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Role of Biomarkers for Detection, Diagnosis and Targeted Therapy of Gynecological Cancers

Dr. Seema Gupta[*1]

[*1]Professor, Department of Radiation Oncology, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India.

[*]**Corresponding author:**

Dr. Seema Gupta

Email ID: yyixia@163.com

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ABSTRACT

Cancer is the uncontrollable abnormal division of cell growth, caused due to the varied reasons. Cancer can be expressed in any part of the body, and it is one of the death-causing diseases. Human reproductive organs are commonly damaged by cancer. In particular, the women reproductive system is affected by various cancers including ovarian, cervical, endometrial, vaginal, fallopian tube, and vulvar cancers. Identifying these cancers at earlier stages prevents the damage to the organs. Different biomarkers and aptamers have been generated against the gynecological cancer, which include, ctDNAs, miRNAs, Antigen 125 (CA125), Folate receptor alpha (FOLR1), Transthyretin (TTR), TIM-3, VEGF, TGF-α, TRAIL, MCP-3, IL-15, PD-L2, SCF, CTCs, Exosomes, TEPs, cfRNA, HE4, CA125, VEGF, OCCA (for ovarian cancer), EGFR, FGFR1, K-ras (for endometrial cancer), HPV E-16, HPV E-7, HPV E-6, tyrosine, and kinase (for cervical cancer), which help to identify the cancers in woman reproductive organs. This review provided an overview of current and potential biomarkers for gynecological cancer such as ovarian, endometrial and cervical cancers for early detection, diagnosis and targeted therapy.

Keywords: *Gynecological Cancer, Endometrial cancer, Ovarian Cancer, Cervical Cancer, Uterine Cancer, Gynecological Cancer Biomarkers.*

1. INTRODUCTION

Cancer is a major societal, public health, and economic problem in the21st century, responsible for almost one in six deaths (16.8%) and one in four deaths (22.8%) from noncommunicable diseases (NCDs)worldwide. The disease causes three in 10 global premature deaths from NCDs (30.3% in those aged 30–69 years), and it is among the three leading causes of death in this age group in 177 of 183 countries [1] In addition to being an important barrier to increasing life expectancy, cancer is associated with substantial societal and macro-economic costs that vary in degree across cancer types, geography,and gender [2]. One recent study illustrated the profound impact of disproportional cancer mortality in women [3]. Gynecological cancers, the most common cancer among women worldwide, disrupt the function of women's reproductive system, significantly impacting the quality of life. The epidemiological patterns of gynecological cancers differ in various regions and alter over time. The main challenge to deal with women's cancers is focusing on potential plans to improve patient outcomes. The epidemiology and general risk elements of gynecological cancers are important in the management of these cancers.[4].

- Risk Factors Overview: [5-20]

❖ Age:

The risk of most gynecological cancers increases with age, particularly after menopause.

❖ Genetics and Family History:

Mutations in BRCA genes and family history of ovarian or other cancers significantly increase risk.

❖ Reproductive Factors:

Nulliparity (never having been pregnant), early menarche, late menopause, and prolonged use of hormone replacement therapy are associated with increased risk for some cancers.

❖ Lifestyle Factors:

Obesity, smoking, alcohol consumption, and a sedentary lifestyle can contribute to the risk of certain gynecological cancers.

❖ Other Medical Conditions:

Endometriosis, previous cancer diagnoses, and certain genetic syndromes and HPV and HIV infections can also elevate risk.

Figure-1: Risk factors of gynecological cancers [6]

2. GLOBAL INCIDENCE AND MORTALITY OF GYNOLOGICAL CANCER

Gynecological cancer, including cervical, endometrial, and ovarian cancer, represents a significant global health challenge, impacting millions of women each year.

In 2009, it is estimated that, worldwide, cervical cancer accounts for 487,300 new cases and 269,500 deaths; uterine corpus cancer for 233,300 new cases and 61,400 deaths; ovarian cancer for 230,000 new cases and 140,100 deaths; cancers of vagina, vulva, placenta, and ill-defined sites together constitute 74,900 cases. Around 70,000 new cases of uterine cancers are reported in India every year [21-28]. Cervical cancer, caused by persistent infection with oncogenic forms of human papillomavirus (HPV), is the fourth most common cancer among women worldwide. The Indian subcontinent had 678,383 new cancer cases in women per GLOBOCAN 2020 data. Almost 380,000 (25%) of these cases were gynaecological cancers [29]. In 2022, there were 1473427 new cases of GCs and 680 372 deaths. The incidence of gynecological cancer reached 30.3 per 100000, and the mortality rate hit 13.2 per 100000. The age-standardised incidence of GCs in Eastern Africa is higher than 50 per 100000, whereas the age-standardised incidence in Northern Africa is 17.1 per 100000. The highest mortality rates were found in East Africa (ASMR (age-standardised mortality rates) of 35.3 per 100000) and the lowest in Australia and New Zealand (ASMR of 8.1 per 100000). These are related to the endemic areas of HIV and HPV. Very High HDI countries had the highest incidence of GCs, with ASIR (age-standardised incidence rates) of 34.8 per 100000, and low HDI countries had the second highest incidence rate, with an ASIR of 33.0 per 100000. Eswatini had the highest incidence and mortality (105.4 per 100000; 71.1 per 100000) and Yemen the lowest (5.8 per 100000; 4.4 per 100000). If the current trends in morbidity and mortality are maintained, number of new cases and deaths from female reproductive tract tumours is projected to increase over the next two decades. [30].

The incidence of gynaecological cancers (GCs) in the female reproductive system have been increasing due to improper lifestyle patterns, dietary habits, and genetic factors [31]. Gynaecological cancers (GCs) include vulvar cancer (ICD-10 C51), vaginal cancer (ICD-10 C52), cervical cancer (ICD-10 C53), uterine cancer (ICD-10 C54), ovarian cancer (ICD-10 C56), and fallopian tube cancer (ICD-10 C57.0) depending on the location of the tumour. Among these cancers, the incidence of fallopian tube tumours is very rare [32,33]. Endometrial cancer, ovarian cancer, and cervical cancer represent the highly

occurring cancers and account for more than one-third of the newly diagnosed cancers globally in females [34,35]. Gynaecological cancers, encompassing ovarian, cervical, endometrial (uterine), vulvar, and vaginal cancers, present a multifaceted landscape of risk factors, spanning genetic predispositions, environmental exposures, and behavioural patterns. Analysing each cancer type reveals a nuanced interplay of these factors [36]. Ovarian cancer, for instance, shows potential links to environmental exposures like asbestos and talcum powder, alongside behavioural influences such as dietary habits and reproductive history. Conversely, cervical cancer's primary environmental risk factor is persistent infection with high-risk HPV types, compounded by behaviours like sexual activity and smoking, and influenced by dietary choices [36]. Endometrial cancer illustrates the significance of hormonal factors, with oestrogen exposure, obesity, and diet playing pivotal roles. Vulvar and vaginal cancers, while sharing HPV infection as a common environmental factor, also exhibit the impact of behaviours like smoking and sexual activity [37,38]. Despite variations among GCs, certain behavioural factors consistently emerge as influential across the spectrum. Lifestyle modifications, including healthy diet choices, avoidance of tobacco, safe sexual practices, and HPV vaccination, offer significant avenues for risk reduction. Regular medical screenings further augment prevention efforts by enabling early detection and intervention [19]. Comprehensive analysis underscores the complex interaction of genetic, environmental, and behavioural factors in shaping the risk landscape of GCs. By addressing modifiable risk factors through proactive lifestyle measures and medical interventions, individuals can substantially mitigate their susceptibility to these diseases, thereby enhancing overall well-being and longevity [6]. Incidence and mortality of GCs could affect the quality of life of women and cause a higher health care burden for health care organisations around the world [39,40]. GLOBOCAN reports provide comprehensive estimates of cancer incidence and mortality for 185 countries or geographical regions worldwide. These findings enable to describe the current global cancer burden, offering valuable insights for policymakers and researchers. Previously, the global burden of individual GCs is still no report on the world burden of corpus uteri and vaginal cancer in 2022, and there is no relevant analysis on the overall incidence and mortality of GCs [6].

