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# A review on Advances in Biomarker-Based Detection Strategies for Ovarian Cancer

**Doppalapudi Prasanthi [1], Yeramanchi Sarah Sujitha[2*], AdepuGeethaSusmita[3], G Naveena[4], Seelam veenasri [5], Ayyavaripalli Sandhya Rani [6] & Dr. S. Prabagar**

[1]Sri K. V. College of Pharmacy, Chickballapur, Bengaluru, India.
[2]Krishna Teja PharmacyCollege, Tirupati, Andhra Pradesh-517501, India.
[3]Annamacharya college of Pharmacy,Rajampeta.
[4]East point college of pharmacy, Virgonagar post, Avalahalli, Bengaluru, Karnataka 560049, India
[5]Krishna Teja Pharmacy College, Tirupati, Andhra Pradesh-51750, India.
[6]Krishna Teja Pharmacy College, Tirupati, Andhra Pradesh-517501, India.
[7]Department of Computer Science and Engineering (Data Science), Vel Tech Rangarajan Dr. Shakunthala (R&D) Institute of Science and Technology, Avadi, Chennai, India.

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**ABSTRACT**

Globally, ovarian cancer ranks as the eighth leading cause of cancer-related mortality among women. As a result of inadequate symptoms in its early stages, most cases are diagnosed at advanced stages, where treatment becomes more challenging. Standard therapeutic approaches primarily surgical tumor reduction followed by systemic chemotherapy is often hindered by the emergence of chemoresistance, affecting nearly three-quarters of patients and resulting in poor clinical outcomes. This underscores the urgent need to re-evaluate existing biomarkers and discover new ones that can enhance diagnostic accuracy and prognostic assessment. Biomarkers capable of identifying disease presence, progression, and treatment responsiveness could significantly improve early detection and patient survival rates. This review explores currently validated ovarian cancer-specific biomarkers and highlights innovative technologies and methodologies being employed to uncover novel diagnostic and prognostic indicators. Although symptoms such as abdominal discomfort, bloating, and urinary or bowel changes may suggest disease onset, they are frequently vague and nonspecific. Age, inherited genetic mutations, and a family history of cancer are recognized as key contributors to ovarian cancer risk. Promising biomarkers like CA-125, HE4, osteopontin, and genetic profiling are being investigated for early detection. Diagnosis typically involves imaging techniques and histopathological confirmation via biopsy. Treatment strategies vary based on cancer stage and type, encompassing surgery, chemotherapy, and targeted therapies. Timely diagnosis and effective intervention rely heavily on routine screenings and heightened awareness of potential warning signs.

## 1. Introduction:

Ovarian cancer is a serious and life threatening illness that endangers the health and lives of women across the globe. It stands as the eighth most common cancer world-wide, contributes to roughly two to three lakh new cases worldwide each year. As ovarian cancer progresses, its symptoms tend to become more noticeable. Unfortunately, this delayed onset contributes to it being the deadliest among gynecological cancers. While early-stage detection offers a strong chance of a cure through therapeutic intervention, this underscores the crucial link between timely diagnosis and survival outcomes [1].When caught in the initial stages, the five-year survival rate can reach up to 95%. However, most cases are identified only once the disease has progressed to stage 3 or 4, where the Survival probability over five years drops below 30%, reflecting a significantly high fatality ratio [2]. Epithelial ovarian cancer represents the most common histological subtype of ovarian malignancies, distinguished by its origin, etiology, molecular alterations, risk factors, and prognosis. It comprises five major histological types. Genetic susceptibility often arises from rare hereditary mutations with moderate to high penetrance. The interplay of genetic and epigenetic modifications alongside the growing genetic heterogeneity within tumor cells as the disease advances pose significant challenges to achieving a cure. Currently, no effective screening method exists for detecting the disease at an early stage. Therefore, identifying reliable tumor markers for early diagnosis is crucial to enhancing survival out comes of affected women [3].

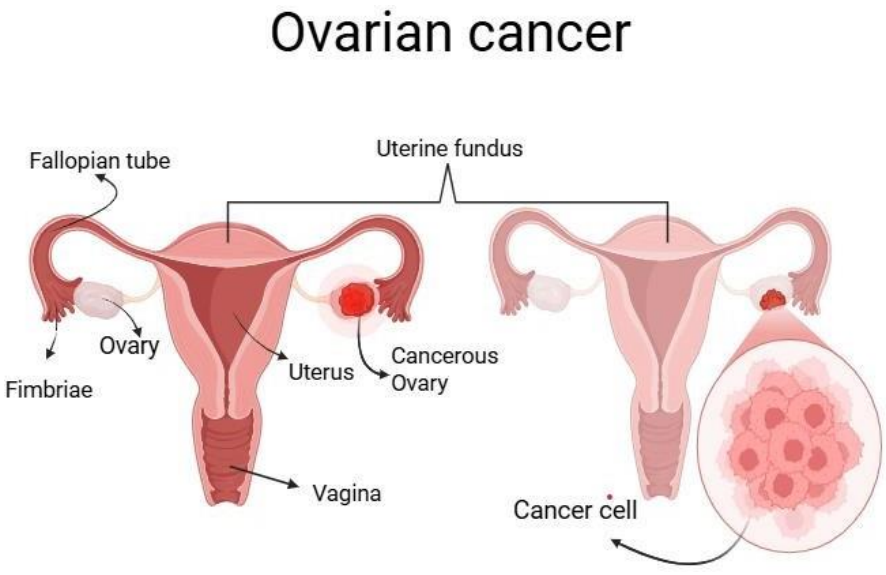


**Figure-1: Malignancy of the ovaries**

## ➢ Classifications of ovarian cancer:

High-serous ovarian cancer is the most prevalent form of thedisease and falls under the category of epithelial ovarian cancers. Both management strategies for primary peritoneal cancer and fallopian tube are largely aligned, as they are considered types of epithelial ovarian cancer.

