properties amplify signals while also improving conductivity. An impedimetric immunosensor using Au—Ag core–shell NPs rapidly (≈20 min) detected CA125 with high specificity and minimal interference, illustrating the gains in speed and sensitivity that AuNPs confer. These biosensors provided measurable changes in their signal associated with CA125 levels increased from 1 to 150 IU/mL ($R^2 = 0.994$), while maximum direct response of 1 to 100 IU/mL has been demonstrated for impedance biosensors to date [83,84]. Two-dimensional MXene materials combine ultrahigh conductivity with rich surface chemistry, yielding “remarkable” low detection limits for ovarian markers [85]. Zhou et al. in 2025 designed a dual-channel immunosensor with vertically aligned $ZnO@TiO_2$ core–shell nanotube arrays, employing dopamine and cytosine redox probes for CA125 detection; differential pulse voltammetry showed a wide linear response range, which was as follows: 0.1–1000 mU/mL with $R^2 = 0.996$ and LOD = 0.0002 mU/mL for cytosine and 0.1–100 mU/mL with $R^2 = 0.992$ and LOD = 0.0025 mU/mL for dopamine, alongside high reproducibility and selectivity [86]. Kivrak et al. in 2025 designed a multiplexed electrochemical biosensor on a carboxylated graphene oxide electrode for simultaneous detection of ovarian-cancer miRNAs (miR-200c and miR-141) using methylene blue- and ferrocene-labeled hairpin probes. This square-wave voltammetry sensor exhibited linear ranges 0.1 pM–10 nM and LODs ≈of 0.03 pM for both miRNAs [87]. Fig. 5C shows the sequential approach to fabricating a biosensor, the “signal-off” technique, for the simultaneous detection of miRNA-related ovarian cancer biomarkers. Semiconducting nanomaterials also boost performance: for instance, a carbon-ink/ZnO–carbon-dot electrode was highly biocompatible and conductive, achieving a CA125 LOD of ~0.1 fg/mL, and L-cysteine–capped ZnS quantum dots on an electrode enabled fM (≈10ˆ–14 M) detection of ovarian cancer miRNAs [74]. Together, these studies show that integrating nanomaterials (AuNPs, CNTs, QDs, MXenes, ZnO, etc.) multiplies signal amplification through enhanced surface area and electron transfer, and often improves biocompatibility of the interface. The net effect is greatly enhanced sensitivity and markedly lower detection limits in ovarian cancer biosensors – advances that bring such devices closer to clinical applicability [88]. In recent years, the design and development of electrochemical aptasensors has received much attention for various medical uses, especially the rapid and accurate diagnosis of ovarian cancer. This type of biosensors designed based on biding Single-stranded DNA or RNA molecules (aptamer) with target molecules [89]. Ni et al. in 2022 designed a label-free electrochemical aptasensor using magnetic α-Fe_2O_3/Fe_3O_4 hollow nanorods decorated with Au nanoparticles to amplify the signal of a CA125 DNA aptamer, achieving a linear range of 5–125 U/mL and LOD 2.99 U/mL [90]. In recent studies related to the development of biosensors with new technologies, design and construction of artificial receptors for the detection of target molecules have received much attention. Wang et al. in 2019 designed a molecularly imprinted polypyrrole (MIP-PPy) sensor on a gold screen-printed electrode for the selective detection of CA-125, achieving a wide linear range (0.01–500 U/mL) and an exceptionally low LOD of 0.01 U/mL in spiked human serum samples [91]. Yang et al. in 2025 designed a disposable immunosensor using a $Ti_3C_2T_x$ MXene/NH_2-carbon-nanotube composite on a screen-printed electrode for CA125 detection, they were able to achieve a linear range 1 mU/mL–500 U/mL with excellent selectivity and stability, and accurate detection method in clinical serum samples [92]. Arezoo Saadati et al. developed electrochemical biosensor for CA125 using a matrix of Ag-DPA-GQDs modified with conductive CysA-Au nanoparticles, onto which an anti-CA125 antibody was immobilized [69]. A matrix composed of Ag-DPA-GQDs (silver nanoparticles on graphene quantum dots functionalized with D-penicillamine) was modified with conductive CysA-Au nanoparticles, on which an anti-