Figure-2. Incidence and mortality of various gynaecological cancers (GCs) and Their Proportions in 2022.[6].

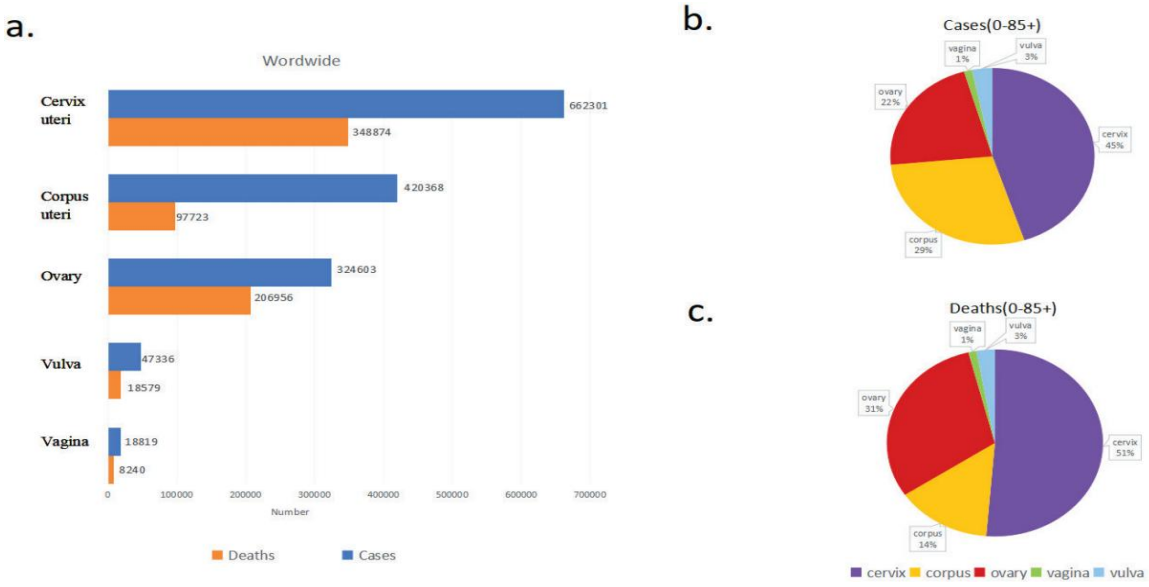


Figure-2, illustrating the (A) incidence and mortality rates of different types of GCs in 2022, illustrating the overall burden of each cancer type on the population. (B) and (C). The proportion of each type of gynaecological cancer cases, deaths relative to the total number of GC cases in age groups 0 to over 85 years. These charts provide a visual breakdown of the distribution of various GCs, highlighting the most prevalent forms and their impact on public health.

Global Incidence of Ovarian Cancer: [6,7]

In 2020, a total of 313,959 new cases of ovarian cancer were recorded globally, with an ASR incidence of 6.6 per 100,000 (Figure 1). The highest incidence was found in Central and Eastern Europe (ASR = 10.7), followed by Northern Europe (ASR = 8.8), Polynesia (ASR = 8.8), North America (ASR = 8.1), and South East Asia (ASR = 8.1). The lowest incidence was observed in Central Africa (ASR = 4.4), the Caribbean (ASR = 4.6), and Southern Africa (ASR = 4.9). The highest incidence of ovarian cancer was observed in countries with a high-income level (ASR = 8.0), followed by countries with an upper–middle-income (ASR = 6.3), low–middle-income (ASR = 6.1), and low income (ASR = 5.3) levels. 3.2. [6].

Global Mortality of Ovarian Cancer:

In 2020, a total of 207,252 new deaths due to ovarian cancer were reported globally, with an ASR mortality of 4.2 per 100,000. The highest mortality was observed in Micronesia (ASR = 7.3), followed by Polynesia (ASR = 6.6), Central and Eastern Europe (ASR = 5.6), South East Asia (ASR = 5.2), and Melanesia (ASR = 5.2). The lowest mortality was observed in the Caribbean (ASR = 3.2), East Asia (ASR = 3.3), and Southern Africa (ASR = 3.3). The highest mortality was found in countries with a low–middle-income level (ASR = 4.3), followed by countries with high-income level (ASR = 4.1), low-income level (ASR = 4.1), and upper–middle-income level (ASR = 3.9) [7].

3. GLOBAL INCIDENCE AND MORTALITY OF CERVICAL CANCER

Globally in 2020, there were an estimated 604 127 cervical cancer cases and 341 831 deaths, with a corresponding age-standardised incidence of 13·3 cases per 100 000 women-years (95% CI 13·3–13·3) and mortality rate of 7·2 deaths per 100 000 women-years (95% CI 7·2–7·3). Cervical cancer incidence ranged from 2·2 (1·9–2·4) in Iraq to 84·6 (74·8–94·3) in Eswatini. Mortality rates ranged from 1·0 (0·8–1·2) in Switzerland to 55·7 (47·7–63·7) in Eswatini. Age-standardised incidence was highest in Malawi (67·9 [95% CI 65·7 –70·1]) and Zambia (65·5 [63·0–67·9]) in Africa, Bolivia (36·6 [35·0–38·2]) and Paraguay (34·1 [32·1–36·1]) in Latin America, Maldives (24·5 [17·0–32·0]) and Indonesia (24·4 [24·2–24·7]) in Asia, and Fiji (29·8 [24·7–35·0]) and Papua New Guinea (29·2 [27·3–31·0]) in Melanesia. A clear socioeconomic gradient exists in cervical cancer, with decreasing rates as HDI increased. Incidence was three times higher in countries with low HDI than countries with very high HDI, whereas mortality rates were six times higher in low HDI countries versus very high HDI countries. In 2020 estimates, a general decline in incidence was observed in most countries of the world with representative trend data, with incidence becoming stable at relatively low levels around 2005 in several high-income countries. By contrast, in the same period incidence increased in some countries in eastern Africa and eastern Europe. It was also observed different patterns of age-specific incidence between countries with well developed population-based screening and treatment services (eg, Sweden, Australia, and the UK) and countries with insufficient and opportunistic services (eg, Colombia, India, and Uganda)[6-8].

4. GLOBAL INCIDENCE AND MORTALITY OF ENDOMETRIAL CANCER

In the past 30 years (1990-2021), the number of cases of endometrial cancer in patients aged 55 years and above worldwide has increased from 141173 (95% CI: 131743–148151) to 360253 (95% CI: 326176–388,545), more than doubling. The incidence rate per 100000 has increased from 39.22 (95% CI: 36.6–41.16) in 1990 to 45.81 (95% CI: 41.47–49.4) in 2021. However, the number of deaths per 100000 postmenopausal patients due to endometrial cancer decreased by 1.82, and DALYs and Years of Life Loss also gradually decreased [6-9] .

In 2021, globally, there were 360253 (326,176–388545) cases and 84630 (75,523–93215) deaths among postmenopausal patients with endometrial cancer. During 1990–2021, the global endometrial cancer incidence in postmenopausal women gradually increased, while the mortality rate gradually decreased. Changes in disease incidence and mortality rates are mainly due to population growth and epidemiological changes, with little influence of age. The risk of endometrial cancer in postmenopausal women gradually increased with age, using age, period, and cohort average as the reference groups. The mortality rate decreased gradually decreased in 2019 and continued to rise thereafter. It is expected that by 2036, the incidence of endometrial cancer in postmenopausal women aged 55 years and above will increase by 6.5%, and the mortality rate will decrease by 8.0% (Table-1). The number of patients with postmenopausal endometrial cancer aged 55 years and above is still increasing, and it is necessary to establish a comprehensive screening and treatment mechanism to ensure prolongation of patient lifespan [9-11].