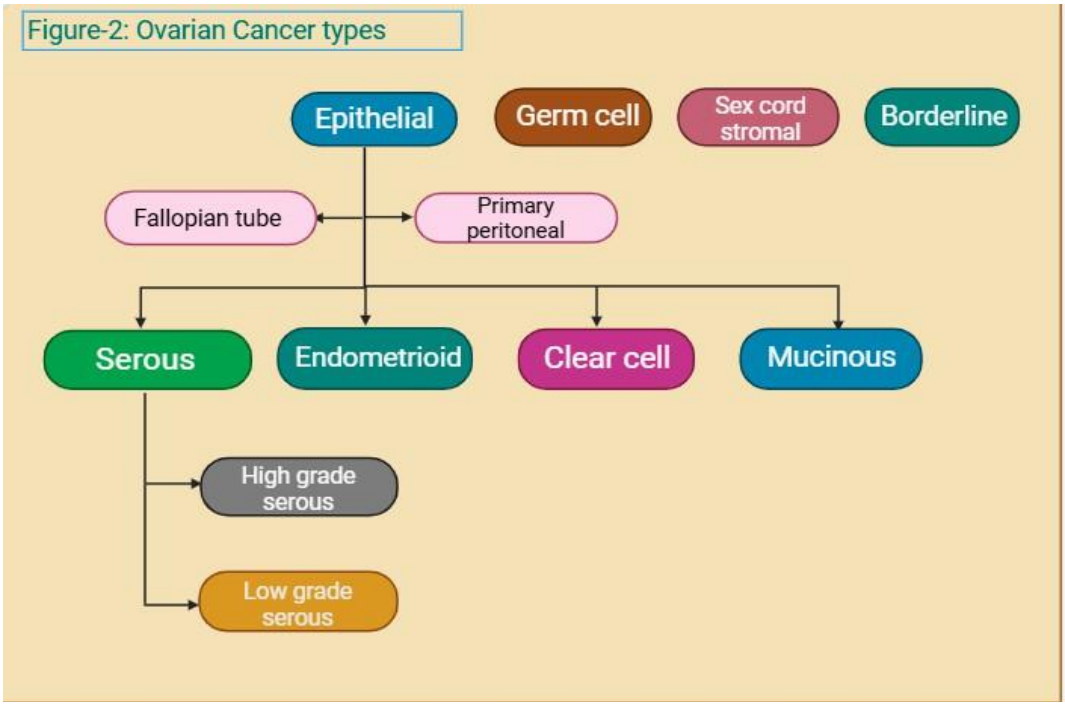


**Figure-2: different categories of ovarian malignancy**

## ➢ Epithelial ovarian cancer:

The most commonly identified form of ovarian cancer is called epithelial ovarian cancer. It's highly diverse and often associated with genetic instability. Around 70% of EOC cases are of the serous type. In 2014, the (WHO) updated its classification, stratifying serous ovarian cancer into two groups: high-grade and low-grade.Around 5-10% of serous ovarian cancers are classified as low grade serous ovarian cancer. LGSOC is usually exhibits clear cellular differentiation and is typically identified in early stages [4, 5],especially when certain genetic changes are present, such as mutations in the BRAF and KRAS genes and there's very little mutation in the TP53 gene, which codes for the tumor-suppressing protein p53 .On the other hand, among epithelial ovarian cancers, high grade serous ovarian cancer stands out as the most commonly identified and aggressive form of ovarian malignancy. It is responsible in the greater part of deaths related to ovarian malignancy [6].

High-grade serous ovarian cancer (HGSOC) patients typically show initial responsiveness to first-line chemotherapy; however, nearly all eventually develop resistance to treatment In contrast, low-grade serous ovarian cancer progresses more slowly and exhibits inherent resistance to chemotherapy, yet shows a response favorably into a highly invasive state cytoreductivesurgical procedure[6].Notably, LGSOC outcome have enhanced with the use of alternative therapies, including angiogenesis inhibitors and MEK inhibitors.The inherent heterogeneity of ovarian cancer presents a significant challenge for the exploration and the identification of novel biomarkers is enhancing early detection strategies, while the introduction of Targeted therapies, including PARP inhibitors, represent a significant advancement in treatment strategiesis transforming therapeutic approaches, has notably enhanced patient survival outcomes among HGSOC patients especially those harboring BRCA mutations highlighting the growing importance of molecular biomarker discovery [7].

Given that ovarian cancer involves diverse genetic and molecular signaling pathways, a deeper understanding of the implicated proteins and genes may unlock new opportunities for biomarker identification. This review synthesizes recent advancements in potential biomarker discovery aimed at improving the clinical assessment and prognosis related to epithelial malignancy. It also revisits currently available clinical biomarkers, assessing their precision in disease management. Furthermore, the article serves as a resource to explore cutting-edge laboratory technologies and methodologies for identifying novel ovarian cancer biomarkers.

**TABLE1.**

- **Established biomarkers in ovarian cancer and their therapeutic relevance**

| Biomarker | Type | Therapeutic relevance | Limitations |
|---|---|---|---|
| **CA-125** | Glycoprotein | - Monitoring treatment response<br>- Detecting recurrence<br>- Risk assessment | - Low specificity for early-stage disease<br>- Elevated in benign conditions |

| | | | |
|---|---|---|---|
| **HE4** | Protein | - Improved diagnostic accuracy (esp. with CA-125)<br>- Useful in ROMA algorithm | - Improved diagnostic accuracy (esp. with CA-125)<br>- Useful in ROMA algorithm |
| **BRCA1/BRCA2**<br><br>**TP53** | Genetic mutation<br><br>Tumor suppressor gene | - Predictive for PARP inhibitor eligibility<br>- Familial risk review<br><br>- Frequently mutated in HGSOC<br>- Prognostic marker | -Some patients have mutations.<br>Doesn't guide initial diagnosis<br>- Not yet a validated diagnostic marker |
| **LPA (lysophosphatidic acid)** | Lipid signaling molecule | - Investigational for early detection | - Requires further clinical validation |
| **FolR1(Folate receptor alpha)** | Surface protein | - Target for imaging and drug delivery in certain EOC subtypes | - Expression varies across histotypes |
| **Circulating miRNAs** | Noncoding RNA | - Emerging role in early detection and prognosis | - Standardization and reproducibility challenges |

## ➢ Risk Factors:

Ovarian cancer is influenced by several risk factors, predominantly affecting postmenopausal women. Advancing age is strongly linked to a higher incidence, more advanced disease stages at diagnosis, and poorer survival outcomes. Interestingly, parity appears to confer protection numerous case-control studies suggest that women who bear children,especially at older maternal ages tend to reduce the chances of developing ovarian cancer. A known history of ovarian malignancy significantly elevates the potential hazard of recurrence or developing related malignancies. Among the most frequently observed peril factors include [8]:

- **Age:** ovarian cancer occurs infrequently among women under 40 and

predominantly occurs post-menopause, with a marked increase in risk observed beyond age 50.

