REVIEW ARTICLE ISSN:3139-8448 (print) & 3108-3218 (online)

BTS International Advanced Pharmaceutical Sciences Journal

Vol 01 | Issue 10 | October 2026 Journal homepage: www.btsempire.com

MANUSCRIPT ID: BTS1026002

OVERVIEW OF BIOSENSORS FOR OVARIAN CANCER DETECTION

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Received: 26 September 2026 | **Revised & Accepted:** 24 October 2026

Keywords: Ovarian cancer; Electrochemical Biosensors; optical biosensors; CA-125; HE4; Point of care diagnosis

Abstract:

Ovarian cancer is one of the leading causes of cancer-related mortality among women worldwide, due to the absence of proper screening methods and difficulty of detection at an early stage. Conventional techniques, such as enzyme-linked immunosorbent assays (ELISA), liquid chromatography mass spectrometry (LC-MS), and fluorescence-based methods, often require sophisticated equipment, trained personnel, and longer processing time, making point-of-care diagnosis difficult. Recently, biosensor technologies have emerged as promising alternatives for the sensitive, rapid, and cost-effective detection of ovarian cancer biomarkers. This review provides an overview of major biomarkers such as CA-125 (Cancer Antigen 125), HE4 (Human Epididymis Protein 4), and others associated with ovarian cancer. Recent advances in biosensors, such as electrochemical and optical, were used for the detection of the above biomarkers while establishing a comparative analysis highlighting their advantages and potential. Further, the integration of AI (Artificial Intelligence) into these technologies as a promising strategy for developments of next generation diagnostic platforms has also been discussed. Overall, biosensor technologies are the key for improving the early diagnosis and management of ovarian cancer, contributing to patient outcomes and reducing mortality.

INTRODUCTION:

According to the International Agency for Research on Cancer, an agency under the WHO (World Health Organisation), cancer is the main cause of deaths worldwide, accounting for 10 million deaths in 2024. Infections such as Human Papilloma Virus (HPV) and Hepatitis are responsible for approximately 30% of cancer cases in low- and lower middle-income countries. [1]

According to the Global Cancer Observatory (GLOBOCAN), India accounts for the highest percent of cancer cases at 57.5%, which may increase to 2.08 million by 2040 [6]. The main sign of cancer is the rapid and abnormal growth of cells invading the adjoining parts of the body and later spreading to other parts by metastasis. Cancer arises from the transformation of normal cells to tumor cells in a multistage process, causing progression from pre-cancerous lesion to malignant tumor. It is due to the interaction between a person's genetic factors and external agents like

Physical carcinogens: UV and ionizing radiation [2]

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Chemical carcinogens: tobacco smoke, alcohol, aflatoxin, and arsenic [2].
Biological carcinogens: Infections, bacteria, and parasites like Helicobacter Pylori, HPV, Hepatitis, and Epstein Barr virus [2, 3].
Based on the site of origin or their histology or tissue types, cancers are classified into several types given in table 1.

Classification based on the site of origin

It refers to the primary site of origin of cancer. Based on this, cancer may be of diverse types like ovarian cancer, breast cancer, lung cancer, prostate cancer, liver cancer, kidney cancer, and brain cancer.

Classification based on tissue type

According to ICD-O-3 (International Classification of Diseases for Oncology, Third Edition, tissue cancers are classified into six types:

A.CARCINOMA

It originates from the epithelial tissue and causes 80-90% of cancer cases. It is of two types: ADENOCARCINOMA (in an organ or gland) and SQUAMOUS CELL CARCINOMA (in squamous epithelium).

B.SARCOMA

It originates in connective and supportive tissues, including muscles, bones, cartilage, and fat.

C.MYELOMA

It originates in the plasma cells of bone marrow and is a type of blood cancer.

D. LEUKEMIA

It affects the bone marrow, the hub of blood cell production. Because bone marrow is cancerous, it produces excessive immature white blood cells, which are incapable of producing any action, making the patient more prone to infections. These are of distinct types:

1. Acute Myelocytic Leukemia
2. Chronic Myelocytic leukemia
3. Acute lymphatic, lymphocytic, or lymphoblastic leukemia
4. Chronic lymphatic, lymphocytic, or lymphoblastic leukemia
5. polycythemia vera or Erythremia

E. LYMPHOMA

It originates in the lymphatic system and is known as SOLID CANCERS as it affects the lymph nodes of the stomach, brain, and intestines. It is of two types- Hodgkin's lymphoma (Presence of Reed Sternberg cells) and Non-Hodgkin's Lymphoma (Reed Sternberg cells are absent)

Sl. No	ORIGIN	NAME
1	Cancer of Bone	OSTEOSARCOMA
2	Cancer of the Cartilage	CHONDROSARCOMA
3	Cancer of Smooth muscles	LEIOMYOSARCOMA
4	Cancer of the skeleton muscles	RHABDOMYOSARCOMA
5	Cancer of the membranous lining of the body cavity	MESOTHELIAL SARCOMA or MESOTHELIOMA
6	Cancer of Fibrous tissue	FIBROSARCOMA
7	Cancer of the Blood Veins	ANGIOSARCOMA or HEMANGIOENDOTHELIOMA

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Sl. No	ORIGIN	NAME
8	Cancer of the Adipose or Fatty tissue	LIPOSARCOMA
9	Cancer of the Neurogenic Connective Tissue in the Brain	GLIOMA or ASTROCYTOMA
10	Cancer of the Primitive Embryonic Connective Tissue	MYXOSARCOMA
11	Cancer of Mixed connective tissue	MESENCHYMOUS or MIXED MESODERMAL TUMOUR

TABLE 1. Classification of cancers based on tissues of origin

F. MIXED TYPES

It is a combination of two or more cancer components, such as carcinosarcoma and teratocarcinoma.

- **Classification based on grade**

Grade 1- Cells are well differentiated with slight abnormalities.

Grade 2- Cells are moderately differentiated and slightly more abnormal.

Grade 3- Poorly differentiated cells and very abnormal

Grade 4- Immature cells and primitive and undifferentiated cells.

2. OVARIAN CANCER

Ovarian cancer is a group of diseases originating in the ovaries as primary lesions slowly spreading to the fallopian tubes, or peritoneum [4,5]. India ranked second in ovarian cancer cases worldwide with a percentage of 76.5, following China [7]. The incidence of ovarian cancer starts at the age of 35, reaching its highest level between 55 and 64 years [4,8]. Due to the lack of effective screening tests and non-specific symptoms, which are usually mistaken for gastrointestinal issues, the early diagnosis of ovarian cancer has become incredibly challenging. According to the International Federation of Obstetrics and gynecology (FIGO), the survival rate for ovarian cancer at stage 1 is high, up to 90% than the advanced stages [10].