5. GLOBAL INCIDENCE AND MORTALITY OF UTERINE CANCER

In 2021, global uterine cancer cases among women≥50 years reached 414,754 (95% UI: 370,388–453,502), causing 90,509 deaths (95% UI: 78,633–101,441) and 2,189,261 DALYs (95% UI: 1,920,396–2,446,737). Age-standardized incidence rate (ASIR) rose (EAPC=0.56, 1990–2021), while mortality and DALYs declined. High-income North America had the highest ASIR (128/100,000), with the United States, China and Russia leading new cases. High Sociodemographic index (SDI) regions exhibited widening disparities, evidenced by a 21% increase in the slope index of inequality (SII) for incidence (47 in 1990 to 57 in 2021) and concentration indices (CI) rising from 0.33 (95% CI: 0.28, 0.37) in 1990 to 0.35 (95% CI: 0.29, 0.4) in 2021. Population growth drove 132.55% of DALY changes, outweighing epidemiological (-32.95%) and aging (0.4%) factors. Projections suggest declining ASIR, the age-standardized mortality rate (ASMR), and DALY rates by 2040, yet absolute cases will rise to 617,571 new cases, 131,961 deaths, and 2,851,768 DALYs [10].

Table-1: Worldwide Prevalence, Incidence Rate, Mortality, YLLs, YLDs, and DALY of Endometrial Cancer Among Women Over 55 years of Age in 1990 and 2021.

	Cases in the Age Group of 55 and Above in 1990 (Number)	Rate per 100000 People Aged 55 and Above in 1990	Cases in the age Group of 55 and Above in 2021 (Number)	Rate Per 100000 People Aged 55 and Above in 2021
Prevalence	933396 (878566, 974040)	259.32 (244.09, 270.61)	2520955 (2295892, 2697219)	320.54 (291.92, 342.95)
Incidence	141173 (131743, 148151)	39.22 (36.6, 41.16)	360253 (326176, 388545)	45.81 (41.47, 49.4)
Deaths	45276 (40910, 48510)	12.58 (11.37, 13.48)	84630 (75523,93215)	10.76 (9.6,11. 85)
DALYs	1049016 (950111, 1129775)	291.44 (263.96, 313.88)	1936376 (1735390, 2129562)	246.21 (220.66, 270.78)
YLDs	68495 (50484, 90275)	19.03 (14.03, 25.08)	176769 (128879, 235268)	22.48 (16.39, 29. 91)
YLLs	980522 (888428, 1049910)	272.41 (246.83, 291.69)	1759608 (1578633, 1941994)	223.74 (200.72, 246.93)

This cancer is challenging to detect early, as symptoms like bloating, pelvic pain, and changes in appetite are non-specific and easily overlooked. Survival rates are also significantly lower than for cervical and endometrial cancers, emphasizing the need for enhanced diagnostic tools, increased awareness, and improved therapeutic intervention. Population-based screening represents the only way by which the incidence of ovarian cancer could be reduced, but there is a lack of biomarkers with sufficient sensitivity and specificity to justify screening. In general, cancer is a chronic disease, and efficient management requires the use of innovative clinical tools at several stages. At the time when symptoms appear, there is a need for precise diagnosis for stratification on alternative follow- up or treatment modalities. After treatment, there needs to be means for efficient monitoring, to detect signs of relapse early [41-46].

Finally, the only way to effectively reduce the incidence of cancer in the population is either by preventative prophylactic treatment, such as the vaccination program against HPV, or by implementing population-based screening using biomarkers to detect early- stage cancer [33-42].

6. BIOMARKERS

According to the US National Institute of Health's (NIH) working group and the biomarkers consortium, “a biomarker is a characteristic that can objectively be measured as an indicator of normal pathogenic processes or a pharmacological response to a therapeutic intervention” [42]. The primary goal of biomarker development is not only focused on upgraded therapeutics but also focused on improved methods to deter- mine an individual's risk assessment in cancer development, and to detect cancers at early stages, when they can be more effectively treated [41]. Biomarkers are generally found in the blood or tissues or other body fluids providing a sign of normal or abnormal processes or conditions. A biomarker may be measured by biosensor, genetics, proteomics, cellular or molecular substances found in higher than normal amounts in the body fluids (blood, urine) of cancer patients [43]. An ideal biomarker test would have 100% sensitivity and specificity but none of the currently available biomarkers achieve this [47]. The clinical significance of tumor markers has been demonstrated in several studies. (guidelines of the National Academy of Clinical Biochemistry (NACB). [Fig-3, Table-2A]

Figure-3: Biomarkers for gynecological cancer:

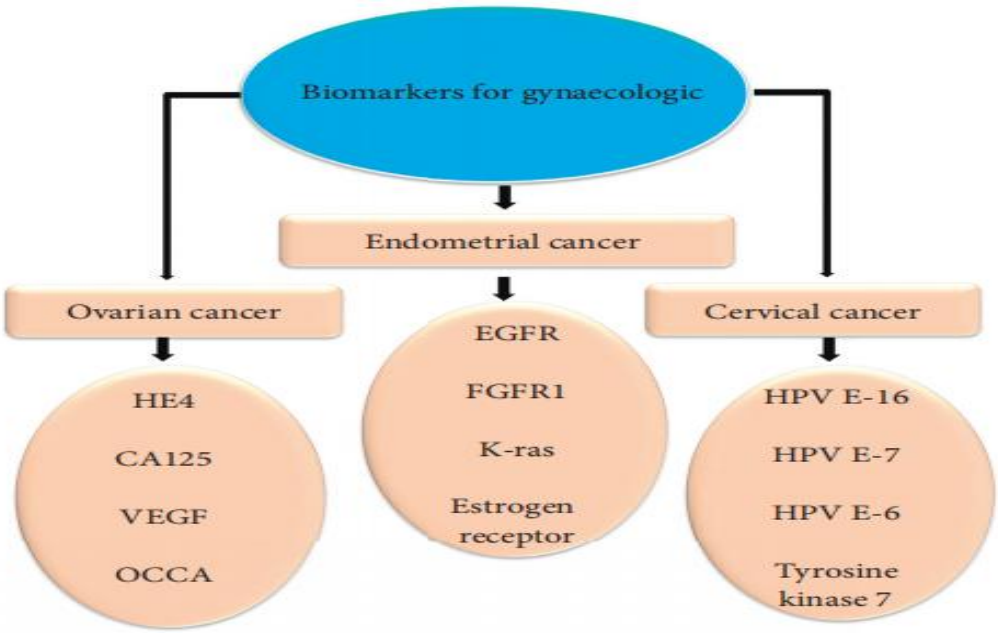


Table-2 A: Biomarkers for gynaecological cancer [14-42]

S. No.	Biomarker	Type of Cancer	Potential utility	Reference
1	BRCA1/2	Breast	Used as a novel potential predictive biomarker for determining the differential chemo-sensitivity at both preclinical and clinical stage.	14
2	HER-2/NEU	Breast	Used to measure HER-2/neu status in breast cancer clinical samples	15
3	ER/PR	Breast	Used as prognostic/predictive biomarkers for clinical use in breast cancer	16
4	TP53	Ovarian	Could be used as a biomarker for malignant progression.	17
5	MLH1	Ovarian	Used as a potential biomarker of risk for colorectal neoplasms	18
6	MSH2	Ovarian	Could be used as a potential modifiable biomarker of risk for colorectal neoplasms.	19
7	MMP	Ovarian	Could be used as diagnostic/prognostic biomarker with disseminated peritoneal/pulmonary metastasis	20
8	MIF	Ovarian	Used as a biomarker in diagnosing renal involvement in children with SLE	21
9	EGFR	Ovarian	Could be used as a potential predictive biomarkers	22
10	M-CSF	Ovarian	Used as a multiple biomarkers improve sensitivity in women at high risk for ovarian cancer.	23
11	FSH	Ovarian	Could be used as a biomarker for estimating the day of ovulation in population based studies	24
12	SMRP	Ovarian	Used for screening asbestos exposed populations, monitoring treatment and predicting prognosis	25
13	CA125 (Cancer Antigen 125)	Ovarian	Used for early detection of Ovarian Cancer	26
14	HE4 (Human Epididymis Protein 4)	Ovarian	Used as a novel serum biomarker in high risk population	27
15	Mesothelin	Ovarian	Eligible as a target for cancer therapy.	28
16	KLK (Kallikreins)	Ovarian	Could be used as tumor markers for the epithelial derived serous carcinomas.and their diagnosis and monitoring.	29
17	PRSS8	Ovarian	Used as novel biomarker for to identify upregulated genes for secretor proteins.	30
18	Glutathione S-Transferase Polymorphism	Ovarian	Used as a novel biomarker for early detection and diagnosis of ovarian cancer	31
19	FOLR1 (Folate Receptor Alpha)	Ovarian	Used as a biomarker in detection, prognosis, and assessing chemotherapy responses of ovarian carcinoma	32
20	miRNA	Ovarian	Used as a potential biomarkers for early detection, diagnosis, and monitoring the overall progress of the disease	33
21	ALDH1	Ovarian	Could be a possible biomarker for early detection of ovarian carcinomas	34
22	HPV E6	Cervical	Used in the screening, early diagnosis, prognostication and prediction of response to therapy.	35
23	HPV E7	Cervical	Could be used for rapidly analyze and display changes in protein expression under different conditions for neoplastic cell subpopulations.	36
24	MCM (Mini Chromosome Maintainance)	Cervical	Used as a potential biomarker for cervical dysplasia	37
25	CDC6 (Cell Division Cycle Protein 6)	Cervical	Could be a biomarker of high grade and invasive lesions of the crvix with limited use in low grade dysplasia	38
26	SCC (Squamous Cell Carcinoma Antigen)	Cervical	Could be used for monitoring the early detection of recurrent or progressive disease after primary treatment, and may therefore be useful in the management of patients.	39
27	PCNA	Cervical	Could be used as a marker with highly effective detector of malignancy.	40
28	Ki-67	Cervical	1. Could be used as a biomarker for both prognostic and predictive value. 1. May be used for pre-analytical, analytical, and post-analytical practice in clinical practice	41
29	$p^{16}INK^{4A}$	Cervical	1. Could be used as a sensitive/specific marker of squamous and glandular dysplastic cells of the cervix. 2. Used as a surrogate marker of high risk HPV suggesting a valuable adjunctive test in cervical cancer screening	42