- **Gene mutation:** If a woman has a genetic variant affecting BRCA1or BRCA2 gene, her chance of getting ovarian cancer represents much higher than average. These are inherited and can run in families.
- **Record or having had breast or colorectal cancer:**a history of breast, colorectal, or other particular cancers is associated with a marginal increase in ovarian cancer susceptibility among women
- **Endometriosis:** endometriosis involves the ectopic presence of endometrial-like tissue, which may contribute to a greater risk of ovarian malignancy.
- **Familial predisposition:**women whose immediate family members have had ovarian, breast, or bowel cancer may face a greater chance of getting ovarian cancer themselves.
- **Has not conceived:**a delayed first full-term pregnancy after age 35, or the absence of pregnancy, has been associated with a slightly higher risk in women.
- **Hormonal treatment:** Using estrogen alone or with progesterone for an extended period after menopause may raise the risk, especially if continued over a span of five years or longer.
- **Adiposity/obesity:**women whose body mass index is 30 or above, are at increased risk for ovarian cancer, though they may be less likely to develop, such as high- grade serous cancer rapid progression and poor prognosis.

## 2. A scientific conspectus on ovarian cancer molecular indicators and cell signaling mechanisms:

A wide range of cancer-related genes and proteins have been investigated as biomarkers for diagnosing, predicting outcomes, and guiding specific interventions in ovarian cancer. Table 1 highlights among the most prominent frequently studied molecular indicators along with their relevance in clinical practice, whereas Figure-2 illustrates their diagnosis accuracy and reliability in early-stage disease (Stages I–II) [9].These biomarkers are frequently upregulated or altered within various signaling mechanisms, diagnostic trajectories among women with ovarian cancer. Notably, ovarian cancer is a complex condition composed of a diverse group of tumors, each impacting distinct molecular and genetic pathways.The following sections detail the key signaling pathways involved during the clinical evaluation, advancement, and therapeutic intervention of ovarian cancer [10].

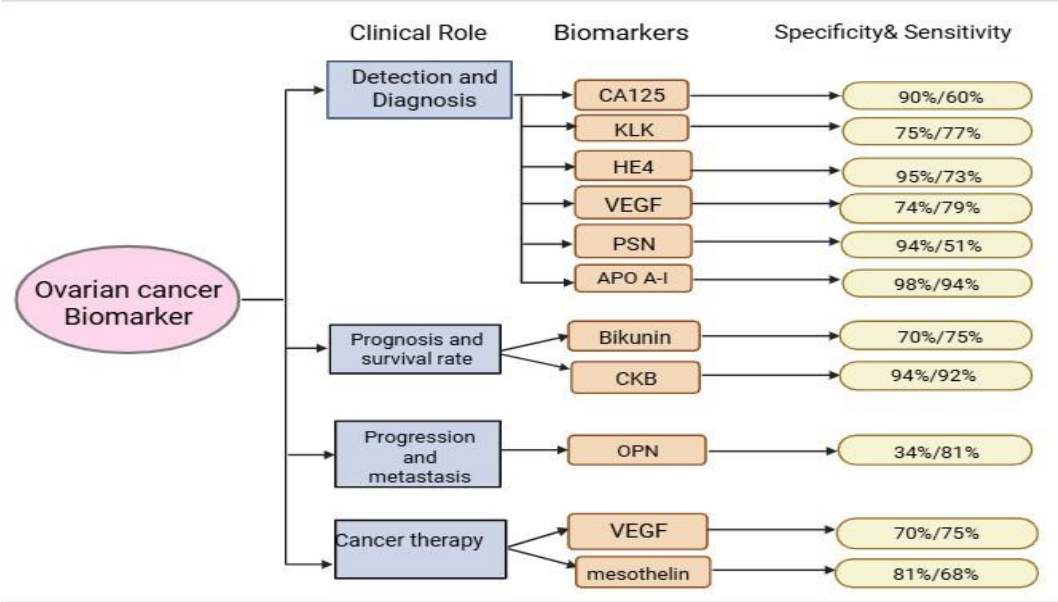


**Figure-2: Sensitivity along with Specificity of Biomarkers in Stage I–II Ovarian Cancer.**

## 2.1. Cell signaling mechanisms in ovarian cancer and their therapeutic relevance:

### 2.1.1. (BRCA1)and(BRCA2)-mediated DNA repair pathway:

BRCA1 and BRCA2 are genes that function as tumor suppressors, playing a key role in cellular protection and maintain genomic stability.Essential for the accurateDNArepair process known as homologous recombination.DNA sequence changes in these genes are linked to hereditary breast and ovarian cancers, among others [12,13]. Moreover, ovarian tumors harboring mutations in BRCA1 or BRCA2 genes exhibit heightened sensitivity to treatments that induce double-strand breaks [14] and interstrand crosslinking in DNA. These include platinum-based drugs like cisplatin and carboplatin, as well as PARP inhibitors such as Olaparib, Iniparib, and Veliparib [15].

### 2.1.2. MAPK/ERK pathway:

Upregulationof the MAPK/ERK signaling route is observed in ovarian canceroften driven by mutations in BRAF and KRAS enhances cell migration, invasion, and contributes to metastasis and chemo resistance. This pathway, typically active in (LGSOC) but rarely in high-grade variants of serous ovarian cancer (HGSOC) [16], involves a cascade ofthreeEnzymes that control cellular growth, specialization, and programmed cell death. External stimuli such as FSH, LH, growth factors, cytokines, and chemotherapeutic agents trigger MAPK signaling via G-protein-coupled and receptor tyrosine kinases. In ovarian carcinoma cells, overexpression of gonadotropin receptors may amplify MAPK signaling, promoting tumor progression [17, 18].

Targeted therapy with BRAF and MEK inhibitors like selumetinib has shown promising outcomes in advanced LGSOC,According to Study 239, conducted by the Gynecologic Oncology Group, was a Phase II clinical investigation; the treatment yielded only 15% of patients responded to treatment, and the median duration/outcome was noted accordinglyprogression-free survival of 11 months an improvement over the 7-month median seen with conventional chemotherapy [18, 19].

### 2.1.3. Epidermal Growth Factor Receptor–mediated activation of the AKT pathway:

Expression of EGFR occurs in a wide range of cellular environmentsapproximately 70% associated with ovarian malignancies. Its activation by ligands such as EGF and TGF influences tumor survival, either promoting or inhibiting growth [20, 21]. Beyond this, EGFR contributes to tumor infiltration, metastasis, and generation of new blood vessels (angiogenesis)[22]. A key downstream effector of EGFR signaling is AKT, which becomes activated through phosphorylation upon receptor engagementupregulation of AKT is a frequent occurrence in ovarian malignancies, correlating with heightened tumor aggressiveness and poor clinical outcomes. Given its involvement in crucial processes like angiogenesis and metastasis, the EGFR/AKT signaling axis has emergedAs a targeted treatment strategy, Cetuximab (Erbitux) emerged as the first monoclonal antibody specifically designed to inhibit the epidermal growth factor receptor, and is currently evaluated across various solid tumors, Such as cancers affecting the breast, colon, head and neck region, kidneys, lungs, and gastrointestinal stromal tissues (GISTs). While anti-EGFR therapies have shown clinical benefit in several solid tumors, their effectiveness in ovarian cancer remains limited, with low response rates observed. Moving forward, in-depth investigations are essential to decode the intricate network of proteins and genes involved in EGFR signaling within ovarian cancer. Such research could lead to the discovery of reliable biomarkers capable of predicting patient responsiveness to EGFR-targeted treatments.