The World Health Organization classifies ovarian cancer into three broad categories based on the cells of origin:

Epithelial Ovarian Cancer: accounts for almost 90% of cases.It includes serous, endometrioid, clear cell, and mucinous subtypes.

Germ Cell Tumors: accounts for about 5% of cases. It arises from the cells that form eggs, that is, gametic cells.

Sex cord-Stromal Tumours- Accounts 2-5% of cases. It arises from the connective and hormone-producing tissues [35].

Since most cancer cases account for epithelial ovarian cancer, most pathophysiological research is carried out or focused solely on this. Based on these studies, the epithelial ovarian cancer pathogenic condition is divided into two based on the respective molecular profiles and clinical progress, namely, TYPE-1 and TYPE-2 tumors.

TYPE-1 tumors: These include low-grade serous, endometrioid, clear cell, and mucinous carcinomas, which tend to be genetically stable, grow slowly, and arise typically through a stepwise progression from a recognized precursor lesion, such as a borderline serous tumor. [36]

TYPE-2 tumors: These tumors are dominated by high-grade serous carcinoma, which is the main cause of major ovarian cancer deaths. These are genomically unstable, grow aggressively, and are diagnosed only at advanced stages [36].

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2.1 TUMOR MICROENVIRONMENT AND SPREAD

Ovarian cancer is shaped not only by tumor cells but also by the surrounding microenvironment:

ANGIOGENESIS- Tumor cells secrete angiogenic factors, particularly vascular endothelial growth factors (VEGF-A), which stimulate new blood vessel growth to support tumor expansion. This pathway is targeted therapeutically by anti-angiogenic agents like Bevacizumab [37].

IMMUNE EVASION- Ovarian Tumours employ multiple mechanisms to escape immune surveillance, including the recruitment of immunosuppressive Tumour-associated macrophages and activation of checkpoint pathways, which contribute to treatment resistance [38].

PERITONEAL EVASION- Unlike many solid tumors that spread primarily through the bloodstream, ovarian cancer characteristically sheds cells directly into the peritoneal cavity. These cells travel with peritoneal fluids and are implanted throughout the abdominal and pelvic peritoneum and omentum, producing widespread intra-abdominal disease and malignant sites typically of advanced stage.

CHEMORESISTANCE- Recurrent and progressive resistance to platinum-based chemotherapy is a major driver of mortality and is linked to DNA-repair pathway restoration, drug efflux mechanisms, and tumor heterogeneity [37].

Although no screening method is recommended for the early detection of ovarian cancer yet, biomarkers play a key role in the early diagnosis of cancer as well as in analyzing the treatment progress [10].

2.2 CURRENT SCREENING GUIDELINES AND CLINICAL CONTEXT

Ovarian cancer is uncommon in the general population (an age adjusted of 11 cases per 1,00,000 women per year in the United States) and produces vague, non-specific symptoms. Most cases are diagnosed only after the disease has already spread beyond the ovary, when survival is markedly poorer than for stage 1 disease [10]. Large, randomized trials of population screening using transvaginal ultrasonography, serum CA-125 testing, or a combination of both have not demonstrated a reduction in ovarian cancer mortality, and screening has been associated with a substantial rate of false-positives results leading to unnecessary surgery. On this basis, the United States Preventive Services Task Force (USPSTF) recommends against ovarian cancer screening in asymptomatic women who are not known to carry a high-risk hereditary cancer syndrome, a position that is consistent with the guidance of other major medical and public health organizations [73]. This lack of a validated population screening test is the central clinical motivation for the development of highly sensitive, low-cost, point-of-care biosensor platforms capable of detecting

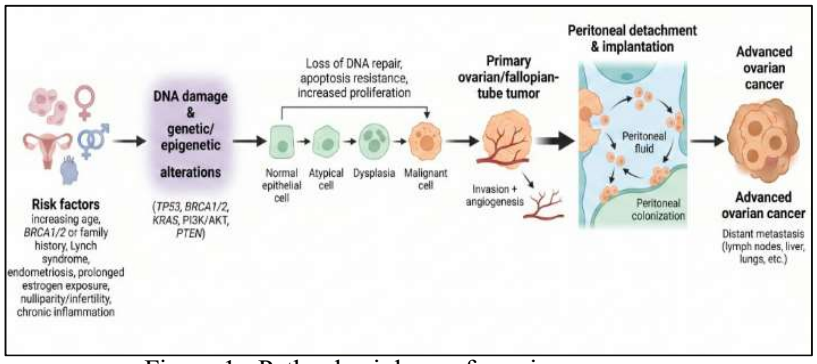

Figure 1 : Pathophysiology of ovarian cancer

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ovarian cancer biomarkers earlier and more reliably than single-analyte immunoassays, particularly in symptomatic women or those at elevated hereditary risk, where a rapid and inexpensive triage test could meaningfully shorten the pathway to specialist referral.

3. BIOMARKERS

Biomarkers are the biological molecules produced or elevated during a pathological process and act as a key factor for the diagnosis of Cancers or any other pathological condition [10].

CA-125 stands for Cancer Antigen 125, and HE4 stands for Human Epididymis Protein 4 are the two major biomarkers indicating the presence of Ovarian cancer. Most of the electrochemical and optical biosensors designed for ovarian cancer detection are selective toward these biomarkers. Cancer Antigen 125 is a mucin-type glycoprotein, which when combined with HE4 causes the risk of Ovarian cancer as per the identifications in clinical practice [16]. Besides these, tumor-derived exosomes, circulating microRNAs, circulating tumor DNA, or circulating tumor cells, and a few proteins like carcinoembryonic antigen (CEA) and mucin 1 (MUC1) [28, 29] also play a key role in ovarian cancer identification [30].

3.1 CA-125 (Cancer Antigen 125)

CA-125 was first described in the early 1980s as an antigen recognized by the monoclonal antibody OC125 [39]. It was subsequently identified as an epitope of MUC16, a member of the mucin family of glycoproteins encoded by a gene located on chromosome 19 [40, 41]. Under normal physiological conditions, MUC16/CA-125 is expressed by epithelial cells derived from coelomic and mullerian epithelia, including the lining of the peritoneum, pleura, pericardium, fallopian tubes, and endometrium [42, 43].