- Aptamer-Mediated Detection of Gynecological Cancer: [17-85]

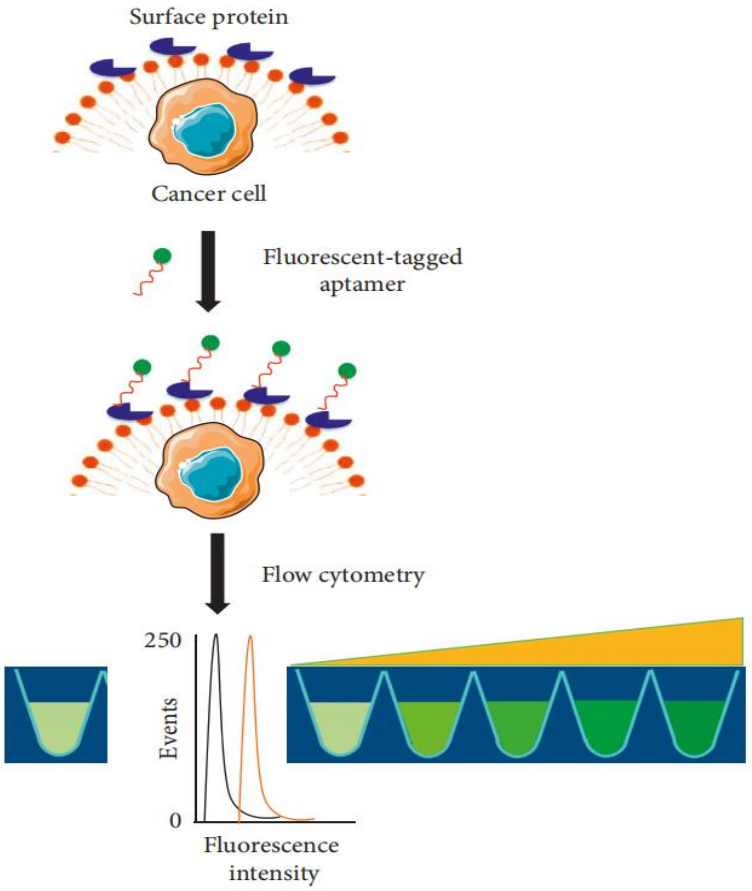
The aptamer is a substitute for the antibody, known as the artificial antibody, and has more positive characteristics, generated against a wide range of biomarkers including ovarian cancer. through the efficient detection of these biomarkers using the specific probe, it is easier to identify ovarian cancer at an earlier stage [48-53]. Since aptamer is one of the specified probes to most of the target molecules, it is possible to detect the cancer targets at a lower level. Various aptamers have been generated against various biomarkers to analyze and identify ovarian cancer. In general cell-SELEX [53], the intact cells have been used to generate the aptamer for the particular cell line. [56] have selected the high-affinity aptamer against two

different cell lines, namely, TOV-21G and OCCA for ovarian cancer. +e DNA aptamer for HE4 biomarker is generated [57] using the capillary electrophoresis SELEX; the dissociation constant of the aptamer for HE 4 is found to be within nanomolar range. +ese selected aptamers are used to detect the ovarian cancer. In another research, [58] used the aptamer to specifically detect CA 125 biomarker for recognizing ovarian cancer. The reference range for CA 125 is 38.3 U/mL, and there is a necessity to identify CA 125 lesser than the reference level [59-68]. A study used the carboxyfluorescein- (FAM) labeled CA 125 aptamer and the fluorescence quenching method to identify CA 125. +e detection limit is found as 0.05 U/mL . Since VEGF is related to many cancers, various aptamers are generated against VEGF [58-69]. The normal range of VEGF is found to be lesser than 500 ng/mL [60]. +e aptamer-based colorimetric assay is used to detect VEGF [69-78]. In this colorimetric assay, the unmodified gold nanoparticle (GNP) has been used, in the presence of target aptamer. +en, the colour of free GNP changes to blue with a high salt concentration, for example, NaCl. In the absence of target, the aptamer binds on the surface of the GNP, and the colour of GNP remains in its original red colour even at a high salt concentration. +e limit of detection of VEGF is to be 185 pM with this assay. Moreover, GNP-conjugated aptamer is also used for the photothermal therapy [78-85].(Table-2B,Fig-4)

Table-2 B: Summary on biomarkers and aptamers with detection strategies.

Gynaecological cancer	Biomarker	Aptamer type	Diagnosing method	Limit of detection	Advantage/disadvantage	Reference
Ovarian cancer	CA125	DNA	Fluorescence quenching	0.05 U/mL	Sensitive, need background optimization	[17]
Ovarian cancer	VEGF	DNA	Colorimetric assay	185 pM	Less sensitive, visual detection	[18]
Cervical cancer	PTK-7	DNA	RAMAN scattering	—	Need training personnel	[19]
Cervical cancer	PTK-7	DNA	Cytosensor	10-10^6 cells/mL	*In vivo* reflects real condition	[20]
Endometrial cancer	EGFR	RNA	Electrical	—	Sensitive, label free	[21]
Endometrial cancer	EGFR	DNA	Electro chemical	50 pg/mL	Sensitive, consume more sample volume	[22]
Cervical cancer	HPV-16 E-7	RNA	Radio isotope	Kd 1.9 μM	Sensitive, aptamer needs stabilization	[23]
Cervical cancer	HPV-16	DNA	ELISA	—	Gold standard, less sensitive	[24]
Ovarian cancer	CA 125	DNA	FET sensor	5.0×10^{-9} U/mL	Sensitive, label free	[25]

Figure-4: Detection of cancer by fluorescent-tagged aptamers.



- Proteomics approach in biomarker discovery for Gynecological Cancer:

The advancement in protein separation, identification, quantification and validation provides a better understanding of protein functions [86]. Complete characterization of proteomes can only be achieved using mass spectrometry techniques such as nanoflow liquid chromatography-tandem mass spectrometry (nanoLC-MS/MS), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDITOF MS) and surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS).[87-88]. To accurately quantify proteins, label-free quantification (LFQ) or labelled-based approaches such as Multidimensional Protein Identification Technology (MudPIT), Isotope-Coded Affinity Tag (ICAT) and isobaric Tag for Relative and Absolute Quantitation (iTRAQ) are the methods of choice.Validation of the identified biomarkers is done using suitable assays including immunohistochemistry, Western Blot, and ELISA. Other immunoassay techniques for the detection of proteins in body fluids include Luminex bead assay, electrochemiluminescence immunoassay (ECLIA), and Simple Plex multi-analyte immunoassay[81-101]. [table-2C].