### 2.1.4. Integrin inhibitor pathway:

A functional integrin receptor is formed through the pairing of distinct alpha and beta subunits [23]. Recent studies have exploredUsed as targeted therapies, integrin inhibitors can prevent tumor progression and metastasis. Early-stage research indicates that multiple agents targeting integrins may exhibit therapeutic potential effectively suppress tumor progression by targeting not only cancer cells but also supportive host components, particularly the angiogenic endothelium. Since ovarian cancer cells initially disseminate by adhering to the peritoneal surface via integrins, therapeutically targeting these receptors presents a compelling strategy to curb disease spread. Despite the lack of compelling efficacy outcomes from current integrin inhibitors, therapies aimed at integrin pathways remain a promising area for continued clinical exploration [24].

### 2.1.5. Glucose-Regulated Protein 78 expression pathway:

Recent studies have identified GRP78 as a potential vehicle for targeted drug delivery in ovarian cancer treatment. Its expression is

significantly elevated in response to endoplasmic reticulum stress a condition commonly observed in tumor cells. Due to its abundant presence on the surface of ovarian cancer cells, GRP78 is being explored as a conduit for transporting cytotoxic agents directly to malignant tissues [25].

#### 2.1.6. P38 Alpha Pathway:

Recent cancer research has increasingly focused on the p38α signaling pathway. Clinical trials involving small-molecule inhibitors of p38α have demonstrated that pharmacological blockade of this pathway can suppress ovarian cancer cell growth and viability [26]. Notably, p38 inhibition triggersthe development of sizable autophagic vesicles containing cytoplasmic glycoproteins and fragments of mitochondria, indicating autophagic cell death. These findings position p38α as an emerging biomarker and potential therapeutic target, it holds significant promise for advancing ovarian cancer treatment and merits deeper clinical exploration [27].

## 3. Current Biomarkers Linked to the Diagnosis, Progression, and Therapeutic Response in ovarian malignancies:

### 3.1. CA125 as a Diagnostic Marker in Ovarian Cancer:

Cancer-associated glycoprotein (CA125), commonly referred to as CA125, a tumor-associated glycoprotein or MUC16 [28],It is a glycosylated protein produced through the expression of the MUC16 gene. In clinical settings, CA125 is frequently utilized as aserum biomarker for diagnostic purposes. Typically, a CA125 concentration ranging from 0 to35 units/mL is considered within the normal range across most laboratories. Approximately 80% of Elevated levels of serum CA125 are commonly observed in Patients presenting with late-stage epithelial ovarian carcinoma [29, 30].

- CA125 is considered more accurate in postmenopausal women, with improved sensitivity and specificity compared to premenopausal individuals. To enhance diagnostic performance, serum CA125 levels are incorporated into the Risk of Malignancy Index, a widely used tool in clinical settings. The (RMI) represents a diagnostic tool used tocalculate by using the following equation:

- Risk of Malignancy Index(RMI**)**, = ultrasonography score × Menopausal condition score ×CA125 (U/ML).
- When compared to CA125 alone, RMI demonstrates superior diagnostic metrics are Sensitivity: 87%**,**Specificity: 97% [31].

- In a recent study involving training and validation cohorts, researcher's evaluated four established clinical tests, such as diagnostic tools such as the (RMI), the ROMA algorithm, and biomarkers like CA125 and HE4 are commonly employed to evaluate the likelihood of ovarian cancer.In a study involving 66 surgical patients with suspected ovarian cancer, a multiplex immunoassay was employed to evaluate the levels of 28 soluble immune biomarkers.

- The research proposed a dual-phase triage strategy aimed at evaluating women suspected of having ovarian masses:
    - Step 1: Initial stratification based on IL-6 > 3.75 pg/mL
    - Step 2: Supplemented with conventional markers (e.g., CA125 or RMI) for improved classification
- This approach significantly reduced misclassification rates:
    - IL-6 + standard testing: ~3.03–4.54%
    - Standard testing alone: ~9.09–10.60%
- Findings suggest IL-6 is a promising adjunct biomarker for triaging patients with potentiallymalignant ovarian masses.However, clinical implementation may face challenges due to IL-6 variability, which can be influenced by infections and inflammatory conditions, affecting its reproducibility [32].

### 3.2. Osteopontin (OPN):

Osteopontin (OPN) is a glycosylated phosphoprotein with adhesive properties, released by immune cells.This includes immune cells such as T cells, macrophages, and various types of white blood cells. It is found within the extracellular matrix, accumulates at inflammatory sites, and is present in multiple bodily fluids [33].Osteopontin (OPN) exhibits elevated expression levels not only in ovarian cancer but also across a wide range of other malignancies, including cancers of the endometrium, cervix, breast, colon, lung (non-small cell type), prostate, liver (hepatocellular carcinoma), and stomach. Functionally, it plays a significant role in tumor progression and metastasis.Osteopontin (OPN) serves as a key contributor in promoting tumor growth, cellular invasion, and the spread of cancer to distant sites, positioning it as a key biomarker in cancer research and clinical oncology.Plasma analysis revealed that OPN concentrations were markedly elevated in cases of epithelial ovarian cancer (EOC), along withlevels averaging 486.5 ng/mL (n = 51). These were significantly higher ($p < 0.001$) compared to [34]:

- The concentration measured in healthy individuals was 147.1 ng/mL,(n=107)
- Individuals with non-malignant ovarian disorders exhibited a concentration of 254.4 ng/mL (n=46), based on a cohort of 46 subjects
- A concentration of 260.9 ng/mL was recorded in patients diagnosed with other forms of gynecological cancer(n=47), based on a sample size of 47 individuals.