3.1.1 BIOLOGICAL FUNCTION

Beyond being a diagnostic marker, MUC16 has also been implicated in mechanisms that promote tumor progression. Experimental work using MUC16 knockdown in ovarian cancer cells has demonstrated increased susceptibility of tumor cells to natural killer cell-mediated lysis, along with improved survival in murine tumor models, suggesting that MUC16 may contribute to immune evasion [43]. In contrast, constitutional knockout of the MUC16 gene in mice is compatible with normal development, viability, and fertility, indicating that MUC16 is not essential for reproduction and that its principal clinical relevance lies in disease states rather than baseline physiology [44]. Serum CA-125 concentrations have also been linked to alterations in glycosylation patterns, with changes such as reduced sialylation correlating with tumor-associated elevations, an observation that has generated interest in glycan-based assays as a refinement of conventional CA-125 testing [45].

3.1.2 CLINICAL APPLICATIONS

CA-125 is used in three principal clinical contexts: as an adjunct in the triage of women with pelvic and adnexal masses to estimate the likelihood of malignancy. It is used as a tool for monitoring response to chemotherapy in women with confirmed epithelial ovarian cancer and for the detection of recurrence during post-treatment surveillance [42, 46]. Longitudinal, serial monitoring of CA-125 is considered more informative than any single measurement and rising trends can precede clinical or radiological evidence of relapse [47]. A conventional reference threshold of 35 U/mL is commonly applied to distinguish normal from elevated values, although this cutoff was derived from postmenopausal populations and its performance varies with age, menopausal status, and comorbid gynecologic conditions [42, 48].

3.1.3 DIAGNOSTIC PERFORMANCE AND LIMITATIONS

CA-125 is elevated in approximately 80% of women with epithelial ovarian cancer overall, but only in about half of those with stage 1 disease, meaning a substantial proportion of early, potentially curable cancers might be missed if CA-125 is used in isolation [49]. Pooled estimates from comparative meta-analyses have reported sensitivity for CA-125 in the range of 0.75–0.82 for distinguishing malignant from benign adnexal masses, with a

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typically lower specificity in the region of 0.75–0.83 and a comparatively high false-positive rate [50]. The specificity of CA-125 is constrained because it can be elevated by numerous benign and non-gynecologic conditions, including menstruation, pregnancy, uterine fibroids, pelvic inflammatory disease, peritonitis, and most notably, endometriosis, as well as by malignancies outside the ovary [42, 49, 50]. A population-based cohort study conducted in UK primary care further demonstrated that the diagnostic performance of CA-125 in symptomatic women differs meaningfully by age group, reinforcing that its interpretation should be contextualized to the clinical setting rather than applied as a uniform threshold [51].

3.2 HUMAN EPIDIDYMIS PROTEIN 4

HE4 is encoded by the WFDC2 gene (Whey-acidic-protein-four-disulfide-core domain protein 2), located on chromosome 20 [52]. The protein was originally identified in the epithelium of the distal epididymis and was later found to be secreted as a glycoprotein of approximately 25 kilodaltons, containing a single peptide chain with two whey-acidic-protein (WAP) domains stabilized by a four-disulfide core of eight cysteine residues [52]. HE4 was subsequently identified as a markedly overexpressed protein in ovarian carcinoma tissue relative to normal ovarian epithelium, prompting its evaluation as a complementary tumor marker [39, 53].

Under physiological conditions, WFDC2/HE4 is expressed across a range of normal epithelial tissues, including the respiratory tract (trachea, nasal epithelium, and pulmonary epithelium), distal renal tubules, and glandular structures such as the salivary glands, where it is thought to contribute to innate host defence of mucosal surfaces [52]. This broader tissue distribution means that CA-125, HE4, is not exclusively ovarian in origin, but its expression is not induced by the common benign gynaecologic conditions that confound CA-125 [39, 54].

3.2.1 BIOLOGICAL FUNCTION

The precise biological role of HE4 in tumorigenesis remains less well characterized than that of MUC16, but its consistent overexpression in epithelial ovarian carcinoma, together with its relative tissue-restricted normal expression pattern, has made it an attractive complementary diagnostic target [39, 53]. Unlike CA-125, serum HE4 concentrations have not been associated with changes in serum protein N-glycosylation patterns, suggesting that the two markers may reflect at least partially distinct aspects of tumor biology and may therefore provide complementary rather than variant information when measured together [45].

3.2.2 CLINICAL APPLICATIONS

HE4 received regulatory clearance in the United States for use, together with CA-125, in the Risk of Ovarian Malignancy Algorithm (ROMA), intended to estimate the likelihood of finding malignancy at surgery in women presenting with an adnexal mass [55]. It is used as an adjunct to clinical assessment and imaging rather than as a stand-alone screening or monitoring test [56]. HE4 has also been investigated in the context of disease surveillance, including the assessment of recurrence and monitoring of HE4 concentration trends across subsequent lines of chemotherapy in women with recurrent disease, although CA-125 remains the more established marker for longitudinal monitoring in routine practice [57].

3.2.3 DIAGNOSTIC PERFORMANCE AND LIMITATIONS

A meta-analysis pooling data from more than 2,600 subjects across multiple studies reported a sensitivity for HE4 of approximately 0.80 and a specificity of approximately 0.92, with a summary area under the receiver operating characteristic curve of roughly 0.95 and concluded that HE4 performed favorably compared with CA-125 on several of these metrics [58]. Other comparative analyses have found broadly similar sensitivity between the two markers, in the region of 0.75–0.80, but consistently more favorable specificity for HE4, typically cited in the range of 0.83–0.94 compared with 0.75–0.83 for CA-125 [50, 59, 60]. A key practical advantage of HE4 is that its serum concentration is unaffected by endometriosis, a condition that commonly causes false positive CA-125 elevations in

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premenopausal women, making HE4 particularly useful in the differential diagnosis of adnexal masses in this population [59, 61]. Reported false positives influences on HE4 include smoking and renal impairment and combined hormonal contraceptives containing estrogen and progestin have been associated with lower HE4 concentrations [59].

3.3 EMERGING AND COMPLEMENTARY BIOMARKERS

Although CA-125 and HE4 remain the most extensively studies circulating protein biomarkers for ovarian cancer, neither biomarker alone provides sufficient sensitivity and specificity for reliable early-stage population screening. Consequently, considerable research has focused on complementary biomarker classes, including tumour-derived exosomes, circulating microRNAs (miRNAs), circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), carcinoembryonic antigen (CEA), and mucin 1 (MUC1). These biomarkers differ substantially in their biological origin, concentration in clinical specimens, analytical requirements, and suitability for biosensor-based detection.