Table-2C: Potential protein tumor biomarkers as a single or combination panel for ovarian, endometrial and cervical cancers [G. Kumarasamy and G. Kaur.Clínica e Investigación en Ginecología y Obstetricia. 2022; 49: 100735]

Protein biomarker	Cancer	Sample	Approach	Proposed application	Specificity	Sensitivity
Cancer antigen 125 (CA125)	Ovarian	638 blood samples; 445 benign ovarian tumors, 31 borderline ovarian tumors, 162 malignant ovarian tumor	ECLIA	Diagnosis	80%	92%
		844 blood samples; 262 benign ovarian tumors, 196 malignant pelvic tumors, 386 healthy	ECLIA	Diagnosis	70.61%	62.75%
		172 blood samples; 125 newly diagnosed ovarian cancer, 30 benign ovarian masses,17 healthy	Simple Plex immunoassay	Diagnosis	87.0%	90.4%
	Endometrial	221 blood samples; 110 uterine endometrial cancer, 111 healthy	ELISA	Diagnosis	74.1%	69%
Human epididymis 4 (HE4)	Ovarian	233 blood samples; 67 invasive epithelial ovarian cancers, 166 benign ovarian neoplasms	ELISA	Diagnosis	95%	72.9%
		140 blood samples; 50 benign ovarian tumors, 60 ovarian carcinoma, 30 healthy	ELISA	Diagnosis	98%	80%
	Endometrial	327 blood samples, 171 endometrial cancer, 156 healthy	ELISA	Prognosis	95%	45.5%
		Blood samples; 101 surgically staged endometrial cancer, 103 benign uterine disease	ELISA	Diagnosis and prognosis	100%	59.4%
Osteopontin	Ovarian	127 blood samples; 25 ovarian cancer, 7 borderline ovarian tumors, 34 benign ovarian tumors, 30 other gynecologic cancers, 31 healthy	ELISA	Diagnosis	33.7%	81.3%
Transthyretin	Ovarian	287 blood samples; 93 stages I & II ovarian cancer, 100 stages III & IV ovarian cancer, 94 control	Singleplex Luminex bead assay	Diagnosis	95%	47%
IL-8	Ovarian	211 blood samples; 44 stages I & II ovarian cancer, 50 stages III & IV ovarian cancer, 37 benign pelvic mass, 80 healthy	Luminex bead assay	Diagnosis	98%	65.5%
IL-6	Ovarian	126 blood samples; 44 early-stage ovarian cancer, 37 benign pelvic tumors, 45 healthy	Multiplex Luminex bead assay	Prognosis	86%	84.1%

Protein biomarker	Cancer	Sample	Approach	Proposed application	Specificity	Sensitivity
Kallikreins	Ovarian	156 frozen tissue samples; 134 epithelial ovarian cancer, 22 low malignant potential	ELISA	Diagnosis and prognosis	90%	72%
B7-H4	Ovarian	326 tissue samples; 251 ovarian cancer, 43 benign ovarian tumor, 32 healthy	ELISA	Diagnosis	97%	65%
Transthyretin (truncated) + ApoA1 + connective tissue activating peptide III + CA125	Ovarian	231 blood samples; 41 stages I & II epithelial ovarian cancer, 51 stages III & IV epithelial ovarian cancer, 40 benign ovarian tumors, 99 healthy	ELISA, SELDI-TOF-MS	Diagnosis	98%	84%
VCAM-1 + CA125 + CEA + HE4	Ovarian	2765 blood samples; 69 stage I ovarian cancer, 114 stage II ovarian cancer, 273 stage III & IV ovarian cancer, 296 benign pelvic tumor, 315 other cancers, 2.031 healthy	Multiplex Luminex bead assay	Diagnosis	98%	86%
CA125 + HE4 + E-CAD + IL-6	Ovarian	172 blood samples; 125 newly diagnosed ovarian cancer, 30 benign ovarian mass, 17 healthy	Simple Plex immunoassay	Diagnosis	84.2%	95.7%
ApoA1 + CA125 + transthyretin	Ovarian	263 blood samples; 118 ovarian cancer, 84 benign ovarian tumor, 61 healthy	Multiplex Luminex bead assay	Diagnosis	95%	93.9%
Transthyretin + CA125 + ApoA1 + transferrin	Ovarian	358 blood samples; 90 stages I & II ovarian cancer; 96 stages III & IV ovarian cancer, 79 benign ovarian tumors, 93 healthy	Chemiluminescence assay	Diagnosis	98%	76%
Squamous cell carcinoma antigen (SCC-Ag)	Cervical	188 serum samples; 138 cervical cancer, 50 healthy	Chemiluminescence assay	Prognosis	54.9%	82.1%
Carcinoembryonic antigen (CEA)	Cervical	139 blood samples; 7 cervical intraepithelial neoplasia, 80 squamous cell carcinoma, 16 adenocarcinoma, 36 healthy	ELISA	Prognosis	98%	33%
Serum fragments of cytokeratin (CYFRA)	Cervical	188 serum samples; 138 cervical cancer, 50 healthy	ECLIA	Prognosis	68.2%	65.2%

- RNA Biomarkers for Gynaecological cancer:

❖ RNA modifications:

RNA modifications play a pivotal role in orchestrating the finely tuned symphony of gene expression, and their dysregulation has emerged as a critical factor in the pathogenesis of cancers. Internal modification in RNA has posttranscriptionally and extensively regulate the behaviors and biological functions of RNAs among which methylation is the most frequent. Among the diverse array of RNA chemical modifications, N6-methyladenosine (m6A) [102]. N1-methyladenosine (m1A)[103-113]. 5-methylcytosine (m5C) and pseudouridine (Ψ) stand out as key players present in eukaryotic mRNA, each contributing unique layers of complexity to the epitranscriptomic coding in governing cellular homeostasis and disease states[115-119].In recent years, multiple studies indicate that m6A contribute to influence the occurrence and progress of tumor by regulating tumor metabolism. The post-transcriptional modification (PTCM) of RNA primarily involves three effectors: (i) writers for writing specific chemical groups into mRNA, which subsequently mediates mRNA modifications; (ii) readers for reading the information contained in these mRNA modifications to maintain mRNA stability and participate in RNA translation and splicing; and (iii) erasers for erasing mRNA modification signals, mediating mRNA modifications, and converting them back into unmodified nucleosides [120-128].

Table-2D: Common writers, erasers, or readers of RNA modifications in human gynecological cancers [128].

Category	m6A	m5C	m1A	Ψ
writers	METTL3/14/16; WTAP; VIRMA	NSUN; DNMT2	TRMT10C/61A/61B; RRP8	PUS7; DKC1
readers	YTHDF1/2/3;YTHDC1/2;IGF2BP1/2/3;HNRNPA2B1	ALYREF; YBX1; FMR1	YTHDF1/2/3; YTHDC1	unknown
erasers	ALKBH5; FTO	TET1; ALKBH1	ALKBH1/3/7; FTO	unknown

➢ microRNA (miRNA): miRNAs have been shown to regulate the expression of many genes, including those that are aberrantly expressed in cancer cells as well as those that are known to promote carcinogenic processes such as cell proliferation, differentiation, and apoptosis [129-142]. Given the differential miRNA expression patterns that have been identified between cancer and healthy patients, miRNAs have the potential to be used as biomarkers for ovarian cancer detection.The level of miR-205 has been reported to be elevated in cancer patients and has been shown to have the potential for distinguishing cancer patients from healthy people; miR-205 was shown to have an AUC of 0.715, a sensitivity of 66.7%, and a specificity of 78.1%. [130-144].