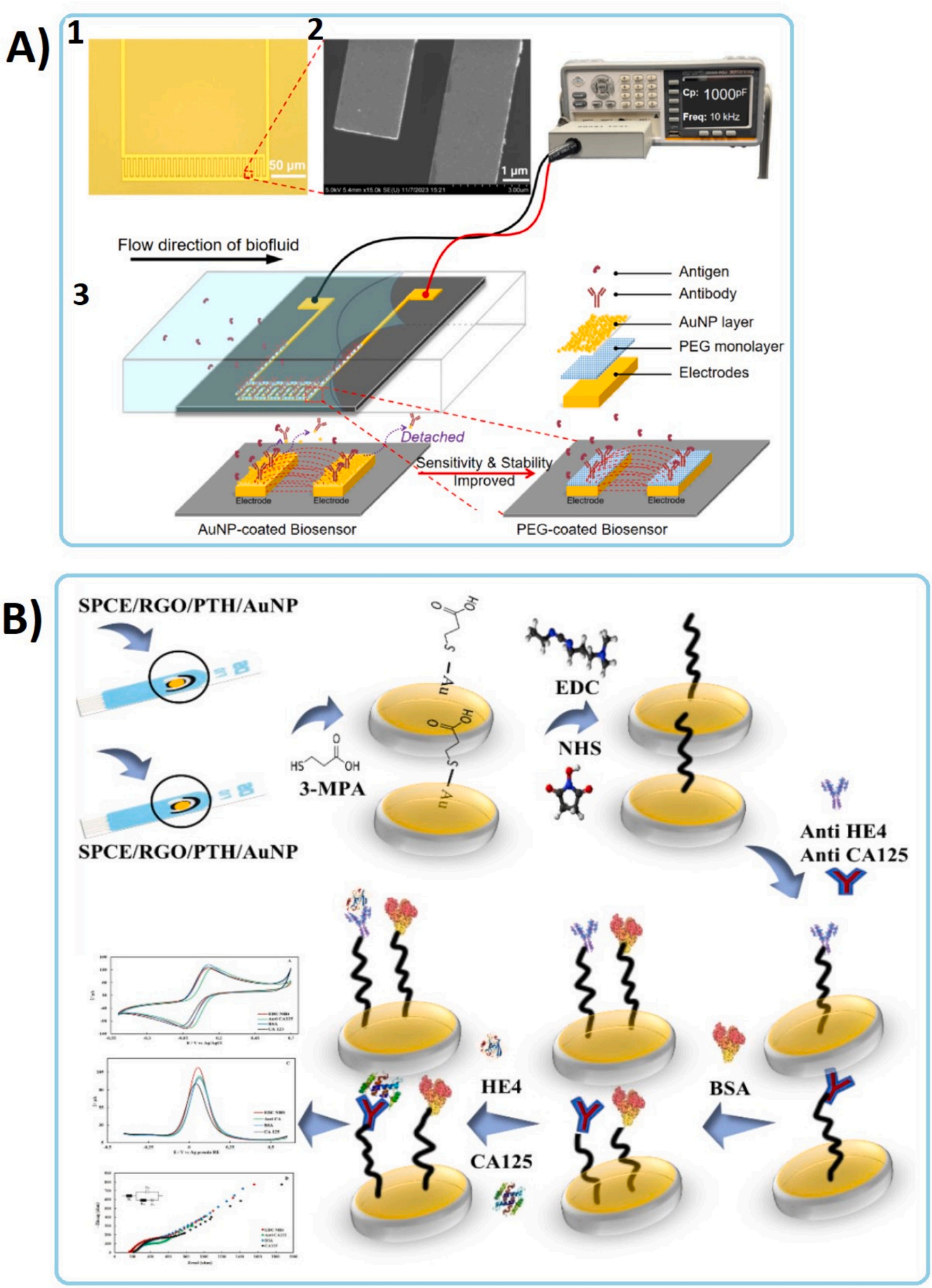

Fig. 5. **A:** (1) A top-down view of the gold interdigitated electrodes at 200× magnification. (2) A scanning electron microscope (SEM) image of the surface of the gold interdigitated electrodes. (3) The experimental setup of the PEG-coated biosensor for detecting CA-125 antigen under microfluidic flow conditions, along with a comparison between AuNP and PEG-coated biosensors [99]. **B:** The scheme illustrates the fabrication phase of CA-125 and HE4 immunosensors [100]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

CA125 antibody was incorporated to adsorb CA125. The process of binding the antibody to the matrix involved creating a covalent link between the carboxyl group of its fragment crystallizable (Fc) region and the amine group of the CysA-Au nanoparticles. Although this immunosensor displays low stability, it demonstrates effective performance in the early detection of CA125. Experiments were conducted using both real plasma samples and in vitro samples. The electrochemical behavior of the immunosensor was analyzed using the differential pulse voltammetry (DPV) method, showing a linear range of 0.001–400 U/mL and a LOD of 0.001 U/mL (Fig. 4B). A summary of optical biosensors is reported in Table 3.