EXOSOMES: Tumour-derived exosomes are nanoscale extracellular vesicles released into biological fluids and contain proteins, lipids, messenger RNA, miRNAs, and other nucleic acids. Their molecular cargo can reflect characteristics of the tumour and therefore provides opportunities for multiplexed disease detection. Serum or plasma is commonly considered a relevant specimen, although urine and other body fluids have also been investigated. Major analytical challenges include efficient exosome isolation, discrimination of tumour-derived vesicles from normal extracellular vesicles, nonspecific adsorption, and the heterogeneity of exosome populations. Biosensor applications include antibody- or aptamer-based capture, electrochemical detection, SERS, and microfluidic platforms [28-32].

MicroRNAs (miRNAs): miRNAs are short non-coding RNA molecules that regulate gene expression and can become dysregulated during ovarian carcinogenesis. Circulating miRNAs are attractive biosensor targets because they can be detected in blood and may remain relatively stable when associated with protein complexes or extracellular vesicles. However, their short sequence-dependent secondary structures create challenges for selective detection. Electrochemical nucleic-acid sensors, molecular recognition probes, nanomaterial-assisted amplification systems, and optical biosensors have therefore been investigated for miRNA detection [28,29]

Circulating Tumour DNA (ctDNA): ctDNA consists of tumour-derived DNA fragments released into the circulation. Because ctDNA can contain tumour-associated mutations, copy-number changes, methylation patterns, and other genomic alterations, it has potential for molecularly specific cancer detection. Plasma is the principal specimen used for ctDNA analysis. However, ctDNA concentrations maybe very low, particularly in early-stage disease, creating challenges in extraction, amplification, sequencing and discrimination from background cell-free DNA. Biosensor approaches based on sequence-specific hybridization, electrochemical detection, and nanomaterial-assisted nucleic-acid recognition are being explored [29,30].

Carcinoembryonic antigen (CEA): CEA is a glycoprotein associated with several malignancies but is not specific to ovarian cancer. Consequently, its major valued is expected to arise from combination with other biomarkers rather than as a stand-alone ovarian cancer marker. Serum or plasma can be used for measurement, while the main analytical challenge is achieving sufficient specificity in the presence of other malignant and benign conditions. Electrochemical and immunosensor platforms can incorporate CEA into multiplex biomarker panels [28,29].

Mucin 1 (MUC1): MUC1 is a membrane-associated mucin that is aberrantly expressed or glycosylated in several epithelial cancers, including ovarian cancer. Its biological relevance to tumour-associated epithelial changes makes it a potential complementary

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biomarker. However, MUC1 is also expressed in normal epithelial tissues and therefore lacks sufficient disease specificity as an isolated marker. Serum/plasma immunodetection and multiplex biosensor approaches have been investigated, particularly in combination with CA-125 and other tumour-associated biomarker [28,29].

Overall, these emerging biomarkers provide complementary biological information rather than simply replacing CA-125 or HE4. Their major potential lies in multiplexed detection, in which protein, nucleic-acid, extracellular-vesicle, and cellular signals can be integrated to improve discrimination between malignant and benign conditions. However, analytical standardization, specimen handling, low-abundance detection, biological heterogeneity, and validation in sufficiently large clinical cohorts remain important barriers to translation.

3.4 COMPARATIVE SUMMARY OF CA-125 AND HE4

Table 2 summarizes the principal molecular, physiological, and diagnostic characteristics of CA-125 and HE4 based on the discussion above.

HE4 assay: FDA 510(k) clearance obtained in 2008; subsequent HE4 assay platforms received additional clearances. ROMA, incorporating HE4 and CA-125 with menopausal status, received FDA 510(k) clearance in 2011.

The combined interpretation of CA-125 and HE4, commonly performed by the Risk of Ovarian Malignancy Algorithm, together with menopausal status imaging, provides proper discrimination between benign and malignant adnexal masses.

4. CONVENTIONAL DIAGNOSTIC METHODS AND THE RATIONALE FOR BIOSENSORS

Because reliable diagnostic methods for ovarian cancer remain limited, and because symptoms are often mistaken for gastrointestinal issues, a number of conventional laboratory methods, including enzyme-linked immunosorbent assay (ELISA), liquid chromatography-mass spectroscopy (LC-MS), electrochemiluminescence (ECL), and fluorescence in situ hybridization or fluorescence spectroscopy, are used to quantify biomarker levels [11,12]. Although these methods offer excellent accuracy, they are expensive, time-consuming, and unsuitable for point-of-care (POC) testing; they require trained personnel and are characteristic of early-stage cancer [12,13,14,15]. This has created a clear need for reliable, noninvasive, low-cost, point-of-care diagnostic tools capable of detecting these biomarkers even at ultra-low levels [10,11].

5. BIOSENSORS

5.1 ELECTROCHEMICAL BIOSENSOR

These biosensors convert a biorecognition event into an electrical signal, that is, current, potential, impedance, or capacitance, at the surface of the working electrode. As they do not require the optical instrumentation step for

Feature	CA-125/MUC 16	HE4/WFDC2
Gene/ Chromosome	MUC16, Chromosome 19	WFDC2, Chromosome 20
Protein Class	High molecular weight (>200 kDa) mucin glycoprotein	Small (~25kDa) glycoprotein with two WAP and four disulfide domains
Normal Tissue Expression	Coelomic and Müllerian epithelia: peritoneum, pleura, pericardium, endometrium	Respiratory and reproductive epithelium; distal renal tubules; salivary glands

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Feature	CA-125/MUC 16	HE4/WFDC2
Reported Sensitivity	~0.75-0.82 for malignant vs. benign confounders	~0.75-0.80, broadly comparable to CA-125
Reported Specificity	~0.75-0.83; lower due to benign confounders	~0.83-0.94; superior to CA-125
Key Confounder/ False positives	Menstruation, pregnancy, endometriosis, fibroids, peritoneal inflammation, other cancers	Smoking status, renal impairment, combined hormonal contraceptives (typically lowers HE4)
Effect of endometriosis	Frequently elevated, reducing specificity	Unaffected, key advantage
Primary established clinical uses	Monitoring treatment response and recurrence in diagnosed epithelial ovarian cancer; adjunct in pelvic mass triage	Adjunct triage of adnexal/pelvic masses; component of the ROMA algorithm
Regulatory status (as an adjunct test)	FDA-cleared for monitoring; used off-label in triage	FDA-cleared (2008/2011) for pelvic mass risk assessment and as ROMA component
Combined performance (CA-125 + HE4/ROMA)	AUC up to ~0.90-0.96 when combined with HE4 and menopausal status	AUC up to ~0.90-0.96 when combined with CA-125 and menopausal status

Table 2. Comparative summary of CA-125 and HE4

transduction, these are compatible with miniaturized, low-cost systems, making them feasible for point-of-care testing [16,17].
These electrochemical biosensors are of diverse types.