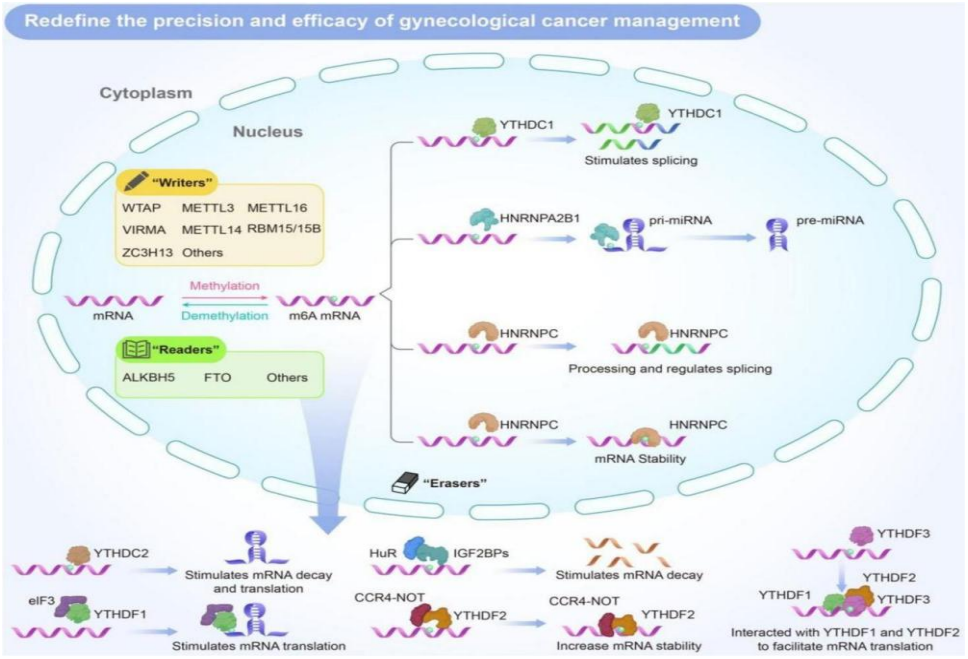


Figure-5: Redefine the Precision and Efficacy of Gynecological Cancer Management. m6A mRNA methylation is orchestrated by three main classes of proteins: methyltransferases ("writ- ers"), demethylases ("erasers"), and m6A-binding proteins ("readers"). Methyltransferases, such as METTL3/14, WTAP, VIRMA, ZC3H13, and RBM15/15B, predominantly catalyze the addition of m6A modifications to mRNA. Conversely, demethylases, including FTO and ALKBH5, facilitate the removal of m6A modifications from bases. The primary role of m6A-binding proteins is to recognize m6A-modified sites and subsequently activate downstream regulatory pathways, including RNA degradation and microRNA (miRNA) processing. The binding of m6A sites to different readers mediates distinct functional outcomes.[Qi y. et al.Cell Biol Toxicol (2024) 40:92]

Figure-6: Unraveling m6A Regulators in Specific Gynecological Cancer:

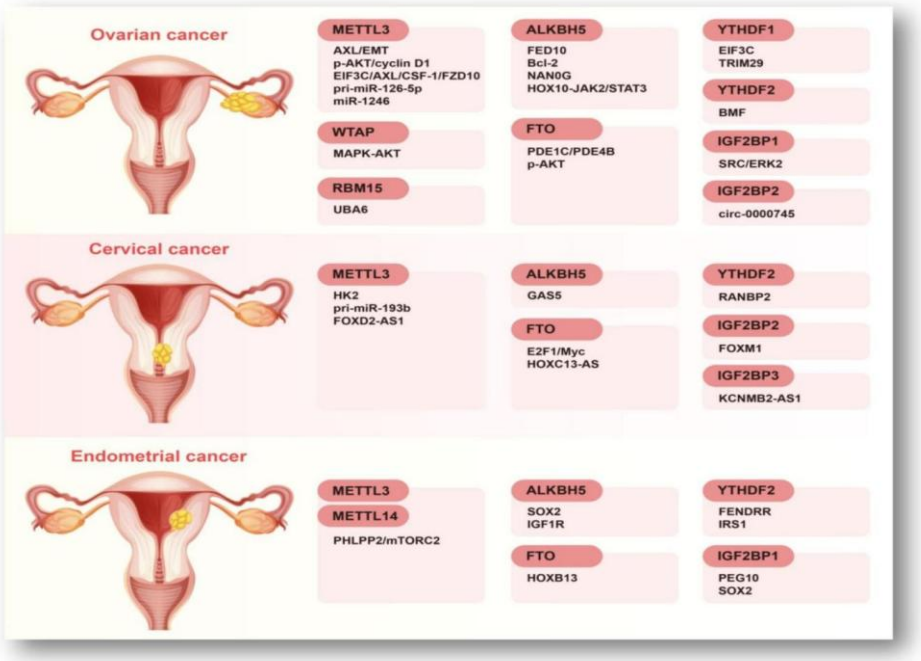


Fig.6, illustrating the unraveling m6A Regulators in Specific Gynecological Cancer, Comprising of Ovarian, Cervical, and Endometrial cancer. m6A writers (the left column), erasers (the middle column), and readers (the right column) functioned in diverse signal pathways in specific gynecological cancers.

- CircRNAs as potential biomarkers of gynecological tumors:

A growing number of studies have focused on the relationship between gynecological tumors and circRNAs. CircRNAs act as miRNA sponges, regulating cellular proliferation. CircRNAs bind to RBPs to regulate cell functions. CircRNAs regulate the transcription of parental genes. CircRNAs with IRESs can be translated into peptides or proteins.A previous study revealed that circRNAs are stable and expressed to a high degree in various cancer cell lines [141-156].

Figure-7:Functions of circRNAs. [Shi Y et al.Oncology Reports. 2020 44: 1787-1798].

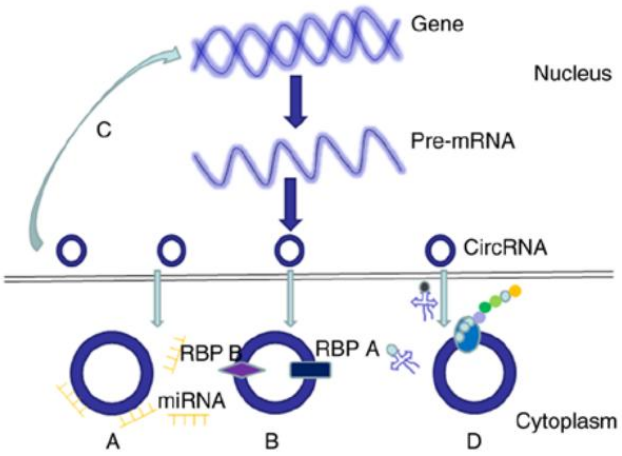
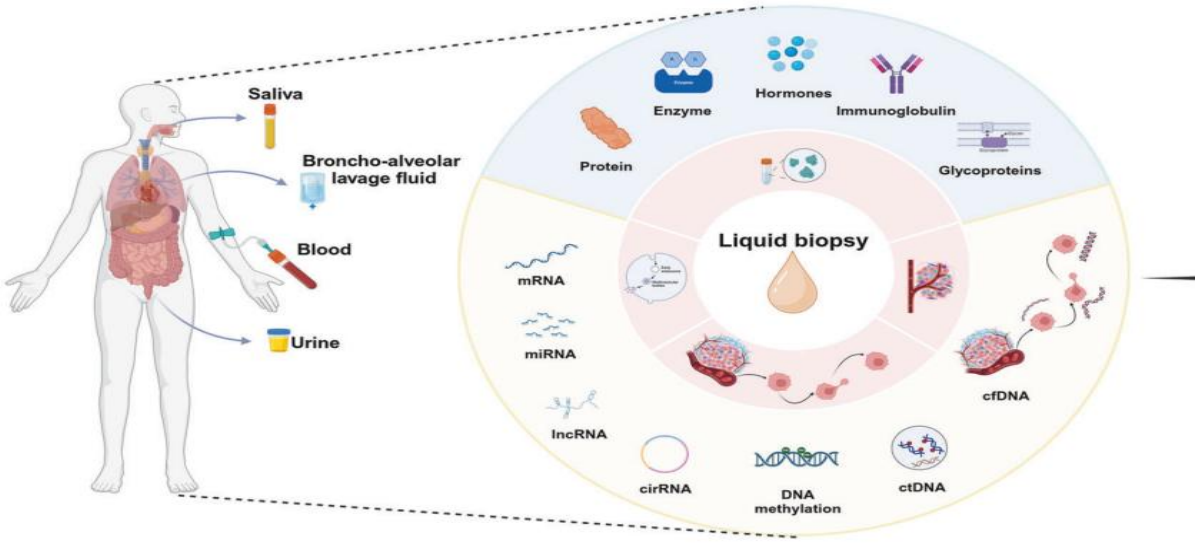


Figure-7, illustrating (A) CircRNAs act as miRNA sponges, regulating cellular proliferation. (B) CircRNAs bind to RBPs to regulate cell functions. (C) CircRNAs regulate the transcription of parental genes. (D) CircRNAs with IRESs can be translated into peptides or proteins. CircRNA, circular RNA; RBP, RNA-binding protein; IRES, internal ribosome entry site.