5. Point of care devices for ovarian cancer biomarkers

5.1. Fundamental principles of point-of-care devices

The main goal of designing Point-of-Care Devices (POC) devices is to create analytical tools that can perform diagnostic tests immediately at the point of care, eliminating the need for a centralized laboratory [93]. POC testing has significantly contributed to rapid, easy, and cost-effective diagnosis by providing immediate results and allowing testing to be performed wherever the patient is, whether in a clinic, ambulance, pharmacy, or even their own home [94]. Most POC devices are integrated, miniaturized analysis systems that act like a complete laboratory workflow on a chip, cartridge, or test strip [95]. The most common architectures are lateral flow immunoassays (LFIA), which includes classic “dipstick” tests used for home pregnancy and COVID-19 rapid antigen testing. These tests are based on immunochromatography, where a sample containing the target analyte binds to immobilized receptor molecules (antibodies) on a nitrocellulose membrane, producing a detectable color or fluorescence change (e.g., via gold nanoparticles or latex beads) [96,97]. Another type is Microfluidic Devices (Lab-on-a-Chip), which are placed inside a plastic cartridge connected to a reader. Very small volumes of sample are agitated using capillary action, pneumatic pumps or centrifugal force, etc. [98].

5.2. Point-of-care devices for biomarker detection

Capacitive sensors use AuNPs to immobilize antibodies, but the problem of gold nanoparticle aggregation leads to instability of biomarker detection in flow-based systems. In this regard, in a study conducted by Yudong Wang et al., a microfluidic-based (POC) diagnostic tool was developed for CA-125 detection under microfluidic shear flow conditions, which was overcome by using a 2 KDa polyethylene glycol (PEG) layer to immobilize CA-125 antibodies on gold-bonded electrodes [99]. Next, a comparison was made to compare the performance of PEG and AuNP-coated biosensors in detecting CA-125 antigens under static drop and microfluidic flow conditions. Under static conditions, the capacitive signal of the PEG-coated biosensor was 2.2 times stronger (5660 pF vs. 2551 pF at 10 kHz) than that of the AuNP-coated biosensor. On the other hand, the PEG-coated biosensor had much more stable detection (only 2.9 % signal reduction) under microfluidic shear flow than the AuNP-coated sensor (32.4 % signal reduction). Therefore, it can be concluded that the results of biomarker detection by PEG-coated biosensor in microfluidic POC devices are more reliable and sensitive (Fig. 5A).

Melike Bilgi Kamaç et al. developed a label-free immunosensor on disposable screen-printed carbon electrodes, modified with reduced graphene oxide, polythionine, and gold nanoparticles, for the simultaneous measurement of CA125 and HE4 [100]. Differential pulse voltammetry, square wave voltammetry, and electrochemical impedance spectroscopy methods were used for the electrochemical determination of antigens in four different linear ranges (1–100 pg/mL, 0.01–10 ng/mL, 10–50 ng/mL, and 50–500 ng/mL). The immunosensors were highly stable and showed 60 days of usability and 16 weeks of storage stability. They showed high selectivity in 9 different antigen mixtures and were reusable for up to 9 re-use cycles. In addition, for point-of-care testing, CA125 and HE4 were detected with a LOD of pg mL − 1 in serum samples (Fig. 5B).

Yuzhen Wang et al. reported an innovative portable microfluidic platform for ultrasensitive detection of ovarian cancer biomarkers CA125 and HE4, which utilizes platinum nanozyme (PtNP)-induced cascade signal amplification with a gas-based visual amplification (VAC) chip [101]. PtNPs act as nanozymes to catalyze the polymerization of dopamine to form polydopamine (PDA). PDA then further amplifies the signal by adsorbing PtNPs modified with 4-mercaptophenylboronic acid. This biosensor is a dual antibody sandwich system consisting of magnetic silica nanoparticles coated with receptor antibodies and PtNPs with diagnostic antibodies. Also, the target biomarkers (CA125, HE4) form a sandwich complex, leading to their accurate detection. Due to the presence of gas-based VAC in the biosensor, POCT was possible and detection was performed with an LOD of 0.001 units/mL for CA125 and 0.1 picograms/mL for HE4.

Luhai Wang et al. used a microfluidic chip system to simultaneously detect protein and nucleic acid biomarkers [102]. For rapid, sensitive, and multiplex detection, microfluidic point-of-care molecular testing (POCT) and microfluidic homogeneous luminescence immunoassay (CLIA) were integrated, combining both homogeneous CLIA and nucleic

Table 3
Types of electrochemical biosensors for ovarian cancer detevtion.