5.1.1 IMPEDIMETRIC AND VOLTAMETRIC IMMUNOSENSORS
Electrochemical Impedance Spectroscopy (EIS) measures the change in the interfacial resistance due to the binding of the target biomarker to an antibody, While the Voltametric method, such as square wave voltammetry (SWV) and differential pulse voltammetry, monitors the resulting change in faradaic current [17]. An ultrasensitive impedimetric immunosensor for CA-125 demonstrated the potential of nanostructured electrode surfaces to improve analytical sensitivity [18]. In another study, a square-wave voltammetry (SWV)-based electrochemical biosensor achieved a reported detection limit of 0.01 U/mL over a linear range of 0.01-500 U/mL, with recovery values of 91-105% in artificial serum [[19]. These findings indicate strong analytical sensitivity and quantitative performance under the reported experimental conditions. However, they should not be interpreted as evidence that electrochemical biosensors have superior

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clinical sensitivity or diagnostic accuracy compared with conventional immunoassays.
Direct clinical comparisons require testing the same patient population using predefined diagnostic endpoints and reporting measures such as sensitivity, specificity, and area under the receiver operating characteristic curve.

5.1.2 APTAMER BASED ELECTROCHEMICAL SENSORS (APTASENSORS)

Aptamers are single-stranded DNA or RNA oligonucleotides selected for high affinity target binding, which offer stability, ease of chemical modification, and low-cost production. Thus, they are widely adopted in electrochemical ovarian cancer diagnosis. An aptasensor has immobilized a CA-125 specific aptamer on a gold electrode modified with graphitic carbon nitride, magnetic nanoparticles, and polyaniline using a hexacyanoferrate redox complex as a probe and achieved a detection limit of 0.298 U/mL over a range of 5-60U/mL and demonstrated high selectivity against interfering biomolecules in patient and healthy donor serum [20].

5.1.3ELECTROCHEMICAL DETECTION OF EXOSOMES AND NUCLEIC ACID MARKERS

During the initial stages of cancer or any other disease, tumor-derived exosomes and microRNAs are released into the circulatory system. Thus, several electrochemical biosensors have been developed especially for ovarian cancer-derived exosomes. One such approach is an entropy-driven autocatalytic DNA circuit combined with circular cleavage reactions to amplify electrochemical signals generated upon exosome capture, enabling the enzyme-free assay, which is also capable of distinguishing ovarian cancer patient samples from healthy controls [20].

5.1.4 NANOMATERIAL-ENHANCED ELECTROCHEMICAL PLATFORMS

Graphene derivatives, MXenes, and transition metal dichalcogenides, which are 2D nanomaterials, are incorporated into ovarian cancer electrochemical sensors to increase the electroactive surface area, improve the electron transfer kinetics, and provide additional sites for receptor immobilization [17]. Gold nanoparticles or reduced graphene oxide composites deposited by one-step electrochemical methods have also been used for building label-free immunosensors for CA-125, thus pushing the nanocomposite electrode engineering to electrochemical assays for clinically relevant sensitivity [21].

5.2 OPTICAL BIOSENSORS

Optical biosensors detect biorecognition events through changes in optical properties, such as refractive index, fluorescence intensity, Raman scattering, or color at or near a sensor surface. As many transduction mechanisms are inherently label-free and compatible with real-time complex measurements, they are extensively used in ovarian cancer detection [16, 22].
Optical biosensors are further of distinct types.

5.2.1 SURFACE PLASMON RESONANCE (SPR) AND LOCALIZED SPR (LSPR)

SPR biosensors monitor the shifts in resonance angle or wavelength of plasmon oscillations at a metal dielectric interface as the biomarker binds to an immobilized receptor layer, providing label-free, real-time detection [22]. Whereas LSPR relies on nanoparticle-supported plasmons than continuous metal film for HE4 biosensors. An early LSPR platform using silver nanoparticles and immobilized anti-HE4 antibody enabled the detection of HE4 in patient serum with results comparable to ELISA [23], while another design incorporating oriented antibody immobilization via Protein G extended the previous approach to non-invasive HE4 detection in urine, gaining a dynamic range spanning 1–10,000 pM [24]. SPR imaging, which uses a CCD camera and records the reflected light across an array of sensing spots, has also been used for HE4 quantification in human plasma, which gave validated results against a commercial Elecys HE4 immunoassay and a clinical

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cut-off around 150 pM differentiating malignant from benign [25].

5.2.2 SURFACE-ENHANCED RAMAN SCATTERING (SERS)

SERS biosensors exploit the enhancement of Raman scattering near the plasmonic nanostructures, which enables extremely sensitive, molecularly specific detection. A gold nanoplate-based sandwich SERS immunoassay developed for HE4 has attained a detection down to 10^{-17} M [26]. Although this value demonstrates the very high analytical sensitivity achievable with plasmonic signal amplification, it should not be interpreted as evidence of equivalent clinical sensitivity for early-stage ovarian cancer.

An analytical limit of detection obtained under controlled experimental conditions does not by itself establish clinical diagnostic utility. Clinical usefulness depends on the biomarker concentration distribution in relevant patient populations, assay performance in complex biological matrices, specificity, reproducibility, and the ability to distinguish early-stage ovarian cancer from benign conditions and healthy controls. Therefore, the reported 10^{-17} M value should be considered primarily an analytical performance characteristic of the reported SERS platform rather than a validated clinical detection threshold.

Where the original study uses buffer, spiked samples, artificial serum, or a limited clinical sample set, this matrix should be explicitly stated and distinguished from validation in independent patient cohorts. Larger prospective studies using clinically representative serum samples and predefined diagnostic endpoints are required before such an analytical LOD can be translated into a claim of early-stage clinical detection.