### 3.3. Kallikreins:

Kallikreins represent a subgroup of serine proteases that participate in various physiological functions and the human genome encodes 15 distinct genes belonging to this family, all situated on the long arm of chromosome 19.These proteolytic enzymes

are mainly found in epithelial and hormone-secreting tissues, with their activity regulated by hormonal signals, especially within the context of cancer. Because kallikreins are secreted and detectable in body fluids [35], they've garnered significant interest asBiomarkers play a crucial role in detecting and predicting the course of cancer, particularly in ovarian malignancies, 12 of the 15 kallikrein-related peptidases (KLKs) are found to be upregulated. Notably:

- KLK 4, 5, 6, 7, 10, and 15 have been linked to unfavorable clinical outcomes and are frequently observed in advanced stages of disease progression.
- KLK 4 and KLK 7 have been linked to resistance against initial treatment with paclitaxel in cancer patients [36, 37].

### 3.4. Bikunin:

Bikunin is a multifunctional glycoprotein known for its role in suppressing tumor cellular infiltration and spread to distant tissues.Evaluating bikunin concentrations in tissue specimens from individuals with malignancies has become a simple and effective approach for predicting disease outcomes.ElevatedPre-surgical levels of bikunin have been recognized as a significant predictor of favorable prognosis in cancer patients [38]. In a large-scale study by Matsuzaki et al. bikunin concentrations Plasma levels in women diagnosed with ovarian cancer (n = 327) were markedly elevated in comparison to those observed in patients with benign ovarian tumors (n=200)and healthy individuals (n=200), suggesting its potential value in predicting clinical outcomes.

Bikunin concentrations at or below 11.5 µg/mL have been associated with late-stage ovarian cancer (Stage III/IV), sizable residual tumor burden exceeding 2 cm, and diminished responsiveness to chemotherapy.Patients with reduced bikunin levels also showed a significantly shorter median survival time 26 months versusPatients with elevated levels showed a median life expectancy reaching 60 months ($p = 0.002$), reflecting a 2.2-fold rise in the risk of death, as indicated by a hazard ratio of 0.45 ($p = 0.023$) [39]. Due to its simplicity and affordability, plasma-based bikunin measurement holdsMay serve as a predictor of prognosis in ovarian malignancies. Nonetheless, the significant overlap in bikunin concentrations among malignant cases, benign conditions, and healthy individuals requires further investigation before it can be adopted in clinical practice.

### 3.5. Human epididymis protein 4 (HE4):

HE4, also known as WAP four-disulfide core domain protein 2 (WFDC2), was first identified in 1999 as a potential biomarker for detecting ovarian cancer [40]. Its expression has been associated with the adhesive properties of tumor cells, migration, and proliferation processes associated with activation of the EGFR-MAPK signaling pathway [41]. Studies have shown that HE4 is absent in normal ovarian surface epithelium, it has been consistently identified in all examined cases of endometrioid epithelial ovarian cancer (n = 16) and in 93% of serous ovarian carcinoma specimens

stained for HE4 (n = 60) [42]. Furthermore, an ELISA assay was used to evaluate serum HE4 concentrations in a cohort of 37 individuals diagnosed with ovarian cancerversus 65 healthy individuals demonstrated that HE4 exhibits comparable specificity and sensitivity to CA125, with a lower rate of false-positive results among non-cancerous cases [43].

HE4 levels are markedly elevated across ovarian and endometrialcancers.However, levels remain relatively low in non-malignant conditions such as endometriosis. While HE4 levels may rise under certain conditions in cases of benign disease, such elevations are generally less frequent compared to CA125 particularly in premenopausal women. The risk of ovarian malignancy algorithm (ROMA)index combines serum levels of HE4 and CA125 with a patient's menopausal status to estimate the likelihood of ovarian malignancy. Across numerous clinical studies, ROMA has proven effective in categorizingPatients are stratified into low- and high-risk categories, each associated with distinct prognostic implications [44].

### 3.6. Vascular endothelial growth factor:

Vascular Endothelial Growth Factor (VEGF) plays a central role in enhancing vascular permeability and orchestrating both normal and abnormal blood vessel formation. Its elevated expression has been notably associated with tumor progression [45], particularly in ovarian cancer, where it contributes to the development of ascitic fluid [46]. A study evaluating preoperative serum samples from 314 ovarian cancer patients found that higher vascular endothelial growth factor concentrationswere found to be independently associated with reduced overall survival times. Additionally, VEGF expression was analyzed viaReverse transcription PCR was performed on tumor samples obtained from 18 individuals diagnosed with advanced-stage serous epithelial ovarian malignancy [47, 48]. Of these, 12 samples showed high VEGF expression, while six displayed low or no expression. Patients with low or undetectable VEGF levels had a median survival of 60 months, significantly longer than the 28-month median observed in the VEGF-positive group. The p-value of 0.058 suggests borderline statistical significance.

### 3.7. Creatine kinase B:

Creatine kinase (CK) acts as a vital role in maintaining potential balance within vertebrate cells. The cytosolic isoform, CKB, was found to show increased expression in various malignancies, such as ovarian cancer [49]. Enhanced protein expression of CKB was previously observed an specific sections of ovarian tumor tissues. Functionally, Creatine Kinase B (CKB) reduces the cellular uptake of glucose and lactate,increasing reactive oxygen species (ROS) production and oxygen consumption. Notably, inhibition of CKB activity leads to G2 cell cycle arrest, mediatedvia activation of the PI3K/AKT and AMPK pathways. Therapeutically, this pathway highlights CKB as a promising biomarker for evaluating tumor aggressiveness and informing personalized treatment strategies in ovarian cancer progression and malignancy cell survival. Serum CKB activity measured before surgery Levels were significantly elevated in women diagnosed with ovarian cancer (N = 45), in contrast to those with benign ovarian tumors

(9.6 U/L, N = 49) and healthy individuals (8.5 U/L, N = 37).with a p-value of 0.0096. Given its elevated expression in early-stage ovarian tumors, CKB holds potential as a biomarker for early detection and warrants further investigation [50].

### 3.8. Mesothelin:

Identified in 1996 by researchers at the National Cancer Institute, mesothelin is a differentiation-related antigen expressed by mesothelial cells that form the lining of the pleura, peritoneum, and pericardium [51]. It shows elevated expression in several malignancies, notably in about 70% of ovarian cancer cases. A range of mesothelin-targeted therapies such as immunotoxins and antibody-drug conjugates (ADCs) have undergone clinical evaluation [52]. Quanz et al. demonstrated the effectiveness of anetumabravtansine, an ADC composed of a human antimesothelin antibody linked via a disulfide bridge to the DM4 maytansinoid tubulin inhibitor, when used alongside standard chemotherapy in ovarian cancer models. Both laboratory and animal studies revealed selective cytotoxic activity against newly expressed mesothelin-positive cells andTumors exhibit a detection accuracy characterized by a sensitivity of 68.2% and a specificity of 80.5% [53]. In preclinical ovarian cancer models, anetumabravtansine showed enhanced therapeutic efficacy when combined with carboplatin, outperforming either agent used alone. Similar synergy was observed withBevacizumab, a therapy targeting VEGF, is being used alongside other treatments. At present, a phase 1b clinical study (NCT02751918) is evaluating the efficacy of combining anetumabravtansine with pegylated liposomal doxorubicin in individuals diagnosed with ovarian cancer.