Bio-sensing Method	Detected biomarker	Signal Transducers	Immobilized molecules	LOD	Sample	Ref.
Immunosensor	CA-125	Glassy carbon	Ab to CA-125	6 μ units/mL	Human serum	[72]
Immunosensor	CA-125	Hierarchical microporous carbon	Ab to CA-125	0.4 μ units/mL	Human serum	[73]
Immunosensor	CA125	Carbon-ink/carbon-dot/ZnO	ITO and Silver@polypyrrole (Ag@PPy)–labeled antibodies	0.1 fg/mL	Human serum	[74]
Immunosensor	CA125 and HE4	Dual screen-printed carbon	–		Blood samples	[79]
Immunosensor	HE4	Titanium-based metal–organic-framework	Prussian Blue (PB)-conjugated secondary antibodies	0.02 ng/mL	human serum	[80]
Nanosensor	ovarian-cancer miRNAs	carboxylated graphene oxide	methylene blue and ferrocene labeled hairpin DNA	0.03 pM		[87]
Aptasensor	CA125	Au NPs	–	2.99 units/mL		[90]
Molecular imprinting biosensor	CA-125	gold screen-printed	Electropolymerization of pyrrole	0.01 units/mL	Spiked human serum	[91]
Molecular imprinting biosensor	CA125	screen-printed carbons	Ti3C2Tx-MXene/amino-functionalized carbon nanotubes		human serum	[92]
Electrochemical Immunosens	CA125	Ag-DPA-GQDs	Anti-CA125 Antibody	0.001 U/mL	human serum	[69]

acid amplification on a single chip. In this biosensor, the protein biomarker HE4 was detected by CLIA and the nucleic acid biomarker miR-92a was detected by microfluidic POCT, achieving high sensitivities of 15 pM for HE4 and 10 fM for miR-92a in human samples. This versatile method shows high potential for measuring diverse cancer biomarkers, enabling multidimensional disease diagnosis. A summary of optical biosensors is reported in Table 4.

6. Challenges and opportunities in clinical application

Despite the excellent performance of the biosensor technologies investigated in research settings, their clinical application for managing ovarian cancer presents challenges. Addressing these challenges is crucial to translating laboratory success into successful use in the patient [103].

6.1. *Analytical and pre-analytical validation*

The transition from a research prototype to a clinically validated tool is only possible with thorough analytical validation that accurately reflects its real-world application [104].

Sample Matrix Effects: Most studies report results related to buffered or spiked serum. Therefore, the performance of biosensors in complex and heterogeneous clinical samples such as plasma, ascites, or urine, which contain multiple interfering substances (e.g. lipids, heterophilic antibodies, other proteins), should be carefully investigated due to the possibility of false positives or negatives [105].

Standardization and Reproducibility: The major challenge in standardizing biosensors across platforms is the variability in bioreceptor (antibody/aptamer) classes, nanomaterial synthesis, and fabrication protocols, which can lead to inconsistent results between laboratories and devices. Therefore, demonstrating high inter- and intra-assay reproducibility is essential for regulatory validation [106].

Stability and Durability: Studies rarely report on the long-term stability of biodetection elements (e.g., antibodies, aptamers) and functionalized sensor surfaces under storage conditions. However, given that a POC device maintains its sensitivity and specificity for months, it is still possible to use it [106].

6.2. *Clinical validation and diagnostic utility*

Superior analytical sensitivity does not automatically equate to clinical utility.

Blind clinical trials: Biosensors must undergo validation in extensive, forward-looking, blinded clinical trials that encompass not only individuals diagnosed with ovarian cancer but also essential control groups, including those with benign gynecological conditions (such as endometriosis and ovarian cysts), other forms of cancer, and healthy participants [107]. This is essential for determining genuine clinical sensitivity and specificity, surpassing the limit of detection (LOD) criterion [108,109].

Early detection capability: The ultimate goal of using biosensors is early detection. Therefore, it is important to validate biosensors in patients with stage I and II ovarian cancer, which are often under-researched in early studies. The ability to detect the disease before the onset of symptoms is key to reducing mortality [110].

Multiplexing for improved specificity: As highlighted throughout this review, no single biomarker is perfect for ovarian cancer diagnosis. The real potential of biosensors lies in their ability to perform multiplex detection of biomarker panels (e.g., CA125, HE4, miRNA-200 family) [21]. Therefore, future work should focus on validating such panels to enhance their predictive value and to more effectively distinguish ovarian cancer from other malignancies and benign diseases than single-analyte tests [111].