5.2.3 FLUORESCENCE, CHEMILUMINESCENCE AND COLORIMETRIC APPROACHES

Colorimetric assays, particularly those based on gold-nanoparticle aggregation or enzyme-linked color development, are popular and attractive for point-of-care use because results can be interpreted visually without the need for laboratory instruments [27].

6. COMPARATIVE ANALYSIS OF ELECTROCHEMICAL AND OPTICAL BIOSENSORS

The table summarizes representative analytical detection limits and reported clinical cut-off values for CA-125 and HE4 biosensors.

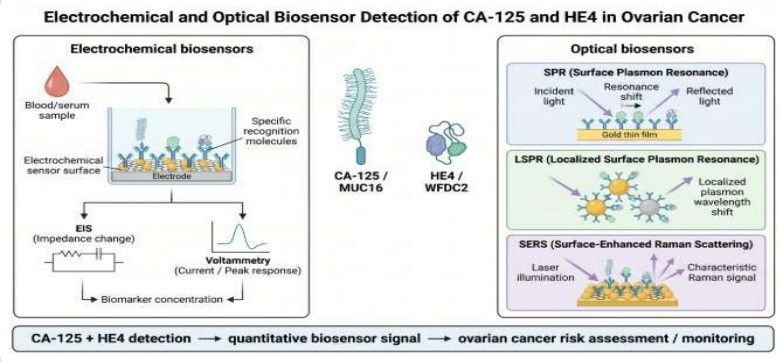

Figure 2. Schematic representation of electrochemical and optical biosensors for CA-125 and HE4 detection in ovarian cancer.

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Biomarker	*Biosensor Type*	*Reported analytical metric*	*Value*	*Unit*	*Sample/ Matrix*	*Reference*
CA-125	Electrochemical/SWV	LOD	0.01	U/mL	Artificial serum	19
CA-125	Aptasensor	LOD	0.298	U/mL	Serum samples	20
HE4	LSPR	LOD	1	pM	Urine	*24*
HE4	SPR imaging	Clinical Cut-off	~150	pM	Human Plasma	25
HE4	SERS	LOD	10^{-17}	M	Experimental assay (matrix not specified)	26

Table 3. Representative analytical detection limit and reported clinical cut-off values for electrochemical and optical biosensors targeting CA-125 and HE4. *pM – Picomolar (unit of concentration)

6.1 ANALYTICAL SENSITIVITY *VS* CLINICAL UTILITY

Very low analytical limits of detection (LODs) reported for ovarian cancer biosensors should not be interpreted as direct evidence of clinical diagnostic effectiveness. Analytical sensitivity describes the smallest concentration of an analyte that can be reliably distinguished from the assay background under defined experimental conditions. Clinical sensitivity, in contrast, describes the ability of a test to correctly identify patients with the disease within a clinically relevant population.

This distinction is particularly important for ovarian cancer because CA-125 and HE4 concentrations vary with disease stage, menopausal status, renal function, benign gynaecological conditions, and other biological factors. A sensor may therefore detect a biomarker at concentrations far below those normally encountered in clinical samples while still lacking sufficient specificity or clinical sensitivity to distinguish early-stage ovarian cancer from benign disease.

Several studies in the reviewed literature demonstrate excellent analytical performance using buffer, artificial serum, or limited clinical samples, whereas relatively fewer biosensor platforms have undergone large prospective validation using well-characterized patient cohorts. For examples, an electrochemical CA-125 sensor reported a detection limit of 0.01 U/mL with recovery of 91-105% in artificial serum [19]. This demonstrates strong analytical performance but does not by itself establish clinical diagnostic accuracy.

Similarly, the extremely low LOD reported for the HE4 SERS platform [26] demonstrates the capability of the transduction system to detect very small quantities of analyte, but the clinical relevance depends on the sample matrix, patient population, disease stage, assay specificity, and validation design.

Consequently, future biosensor studies should report not only LOD and linear range but also diagnostic sensitivity, specificity, receiver operating characteristic (ROC) analysis, confidence intervals and performance in independent patient cohorts. Comparison with clinically established assays should also be performed using predefined clinical endpoints. This distinction is essential for determining whether a highly sensitive laboratory biosensor can provide meaningful clinical benefit.

7. POINT OF CARE

Integration of these electrochemical and optical sensing technologies into microfluidics or lab on a chip format would enable the point of care for ovarian cancer testing. If these devices meet the World Health Organization's criteria of ASSURED, i.e., Affordable, Sensitive,

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Specific, User-friendly, Rapid and Robust, Equipment-free, and Deliverable to end users, then such platforms could represent a major step forward in reducing barriers to early ovarian cancer detection [31]. Nanostructured microfluidic exosome devices, which combine nanomaterial-modified electrodes or optical surfaces with microfluidic sample handling, have also been highlighted for early ovarian cancer diagnosis through exosome capture and quantification from small volumes of clinical samples [32].

8.ADDITIONAL BIOSENSOR PLATFORMS FOR OVARIAN CANCER DETECTION

Besides electrochemical and optical biosensors, several other classes of biosensors are used for CA-125 and HE4 detection, each offering a distinct sensitivity, instrumentation complexity, and POC. These biosensors include field-effect transistor (FET), piezoelectric (mass sensitive), photoelectrochemical (PEC), paper-based/microfluidic, and AI-integrated smart biosensors.

8.1 FIELD EFFECT TRANSISTOR (FET)

Field-effect transistor biosensors detect biomarker binding as a change in the conductance or voltage of a semiconductor channel functionalized with a recognition layer, offering label-free, real-time detection with the possibility of extremely low limits of detection due to direct electronic signal transduction [62]. Graphene and reduced graphene oxide (rGO) channels are particularly attractive because their high carrier mobility and large surface-to-volume ratio make them highly sensitive to the electrostatic perturbation caused by antigen aptamer or antigen antibody binding at the gate surface [62, 63].

An early flexible aptasensor combined carboxylated multi-walled carbon nanotubes with an rGO-based FET channel deposited on a polymethyl methacrylate substrate, enabling label-free, ultrasensitive detection of CA-125 while retaining mechanical flexibility suitable for wearable or conformal sensing formats [63]. More recent designs have pursued simultaneous detection of both molecularly imprinted polypyrrole nanotubes that created antibody-free recognition sites selective for the stability limitations associated with antibody-based receptors [64]. Separately, a genetic code expansion-assisted FET architecture used site-specifically oriented nanobodies to achieve highly reproducible signal amplification, reporting molar level detection of HE4 and CA-125 directly in serum within a portable POC prototype [65]. FET biosensors for CA-125 and HE4 detection act as a promising route toward decentralized, antibody-free ovarian cancer screening [62,66].