- Liquid biopsy and Biomarkers:

Liquid biopsy is a mini-invasive sample collection method that focuses on blood or body secretions for the detection of molecular alterations, tumor cells, and metabolites. [157,158] Compared to tissue biopsies, liquid biopsies provide a role in early screening. Common specimens for liquid biopsy are blood and urine.[115,158-162]. Therefore, liquid biopsies are easier to perform than tissue biopsies and are virtually non-invasive to the patient,5,6 which makes liquid biopsies have the potential for continuous monitoring of tumor progression.[163]. Several molecular markers can be detected by liquid biopsy, such as circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), tumor-derived extracellular vesicles (EVs), tumor-educated platelets (TEPs), and circulating free RNA (cfRNA) [163-173].

Figure-8: Applications of liquid biopsies and types of biomarkers for liquid biopsies for gynecological cancer.



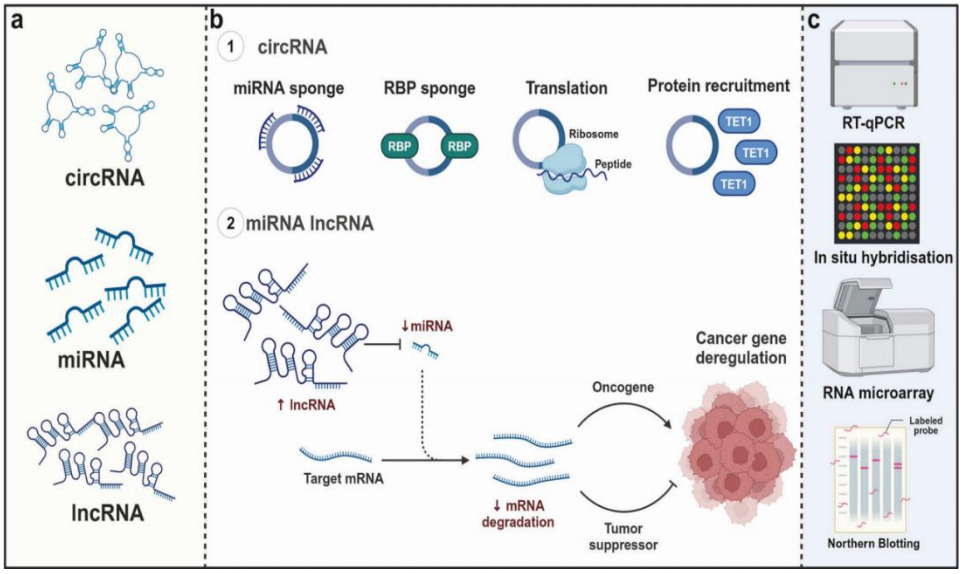


Figure-9: Liquid biopsy markers—RNA. a Types of ncRNA. b The role of ncRNA. c The detection methods for ncRNA

Table-2E: Liquid biopsy biomarkers in gynecological cancers:

Biomarker	Source and Mechanism	Detection Methods	Advantages	Challenges	Clinical Applications
Circulating Tumor DNA (ctDNA)	- DNA fragments released during cell death (apoptosis, necrosis) or secreted in vesicles - Rapid turnover (~114 min half-life)	- ddPCR (e.g., TP53, KRAS mutations) - NGS panels (e.g., CancerSEEK) - Bisulfite sequencing (methylation)	- Reflects real-time genetic profile - Useful for MRD detection - Some FDA-approved assays (Guardant360, etc.)	- Low abundance in early-stage disease - Requires high-quality, standardized sample handling - Rapid degradation	- Early detection in high-risk cohorts - Monitoring therapy response - Detecting emerging drug resistance
Circulating Tumor Cells (CTCs)	- Intact cancer cells shed from primary or metastatic tumors - Extremely low concentrations (<10 cells/ml)	- Enrichment by EpCAM-based methods - Immunoaffinity or size-based capture - Single-cell sequencing	- Offers insight into metastatic potential - Enables phenotypic/molecular profiling (EMT, etc.)	- Epithelial-mesenchymal transition can mask surface markers - Limited sensitivity for early-stage cancers	- Evaluating micrometastatic disease - Prognostic indicator of relapse
Exosomes	- 30–100 nm vesicles carrying DNA, RNA, proteins - Actively secreted by tumor cells	- Tetraspanin-based isolation (CD63, CD9, CD81) - Ultracentrifugation or size-exclusion chromatography - Microfluidic platforms	- Reflect molecular makeup of parent tumor - Stable in circulation - Potentially high abundance	- Isolation protocols vary widely - Tumor-derived exosomes can be <2% of total exosomes	- Noninvasive biomarker for diagnosis - Monitoring disease progression - Distinguishing benign vs. malignant processes
Tumor-Educated Platelets (TEPs)	- Platelets that have absorbed tumor-derived RNAs, proteins, and vesicles - Undergo alternative splicing events	- RNA-seq of platelet RNA - Microarray or qPCR for TEP-specific transcripts	- Abundant and easy to isolate - Reflect real-time tumor influence - Inexpensive sample collection	- Standardization of isolation/analysis needed - May capture only partial tumor signals	- Early detection or screening tool - Potential for identifying molecular alterations in real time
MicroRNAs (miRNAs)	- 21–25 bp non-coding RNAs with oncogenic or tumor-suppressor roles - Circulate in protein-bound form or within exosomes	- qPCR or microarray (single or panel) - Next-generation sequencing - Microfluidic and immunoaffinity platforms	- High stability in biofluids - Tissue-specific expression - Detectable in small sample volumes	- Isolation procedures can affect data quality - Requires careful validation of target miRNAs	- Discriminating benign from malignant lesions - Combining with CA-125 for improved diagnostic accuracy (ovarian CA) - Potential screening tool

Table-2F: Liquid biopsy in reproductive system cancers

Cancer	Liquid biomarker	Origin	Tendency	Downstream target	Function
Cervical cancer	CTCs	Peripheral blood	up		Prognostic biomarker
	ccfHPV-DNA	Plasma			Efficacy monitoring biomarker
	HOTAIR, PVT1, XLOC_000303, AL592284.1	Plasma	up		Early diagnostic biomarker
	miR-21, -25, -29a, -200a, -486-5p	Serum	up		Early diagnostic biomarker, Disease progression biomarker
	miR-196a	Serum	up		Disease progression biomarker, Prognostic biomarker
	miR-425-5p	Serum	up		Prognostic biomarker
	ESR1, ERBB2 mutation	Plasma	up		Efficacy monitoring biomarker
Endometrial cancer	CTCs	Peripheral blood	up		Early diagnostic biomarker
	CK-20	Peripheral blood	up		Tumor aggressiveness biomarker, Tumor recurrence biomarker
	CTNNB1, KRAS, PTEN, PIK3CA	Plasma	up		Tumor recurrence biomarker, Efficacy monitoring biomarker
	DNA methylation	Urine	up		Early diagnostic biomarker
Ovarian Cancer	claudin	Serum exosome	up		Early diagnostic biomarker
	miR-1307, miR-375	Serum exosome	up		Early diagnostic biomarker
Prostatic carcinoma	CTCs	Peripheral blood	up		Prognostic biomarker
	cfDNA mutation	Serum	up		Early diagnostic biomarker
	cfDNA	Plasma	up		Efficacy monitoring biomarker, Prognostic biomarker
	miR-21	Serum	up		Efficacy monitoring biomarker
	miR-141, miR-146b-3p, miR-194	Serum	up		Prognostic biomarker