6.3. *Regulatory and commercialization barriers*

Unfortunately, the path to converting an academic diagnostic device into a commercial diagnostic device is a complex and costly one. For example, regulatory approvals such as regulatory approval from agencies such as the FDA (US Food and Drug Administration) or CE (European Commission), which include a comprehensive record of safety, efficacy, and manufacturing quality (Good Manufacturing Practices, GMP), are required, a process that is often unfamiliar to researchers [112]. Despite the advertising of biosensors as being inexpensive, cost estimates often include the cost of the raw materials for each assay. In contrast, when the cost of larger-scale production is low, the reader device for optical or electrochemical systems must be manufactured cheaply enough to be economically viable for healthcare systems [113]. For POC applications, the device should be exceptionally straightforward, requiring only a few steps to ensure it can be operated by individuals without specialized laboratory training. A key aspect that is frequently absent in devices at the research stage is integrated sample preparation, such as blood separation implemented on a microfluidic chip [114]. It is by proactively exploring and reporting on these practical challenges that future research can fulfill its promise to revolutionize the diagnostic paradigm for ovarian cancer and accelerate the adoption of biosensors [115].

7. Conclusion and future perspective

This review highlights the crucial relationship between the changing realm of ovarian cancer biomarkers and the swift progress in biosensor technology. We have outlined the transition from traditional glycoproteins such as CA-125 and HE4 to innovative molecular markers like miRNAs, ctDNA, and CTCs, which together establish the foundation for a new wave of diagnostic methods. The operational principles and latest advancements of optical (e.g., fluorescence, SPR, SERS) and electrochemical biosensors have been discussed as formidable platforms. Optical sensing methods have shown improved sensitivity and the ability to

Table 4
Summary of POC biosensors characteristics.

Bio-sensing Method	Detected biomarker	Device Type	Transducer	Immobilized molecules	LOD	Sample	Ref.
Capacitive immunosensor (PEG-coated Au electrodes) immunosensor	CA-125	Microfluidic lab-on-a-chip	Au interdigitated electrodes (IDEs)	CA-125 antibodies (immobilized via PEG layer)	Not explicitly stated * (Inferable from signal: ~1 U/mL likely)	Not explicitly stated	[99]
electrochemical immunosensor	CA125 and HE4	(Screen-printed carbon electrode) SPCE/rGO/AuNP	AuNPs, rGO	CA125 and HE4 antibodies	pg mL − 1	human serum	[100]
microfluidic-based immunosensor	CA125 and HE4	portable microfluidic biosensor	PtNPs	CA125 and HE4 antibodies	0.001 units, mL 0.1 picograms/mL	Human Serum	[101]
microfluidic-based immunosensor	HE4, miR-92a	Microfluidic Chip System	magnetic beads	HE4, miR-92a antibodies	15 pM, 10 fM	Artificial samples and Human Serum	[102]

analyze multiple targets simultaneously, while electrochemical sensors present unique benefits, including high sensitivity, portability, and affordability, making them well-suited for point-of-care uses. Additionally, the incorporation of nanomaterials such as gold nanoparticles, graphene derivatives, and quantum dots has proven to greatly enhance the sensitivity, durability, and overall effectiveness of these devices.

The review has also thoroughly assessed the considerable challenges in moving these biosensors from research laboratories into everyday clinical use. Looking forward, addressing these challenges is essential. The future direction involves the discovery and validation of novel genetic and epigenetic biomarkers to provide richer diagnostic insights. At the same time, efforts will concentrate on developing integrated, multimodal lab-on-a-chip systems that merge electrochemical and optical detection technologies to allow simultaneous analysis of various targets from minimal samples. Incorporating artificial intelligence and machine learning will be vital for interpreting the intricate data produced, consequently improving diagnostic precision. The ultimate objectives remain the creation of affordable, user-friendly, and portable devices for broad screening and the successful transition of these technological advancements from the lab to clinical settings. This will necessitate overcoming barriers in large-scale clinical validation, ensuring the stability of reagents, and establishing standardized manufacturing processes. By achieving these goals, the next generation of biosensors has extraordinary potential to transform the landscape of ovarian cancer treatment, ultimately enhancing patient survival through early detection and tailored therapeutic approaches.

CRediT authorship contribution statement

Yalda Jahanbani: Project administration. **Farzaneh Fathi:** Project administration, Data curation. **Hosein azizi:** Writing – review & editing. **Parvin Bastani:** Writing – review & editing. **Faride Ranjbari:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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