8.2PIEZOELECTRIC (MASS SENSITIVE) BIOSENSORS

Piezoelectric biosensors, most commonly implemented as quartz crystal microbalance (QCM) devices, detect biomarker binding as a shift in the resonant oscillation frequency of a piezoelectric crystal caused by the added mass of the captured analyte, providing a label-free detection mechanism that does not depend on optical or redox active reporters [67,68]. A self-assembled monolayer of cysteamine on a gold-coated QCM chip has been used to immobilize antibodies against mesothelin, a glycoprotein biomarker expressed in ovarian and other malignant tumors, illustrating the general immunosensor architecture adaptable to CA-125 class glycoprotein antigens [67]. Similar QCM immunosensor designs have used nanoparticle-modified chip surfaces to increase the antibody-binding surface area, improving both sensitivity and reproducibility for cancer-associated antigens and cells [69].

QCM-based platforms have also been applied directly to ovarian cancer serum samples, where the frequency shift produced by antibody binding to immobilized tumor cell antigens was shown to correlate linearly with antibody mass over a defined concentration range, enabling rapid discrimination between positive and negative samples [70]. Because piezoelectric sensing requires no labeling and can, in principle, be miniaturized alongside microfluidics, it is considered a complementary, label-free alternative to electrochemical and optical CA-125/HE4 immunosensors, although sensitivity to viscosity, temperature, and non-specific mass

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adsorption in complex serum matrices remains a practical limitation for clinical translation [68, 71].

8.3 PHOTOELECTROCHEMICAL (PEC) BIOSENSORS

Photoelectrochemical biosensors combine optical and electrochemical sensing. A photoactive semiconductor electrode generates a photocurrent under light illumination, and antigen-antibody binding at the electrode surface modulates this photocurrent, which is then measured electrochemically [72]. Because excitation (light) and detection (current) use separate energy forms, PEC biosensors can achieve very low background signal and correspondingly high sensitivity while retaining the low-cost, miniaturable instrumentation associated with electrochemical readout [72, 73]. Dual-signal amplification strategies employing semiconductor nanomaterials as photoactive labels have been used to push photoelectrochemical immunosensing of other tumor-associated antigens to sub-nanogram sensitivity, a strategy considered directly transferable to CA-125 and HE4 sensing given the structural similarity of the sandwich immunoassay format used across PEC and conventional electrochemical platforms [72]. PEC biosensing for ovarian cancer biomarkers remains comparatively less developed than voltametric or impedimetric electrochemical immunosensors but is increasingly cited as a promising next-generation transduction strategy because of its inherently low background and dual-mode (optical excitation, electrochemical readout) design flexibility [10, 72].

8.4 PAPER BASED AND MICROFLUIDIC (LAB-ON-CHIP) BIOSENSORS

Paper-based biosensors use capillary-driven flow through cellulose or nitrocellulose substrates to transport samples and reagents to a detection zone, where a colorimetric, fluorescent, or electrochemical signal is generated, offering an especially low-cost and equipment-free route to point-of-care testing that aligns closely with the WHO ASSURED criteria, i.e., Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment free, and Deliverable to all users [27, 31]. When integrated with nanomaterial-enhanced electrodes printed directly onto paper or polymer substrates, these platforms can retain much of the sensitivity of conventional electrochemical immunosensors while eliminating the need for benchtop instrumentation, syringe pumps, or external power in some configurations [31,33].

Microfluidic and lab-on-chip formats extend this concept by integrating sample handling, biomarker capture, and signal transduction on a single miniaturized device. Nanostructured microfluidic devices designed for exosome capture and quantification, for example, combine nanomaterial-modified capture surfaces with microfluidic channels to isolate and quantify ovarian cancer-derived exosomes from small volumes of clinical samples, reducing both reagent consumption and processing time relative to bench-top ELISA-based exosome assays [32]. These formats are considered a key enabling technology for translating the electrochemical, optical, FET, and piezoelectric sensing chemistries described above into deployable POCs, since they address sample handling and reagent delivery [31,32,33].

8.5 AI-INTEGRATED AND WEARABLE SMART BIOSENSORS

Artificial intelligence (AI) and Machine Learning (ML) are increasingly being integrated with biosensor platforms to improve interpretation of complex sensor signals, multiplex biomarker classification, and diagnostic decision support. Rather than relying exclusively on a signal features obtained from electrochemical, optical, Raman, or other measurements.

A representative example is the Exosome-SERS-AI approach reported by Shin et al [111]. The study used surface-enhanced Raman scattering (SERS) measurements of exosome samples and applied machine-learning methods for cancer classification. The dataset included 753 samples, with 233 samples used for model development and 520 independent samples used for testing. After anomaly filtering, 23,051 SERS signals were available for model training.

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A convolutional neural network (CNN) – based binary classification model was used to distinguish cancer from healthy controls, while a multilayer perceptron (MLP) model was subsequently used for cancer-type classification.

For cancer – versus – healthy classification, the reported area under the receiver operating characteristic curve (AUC) was 0.970 (95% confidence interval, 0.957-0.982), with sensitivity of 89.4% and specificity of 96.3% at the selected cutoff. In the analysis by disease stage, the sensitivity reported for early-stage cancer was 88.1% [111]. Importantly, the study used as independent test set that was not used to construct the final diagnostic model, providing a stronger validation strategy than simple training – set performance.

However, this study should not be interpreted as a validated ovarian – cancer – specific screening test. The model was designed for classification of multiple cancer types using exosome SERS signals rather than as a dedicated CA-125/HE4 ovarian cancer biosensor. Therefore, its results demonstrate the feasibility of combining high-dimensional biosensor data with AI rather than establishing the clinical utility of an ovarian cancer point – of – care device.

For ovarian cancer specifically, future AI-integrated biosensors should use clinically characterized datasets containing sufficient numbers of early – stage cases, benign gynaecological conditions, healthy controls, and relevant demographic and physiological subgroups. Model development should include patient – level separation between training and test datasets, cross – validation during model development, independent external validation, and reporting of sensitivity, specificity, AUC, confidence intervals, calibration, and clinically relevant predictive values. External validation across different institutions and populations will be particularly important before AI – assisted biosensors can be considered for routine clinical decision – making.