### 3.9. Transthyretin:

Transthyretin (TTR) is an endogenous protein found in the bloodstream, predominantly produced by the liver [54]. It facilitates the transport of thyroid hormones and vitamin A by interacting with the retinol-binding protein complex [55, 56].Research indicates that individuals with ovarian cancer tend to have lower serum concentrations of transthyretin (TTR), and when combined with other biomarkers, it can aid in cancer detection [57].Kozak and colleagues utilized liquid chromatography combined with tandem mass spectrometry to show that a biomarker panel comprising transthyretin (TTR) and the combined use of beta-hemoglobin, apolipoprotein A-I, transferrin, and CA125 has significantly enhanced the detection of early-stage ovarian cancer [58]. Additionally, transthyretin (TTR) has emerged as a promising biomarker for early diagnosis.Demonstrating 78.6% sensitivity and 68.8% specificity in detecting stage I–II disease.

### 3.10. Transferrin:

Transferrin is primarily synthesized by hepatocytes and is crucial for transporting plasma iron to cells, plays a crucial part in cellular division and proliferation [59].A reduction in transferrin levels within the serum of ovarian cancer patients was documented by Ahmed and colleagues [60].As a part of case-control study, transferrin concentrations were measured using an immunological turbidimetric method in the study involved 37 female

participants with ovarian cancer, whose results were contrasted with those of non-cancer subjectsin 31 patients with benign ovarian disorders and 31 healthy individuals matched by age. The findings indicated that transferrin alone offers limited diagnostic value for ovarian cancer,diagnostic performance yielded sensitivity and specificity values of 72.9% and 74.1%, respectively [61]. Consequently, transferrin should be utilized for conjunction together with other molecular indicators toenhance its therapeutic utility in cancer detection.

## 4. Identifying the most frequently utilized biomarker combinations in guiding therapeutic strategies for ovarian cancer:

Research has shown that integrating select biomarkers significantly improves both the early detection and therapeutic planning of ovarian cancer. Widely used combination is CA125 with PSN, which significantly improves diagnosticperformance yielded a sensitivity of 92% and a specificity of 94%. This is notably higher than CA125 alone (64.9% sensitivity at 94% specificity) or PSN alone (51.4% sensitivity at 94% specificity) [62].

Another promising panel includes Apo-A1, transthyretin (TTR), Connective tissue-activating peptide III and cancer antigen 125 (CA125), which collectively combination of Apo-A1 with CA125 andtransthyretin (TTR) demonstrated 84% sensitivity and 98% specificity in accurately distinguishing early-stage ovarian cancer cases from healthy individuals [60], the resulting biomarker panel not only improved overall sensitivity and specificity but also provided robust discrimination across non-cancer cases,ovarian cancer diagnosed in its initial phases (Stages I–II) as well as across all clinical stages (I–IV) [63].

In a similar vein, Kozak et al. demonstrated that combining TTR, hemoglobin (Hb), Apo-A1, and transferrin (TF) with CA125 markedly improves the detection of early-stage ovarian cancer [64]. This finding was further reinforced by Kim et al., who provided additional evidence supporting the diagnostic value of this biomarker panel. Highlighted the diagnostic value of combining TTR, Apo-A1, and CA125. A proteomic analysis involving CA125, transferrin, TTR, andApo-A1 demonstrated a diagnostic sensitivity of 89% and specificity of 92% in detecting early-stage ovarian cancer [65,66].

## 5. Recently identified indicators for ovarian cancer prediction

### 5.1. Current molecular approaches used to discover new biomarkers for ovarian cancer:

The discovery of novel biomarkers demands highly specialized and advanced technologies capable of detecting molecular, genetic, and protein-level changes within human tissues and bodily fluids. This section highlights several cutting-edge techniques that have recently been employed in the identification of ovarian cancer biomarkers.

### 5.1.1. Whole Genome Analysis:

Comparative Genomic Hybridisation is a technique used to analyze genetic variations across the entire genomeused to identify variations in gene copy number, such as amplifications or deletions. This technique has revealed several chromosomal Genomic segments exhibiting atypical copy number variationsassociated with ovarian cancer [62]. Additionally, analysis of gene expression patterns in epithelial ovarian cancer across various histological subtypes has provided the overall gene activity and associated cellular signaling mechanisms. These studies not only help differentiate and characterize each cancer subtype but also uncover potential prognostic biomarkers [67].

### 5.1.2. Transcription profiling:

Transcription profiling, similarly referred to as "expression profiling," is a widely used analytical technique that quantifies gene expression across multiple genes within the RNA transcriptsderived from cellular or tissue specimens. This quantification is typically performed following treatment; RNA is isolated from collected biological samplesor at predetermined intervals in a time-series, thereby producing “snapshots” of gene expression dynamics.Ovarian cancer presents in multiple histological forms, each carrying its own prognostic implications, as demonstrated by numerous studies analyzing gene expression profilesmust aimed to identify biomarkers capable of distinguishing these subtypes. Findings from several studies suggest that despite subtype-specific gene expression signatures, there remains a degree of overlap, pointing to shared molecular mechanisms in ovarian carcinogenesis [68]. Furthermore, transcription profiling has led to the identification of markers with potential to predict patient survival outcomes [69].

### 5.1.3. MicroRNA profiling:

The discovery of microRNAs dates to 1993, when they were first found in Caenorhabditiselegans [68]. These small non-coding RNAs, generally consisting of 19 to 24 nucleotide bases, do not translate into proteins. Instead, they bind to the 3′Regulatory regions within target mRNAs that are not translated into protein,leading to the breakdown of mRNA or inhibition of its translation into protein[70].

Extensive research has demonstrated that microRNAs are differentially expressed in tumor tissues compared to their normal counterparts across various solid and hematopoietic malignancies. In some instances, distinct microRNA expression profiles can effectively distinguish tumor samples from normal tissues and are closely linked to clinical outcomes. Notably, one study analyzing microRNA signatures across multiple tumor types found thatthe expression profiles of approximately 200 microRNAs have demonstrated superior accuracy in classifying cancer compared to conventional cDNA microarray techniques. This highlights the potential of microRNA-based profiling as a powerful tool for improving cancer diagnosis and predicting clinical outcomes [70].