Platform	*Transduction principle*	*Key feature*	*Main Limitation*	*Reference*
FET/Nanowire	Change in channel conductance upon binding	Label-free detection; flexible and miniaturizable formats	Signal affected by ionic strength and surface effects	62-66
Piezoelectric/QCM	Resonant frequency shift caused by added mass	Label-free mass-sensitive detection	Sensitive to nonspecific adsorption, viscosity and temperature	67-71
Photoelectrochemical (PEC)	Light-induced photocurrent modulated by biomolecular binding	Low background signal; optical excitation with electrochemical readout	Requires controlled illumination and photoactive materials	10, 72, 73
Paper-based/ Microfluidic	Capillary flow with colorimetric or electrochemical detection	Low cost; minimal instrumentation; integrated sample handling	Quantitative performance and reproducibility can be challenging	27, 31-33
AI-integrated/ Wearable	Machine Learning-assisted interpretation of sensor signals	Multiplex signal processing and connected monitoring	Requires adequately sized, representative and independently validated datasets	29, 34

Table 4. Summary of additional biosensor platforms for CA-125/HE4 detection

Wearable and smartphone – integrated biosensor systems may further extend this approach by enabling decentralized acquisition and repeated measurement of biological signals. Nevertheless, no wearable CA-125/HE4 biosensor has yet established routine clinical use, and substantial work remains in sensor stability, data standardization,

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cybersecurity, clinical validation and regulatory evaluation.

9.REGULATORY AND COMMERCIAL TRANSLATION LANDSCAPE

Most ovarian cancer biosensors described in the research literature remain at the analytical or proof – of – concept stage. Consequently, their analytical performance should be distinguished from the regulatory status of established clinical assays.

HE4 immunoassays have received FDA 510(k) clearances for defined clinical uses. For example, the HE4 received a 510(k) decision in June 2008. Subsequent HE4 assay platforms have also received additional FDA clearances. The Risk of Ovarian Malignancy Algorithm (ROMA), which combines HE4 and CA-125 results with menopausal status, received FDA 510(k) clearance in September 2011 as an aid to assessing the likelihood of malignancy in women presenting with an adnexal mass [55]. These regulatory clearances should not be interpreted as approval of HE4 or CA-125 as stand-alone population-screening biomarkers.

The regulatory pathway for a new biosensor therefore depends on its intended use, target population, specimen type, clinical claim, analytical performance, and clinical validation. For research – stage electrochemical, optical, FET, or multiplex biosensors, successful translation will require demonstration of analytical validity followed by appropriate clinical validation and manufacturing reproducibility. Comparison with established clinical methods should be performed using predefined clinical endpoints rather than relying only on a lower analytical detection limit.

This distinction is particularly important for ovarian cancer because a device intended for population screening would face different clinical requirements from a device intended to assist in the evaluation of women who already have an adnexal mass. Therefore, future biosensor development should clearly define its intended-use population and clinical claim before regulatory evaluation.

10. CURRENT CHALLENGES AND FUTURE SCOPE

- Most electrochemical and optical biosensors are only validated in spiked buffers or artificial serum, but larger studies need real patients with different disease stages to get a clinical translation [28, 29].
- Simultaneous detection of biomarkers by a single device is still a limited process, and multiplex format must be established [22].
- Nanomaterial-based electrodes and plasmonic substrates may show batch-to-batch variability, which complicates reproducibility across laboratories [33].
- Matrix effects from complex biological fluids (serum, plasma, urine) including non-specific protein adsorption and interference from endogenous confounders such as endometriosis-related elevations in CA-125 are frequently under-characterized outside of controlled buffer conditions [42,50].
- Long-term storage stability, shelf life, and cold chain requirements of antibody and aptamer-functionalized sensor surfaces have rarely been reported, yet they are essential for real-world point-of-care deployment [68,71].
- Regulatory translation requires prospective clinical validation against an existing FDA-cleared comparator (ROMA, OVA1, or Overa) and demonstration of manufacturing reproducibility

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under CLIA-type quality standards, a step that few academic biosensor prototypes currently undertake.

- Growing interest in combining nano biosensors with AI assistance would support decentralized point-of-care ovarian cancer screening [29,34].

A major limitation of the current biosensor literature is the difference between analytical performance and demonstrated clinical utility. Many reported platforms achieve very low detection limit under controlled laboratory conditions, whereas relatively fewer have been evaluated prospectively in sufficient large and clinically heterogeneous patient cohorts. Performance can be affected by specimen matrix, biomarker heterogeneity, disease stage, menopausal status, renal function, benign gynaecological conditions, and pre – analytical samples handling.

Accordingly, future studies should report standardized analytical validation together with clinical diagnostic performance. Important parameters include limit of detection, limit of quantification, linearity, precision, recovery, interference, cross-reactivity, stability, diagnostic sensitivity, diagnostic specificity, receiver operating characteristic analysis, area under the curve, and confidence intervals. Studies should also include appropriate benign disease controls and independent validation cohorts. For AI-assisted systems, external validation and prevention of patient-level data leakage are essential. Such evidence would provide a more reliable basis for determining whether an experimental biosensor can progress from proof – of – concept analytical detection to clinically useful diagnosis.

11.CONCLUSION

Electrochemical and optical biosensors have demonstrated substantial progress in the analytical detection of ovarian cancer-associated biomarkers, particularly CA-125 and HE4. Electrochemical and aptamer-based systems offer opportunities for miniaturized and potentially low – cost detection, whereas optical platforms such as SPR, LSPR and SERS provide label-free or highly amplified signal transduction. Emerging FET, piezoelectric, photoelectrochemical, paper-based, microfluidic, and AI-integrated platforms further expand the technological possibilities for decentralized biomarker analysis.

However, exceptionally low analytical detection limits should not be equated with clinical diagnostic sensitivity or early-stage screening capability. The principal translational challenges remain validation in real patient specimens, adequate representation of early-stage disease and benign controls, multiplexed biomarker analysis, reproducibility, matrix effects, long-term stability, and independent clinical validation. AI- integrated biosensors additionally require sufficiently large and representative datasets, rigorous model validation, and external testing.

Future development should therefore focus on clinically relevant analytical ranges, standardized validation protocols, multiplex detection of complementary biomarkers, integration with microfluidic sample handling, and prospective comparison with established clinical assays. These steps are necessary for transforming promising biosensor technologies from laboratory proof – of – concept systems into clinically useful tools for ovarian cancer diagnosis and risk assessment.

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