### 5.1.4. Proteomic profiling:

A significant limitation of transcriptional analysis is that fluctuations in mRNA abundance avoid consistently reflect variations in protein levels. Consequently,

proteomic approaches have gained prominence as a more precise and insightful method for uncovering biomarkers relevant to ovarian cancer diagnosis and prognosis. Within the field of proteomics, mass spectrometry stands out as a pivotal technology.

Proteomic analysis of ovarian cancer can be conducted using two primary strategies: one involves detecting distinct peptide patterns specific to cancer samples [1], while the other focuses on identifying individual peptides capable of differentiating cancerous tissues from normal ones.In addition to serum and plasma, proteomic analysis has been extended to various other bodily fluids. Key molecules discovered include glycosylated eosinophil-derived neurotoxins and C-terminal segments of osteopontin. Extensive analysis of ascitic fluid from ovarian cancer patients has led to the identification of approximately 80 candidate biomarkers that could support early diagnosis.

### 5.2. Innovative biomarkers relevant to ovarian cancer identification and prognosis:

Current diagnostic approaches for ovarian cancer primarily rely on limited imaging modalities and the measurement of specific circulating biomarkers, which possess defined levels of sensitivity and specificity. However, there is a growing need for novel biomarkers to enhance and complement the effectiveness of existing clinical tests. Emerging candidates include circulating tumor DNA,Proteins linked to tumors found in the bloodstream, free-floating cancerous cells, and minor serum elements like copper and zinc. These new biomarkers hold promise for improving the accuracy and reliability of ovarian cancer diagnosis [71, 72]. Table 2 outlines the key findings related to the new biomarkers.

**Table-2: Recent advances in biomarker discovery for ovarian cancer diagnosis and prognosis**.

| Biomarker | Biological source | Clinical relevance |
|---|---|---|
| Copper isotope variants | Serum | Potential tool for early cancer detection |
| Exosomal components | Ascitic fluid | Indicator for tumor progression |
| Long non-coding RNAs (IncRNAs) and mRNAs | Tumor tissue | Useful for early diagnosis and therapeutic targeting |
| Aldehyde dehydrogenase 1 (ALDH1) | Blood/Cytosolic fraction | Associated with early detection and disease advancements |
| FolateReceptor Alpha (FOLR1) | Blood/Genetic material | Linked to cancer Progression and cancer therapy |
| GSTP gene polymorphisms | Blood/DNA | Predictive of response to anticancer medications |

### 5.2.1. Copper isotope:

Two major organs play a central role in maintaining copper (Cu) concentrations within the bloodstream: the intestine, which facilitates absorption, and the liver, which manages transport [73]. Alterations in Cu concentration due to changes in metabolic activity can significantly impact health and disease outcomes.In a recent investigation, copper isotope ratios ($^{65}Cu/^{63}Cu$), expressed as $\Delta^{65}Cu$, were assessed in blood samples from 44 ovarian cancer patients and in 13 ovarian tissue biopsies using multicollector inductively coupled plasma mass spectrometry (MC-ICP-MS). The findings revealed a link between copper isotopic composition and cancer progression [74]. Specifically, the plasma of ovarian cancer patients exhibited a lower $\delta^{65}Cu$ value compared to healthy donors (n = 48), indicating an enrichment of $^{63}Cu$ in the serum.

### 5.2.2. Exosomes:

Exosomes are diverse, membrane-enclosed vesicles derived from the endocytic pathway, released by a wide range of cell types, and detectable through electron microscopy. Recent studies emphasize their role in regulating immune responses, exosomes contribute to cell-to-cell signaling and are involved in essential physiological functions like blood clotting and maintaining the tissue microenvironment [75]. In addition, they are critically implicated in tumor progression, the spread of cancer cells, and the development of resistance to therapeutic drugs [76].

A recent clinical trial revealed that circulating exosome levels in ovarian cancer patients were three to four times higher than those in healthy individuals. This finding has sparked growing interest in exploring the therapeutic potential of exosomes in oncology. Their cargo comprising nucleic acids, proteins, and lipids often reflects tissue or disease specific signatures, positioning exosomes as promising sources of novel biomarkers. Despite their unique properties that make them ideal candidates for cancer diagnostics, the development of reliable exosome-based assays remains an ongoing challenge [77].

### 5.2.3. lncRNA(long non-coding RNA) and mRNA(messenger RNA) Biomarkers:

Recent studies highlight the role of transcriptomes including lncRNAs, miRNAs, and mRNAs in advancingpredictive, preventive, and personalized approaches to ovarian cancer management have demonstrated both clinical effectiveness and economic efficiency [78]. A 2019 study mapped lncRNA-miRNA-mRNA and lncRNA–RBP–mRNA networks, the identification of distinct lncRNAs and mRNAs within ovarian cancer models supports their potential utility as diagnostic biomarkers and targets for therapeutic intervention [79].

In epithelial ovarian cancer (EOC), 663 long non-coding RNAs (lncRNAs) exhibited altered expression levels when compared to benign and healthy tissue samples [80]. Insights from TCGA data uncovered a platinum resistance-associated lncRNA–mRNA coexpression network comprising 124 pairs involved in metabolic pathway regulation, highlighting the potential of lncRNAs as prognostic indicators and

therapeutic targets in high-grade serous ovarian cancer [81].

### 5.2.4. Aldehyde dehydrogenase1 (ALDH1):

ALDH1A1, a member of the aldehyde dehydrogenase enzyme group, is expressed in a distinct subset of cells with stem-like properties and is being explored as a promising target in cancer therapy. A study conducted by Chang et al. employed immunohistochemical analysis on tissue microarrays to investigate its expression, ALDH1 was shown to aid in tumor classification, disease staging, assessment of therapeutic response, and prediction of overall survival in ovarian cancer. Elevated ALDH1 expression correlated with improved patient survival, suggesting its role as a favorable prognostic marker [82].

Further analysis of epithelial ovarian cancer (EOC) stem cells revealed increased ALDH1 expression in $CD44^{+}$ stem cell clones; these findings reinforce ALDH1's value in identifying cancer stem-like cells. Elevated ALDH1 expression within tumor cells showed a strong correlation with particular histological types, early FIGO stages, higher differentiation grades, and improved patient survival ($p < 0.05$). Conversely, ALDH1 levels in stromal cells did not exhibit any statistically significant associations with clinical or pathological features ($p > 0.05$) [83].

### 5.2.5. Folate receptor alpha (FOLR1):

FOLR1, a receptor anchored in the cell membrane, facilitates folate uptake and supports multiple cellular activities. Its elevated expression has been identified in nearly 69% of uterine serous carcinoma cases and in cells exhibiting rapid proliferation [84]. FOLR1 expression is influenced by factors such as extracellular folate depletion, homocysteine accumulation, steroid hormone levels, and genetic mutations. Early studies have identified a significant association between folate levels and both tumor development and progression, highlighting the need for further investigation into FOLR1 gene regulation and expression [85].

Moreover, increased levels of FOLR1 have been observed in several epithelial cancers that lack mucin production, including ovarian cancer. Although its role as an early diagnostic marker is still under investigation, it holds potential clinical significance, FOLR1 overexpression in serous ovarian carcinoma has been linked to distinct clinicopathological features, patient outcomes, and chemoresistance.

### 5.2.6. Glutathione S-Transferase Polymorphisms:

Genes from the Glutathione S-transferase (GST) family, such as GSTM1, GSTT1, and GSTP1, play a crucial role in detoxifying harmful substances and metabolizing medications. Changes in these genes (called polymorphisms) can affect how well cancer treatments work [86]. In ovarian cancer, some people with missing or low GST activity may struggle to remove harmful substances [87]. However, recent studies show that certain GST gene combinations may improve survival rates and reduce drug

resistance, making them important for treatment planning [88].

## 6. Summary and Discussion:

Despite the use of both established and advanced procedure like radiographic scans, tissue biopsies, tumor markers, and transvaginal ultrasound paired with biomarkers for detecting ovarian cancer, it continues to be the most common gynecological cancer and is associated with the highest death rate among these malignancies. To improve early detection, researchers are focused on identifying highly specific early-stage biomarkers and developing minimally invasive screening methods that can reliably signal the initial stages of ovarian cancer.Figure 3 presents a epitome of recent identified ovarian cancer biomarkers, emphasizing their predominant presence in human body fluids. Evaluating these promising markers for early detection could lead to major progress in both the diagnosis and therapeutic approaches for ovarian malignancy.

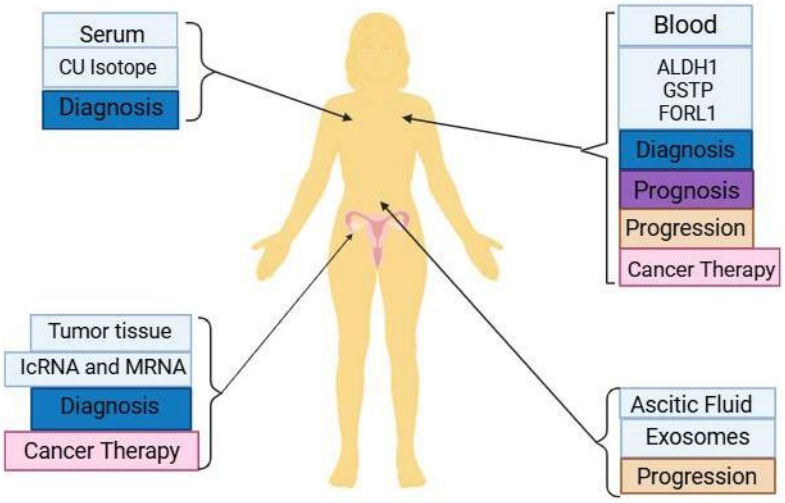


**Figure-3: Recent discoveredbiomarkersfor ovarian cancer, with a focus on their primary detection in human bodily fluids.**

Recent advances in Studies focused on the protein composition of human serum have led to Discovering improved methods for to biomarker candidates for early ovarian malignancies detection a critical step forward, when caught early, the chances of surviving for five years can surpass 90%. Among these, CA125 remains one of the most extensively studied and highly discriminative tumor markers, particularly in postmenopausal women, with elevated levels often preceding clinical symptoms.

However, CA125's diagnostic reliability is compromised by its low sensitivity in early-stage disease and its tendency to rise in other

malignancies, benign ovarian conditions, endometriosis, inflammatory disorders, and even during ovulation. These limitations make it unsuitable as a standalone screening tool.To enhance diagnostic accuracy, a multibiomarker panel is now recommended, combining CA125 with markers such as HE4, mesothelin, or other complementary candidates. This approach significantly improves both sensitivity and specificity. Notably, the pairing of CA125 with HE4 or mesothelin has shown the most promise in clinical applications.

According to Häusler'sresearch, reported Upregulated levels of this group comprise microRNAs such as miR-21, miR-141, miR-200a, miR203, miR205, and miR214observed inovarian cancer patients, along with consistent exosomalmiRNA profiles. These findings suggest that miRNA profiling holds promise as a novel approach for early detection, biopsy-based diagnostics, and screening in asymptomatic individuals.Additionally, research indicates ovarian cancer cells expressing ALDH1contribute to enhanced potential for tumor formation andresistance to chemotherapy. Therefore, early identification of ovarian carcinomas alongside genetic markers.Such as (Table 2) highlights several key genes associated with ovarian cancer, including BRCA1, BRCA2, PRSS8 (prostatin) GSTT1, FOLR1, KLK6, KLK7 and ALDH1, warrants further exploration through clinical trials.

## 7. Future Directions:

Future advancements in ovarian cancer detection are poised to transform clinical practice through the integration of minimally invasive technologies and highly specific biomarker strategies. Liquid biopsies analyzing circulating tumor DNA, exosomes, and microRNAs from body fluids offer promising avenues for early-stage diagnosis without the need for invasive procedures. The convergence of multi-omics approaches genomics, proteomics, and metabolomics will enable the identification of robust biomarker signatures, while artificial intelligence models trained on clinical and molecular data are expected to enhance predictive accuracy. Portable point-of-care diagnostic devices and biosensors may facilitate rapid screening in both clinical and low-resource settings. Additionally, longitudinal tracking of biomarker levels and the development of multi-marker panels tailored to individual risk profiles will improve early detection and patient stratification. Coupling non-invasive imaging techniques with biomarker data could further refine diagnostic precision, paving the way for earlier.

## 8. Conclusion:

Among all cancers, ovarian cancer still ranks as one of the most fatalgynecologicalCancer cases across the globe, with persistently low detection rates and five-year survival outcomes despite notable advancements in diagnostic technologies. This challenge stems largely from the lack of reliable early-stage biomarkers and clearly defined therapeutic targets.To greatly enhance patient outcomes and overall well-being, it is crucial to discover novel molecular indicators and therapeutic pathwaysthat enable early detection through minimally invasive

methods, while maintaining high sensitivity and specificity.

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