- Current Biomarkers for Ovarian Cancer:

❖ Cancer Antigen 125 (CA125):

CA125, a glycoprotein encoded by MUC16, is secreted from the coelomic and müllerian epithelia into the bloodstream [175]. CA125 is overexpressed in more than 80% of ovarian cancer patients and can be detected in serum, creating an opportunity to discriminate malignant ovarian tumors from the normal population [176]. In 2011, CA125 was recommended by the National Institute for Health and Care Excellence (NICE) of the UK as a screening test for women with symptoms of possible ovarian cancer [177-183]. Postmenopausal women with a CA125 level higher than 35 U/mL are considered to have a high risk of a malignancy. The accuracy of CA125 for detecting early-stage ovarian cancer is limited; only 50% of early-stage patients have elevated CA125 levels, leading to a low sensitivity (50–62%) for detecting early-stage ovarian cancer. Serum CA125 levels were only able to differentiate advanced-stage patients from healthy controls. Furthermore, the specificity of CA125 is relatively low (generally 73–77%) and more than 60% of patients with increased CA125 levels do not have ovarian cancer [18]. Elevated CA125 levels can be detected due to pregnancy; the menstrual cycle; other malignancies such as breast cancer, uterine cancer, stomach cancer, pancreatic cancer, liver cancer, and colon cancer; and other benign conditions such as acute pelvic inflammation, adenomyosis, uterine myoma, and endometriosis [182-191].

❖ Human Epididymis Secretory Protein 4 (HE4)

HE4 is a member of the whey acidic four-disulfide core (WFDC) protein family that was originally identified in the epithelium of the distal epididymis [191]. It is a peptide protease inhibitor involved in the innate immune response of epithelial tissues [192, 193]. HE4 is not found in the ovarian surface epithelium; however, it is overexpressed in ovarian cancer tissue, where it is secreted into the extracellular environment and can be detected in the blood stream [194]. Therefore, the detection of serum HE4 is another potential biomarker for the diagnosis and monitoring of ovarian cancer. The HE4 levels provides an ability to detect ovarian cancer with a specificity of 96% and a sensitivity of 67% [195]. Compared with CA125, HE4 is less frequently affected by benign gynecological conditions; it is not elevated in endometriosis and it has only been found to increase in adenomyosis patients [196].

❖ Potential Protein Biomarkers for Ovarian Cancer Detection

Protein biomarkers have been widely studied during the past 3 decades and more than 100 potential biomarkers have been evaluated. Folate receptor alpha (FOLR1) is a membrane protein regulating the binding and cellular uptake of folic acid into cells [173-180]. The FOLR1 expression is restricted to the luminal surfaces of the epithelial cells in healthy populations, but it is highly expressed in many epithelial cancers, including breast cancer, ovarian cancer, clear cell renal carcinomas, endometrial carcinomas, and lung cancer [174]. Around 76% of high-grade ovarian cancer patients show a FOLR1 overexpression [175]. Serum FOLR1 has also shown an increased specificity compared with CA125, which has demonstrated a better diagnostic performance [177].

CA72-4 : It is a tumor-associated glycoprotein, a distinct epitope on the MUC1 mucin and its abnormal elevation has been detected in ovarian cancer [178]. Its level is not influenced by pregnancy, the menstrual cycle, or endometriosis [179,180] and is only slightly affected by inflammatory conditions [81]. Therefore, the addition of CA72-4 to CA125 could increase the diagnostic specificity, but at the cost of the sensitivity [157]. Furthermore, its overexpression has been detected in many ovarian clear cell carcinomas and mucinous tumor cases whereas CA125 and HE4 levels are generally not elevated in these two histotypes, which means that CA72-4 may have the potential to detect cases missed by CA125 and HE4 [182,183]. However, the sensitivity of CA72-4 as a single marker is limited [184].

Transthyretin (TTR): It is another potential biomarker that is downregulated in ovarian cancer patients. The TTR performed better than CA125 and HE4 in the detection of early-stage (stages I and II) ovarian cancer [85]. Other molecular biomarkers for the detection of early ovarian cancer are under investigation, including CA15-3 [199], glycodelin [200], and kallikrein 11 [198].

Autoantibodies (AABs): The genetic alteration of cancer cells leads to an aberrant expression of tumor-associated antigens (TAA) that can be recognized by the immune system, resulting in the generation of corresponding AABs [98]. AABs are stable proteins that can be detected in the circulation for long periods of time and typically have higher concentrations due to an immune system-induced amplification, such that they can detect aberrant antigens at low concentrations [199]. AABs provide a new insight into ovarian cancer detection.

The anti-TP53 autoantibody: It is the best-studied for ovarian cancer detection. The tumor suppressor gene TP53 is mutated in more than 95% of high-grade serous ovarian cancer patients [200].

Circulating Tumor DNA (ctDNA):ctDNAs are DNA fragments that are released from cancer tissues into circulating bodily fluids such as blood, urine, and ascites through apoptosis, necrosis, lysis, and active secretion [201]. ctDNAs can be detected and quantified using PCR, BEAMing technology, and sequencing. Cancer tissues are characterized by specific genetic alterations such as point mutations, copy number alterations, deletions, and epigenetic alterations. Studies have identified that these tumor-related genetic changes are also present in ctDNAs, even in patients at early stages of ovarian cancer.

Table-3: Diagnostic Serum Biomarkers Markers for Ovarian Cancer:

	Cut-off	Ref. No.	SE (%)	SP (%)	PPV	NPV
CA125	>35 U/mL	26	82.2	67.3	47.1	91.4
	>65 U/mL	26	75.6	86.6	66.7	90.9
CA19-9	>40 U/mL	26	35.6	81.1	40	78
CA15-3	>32 U/mL	26	57.1	93.9	75.9	86.7
CA72-4	>3.8 U/mL	26	70.7	91.8	75.7	89.6
CEA	>3 ng/mL nonsmoke, >5 ng/mL smoker	37	16	93	37	83
HE4	>70 pmol/L	41	72.9	95	NA	NA
LPA	1.3 mmol/L	41	98	90	NA	NA
IAP	482 mg/mL	34	93.3	91	NA	NA
HP-a	65 mg/mL	44	64	90	NA	NA
OVX-1	7.2 m/mL	49	70	95	NA	NA
Methothelin	–	43	60	98	NA	NA

IAP, immunosuppressive acidic protein; NA, not assessed; NPV, negative predictive value; Ref. No., reference number; SE, sensitivity; Spec, specificity;

Table-4:. Expression and functional characterization of circRNAs in ovarian cancers.

circRNAs	Expression	Binding miRNA	Function	Biomarker	(Refs.)
circMAN1A2	Up	NA	NA	Serum biomarker	(70)
hsa_circ_0013958	Up	NA	Plays a role as an oncogene in ovarian cancer	FIGO stage and lymph node metastasis	(71)
circLARP4	Down	miR-424	NA	Prognostic biomarker	(72)
CircRNA_MYLK	Up	microRNA-652	Promotes the malignant progression	Prognostic biomarker	(73)
hsa_circ_0051240	Up	miR-637	Promotes ovarian cancer cell proliferation, migration and invasion	NA	(74)
circ-ABCB10	NA	miR-1271 miR-1252 miR-203	Promotes cell proliferation but reduces cell apoptosis	Poor prognosis and advanced FIGO stage	(75)
Circ-SMAD7	Up	NA	Promotes the progression	NA	(76)
VPS13C-has-circ-001567	Up	NA	Inhibits apoptosis and promotes proliferation	NA	(77)
hsa_circ_0078607	Down	miR-518a-5p	Leads to cell apoptosis	NA	(79)
circ_100395	Down	miR-1228	Inhibits cell growth and metastasis	NA	(80)
circSETDB1	Up	NA	Predicts chemotherapy response	Chemoresistant	(81)
CDR1as	Down	miR-1270	Suppression of cisplatin resistance, cell proliferation, and apoptosis. Enhances the sensitivity of ovarian cancer to platinum	NA	(82)

- Endometrial cancer:

Endometrial cancer is classified into type 1 estrogen-responsive and type 2 estrogen-non-responsive cases, based on the mechanism of development. Type 1 endometrial cancer, caused by estrogen stimulation, is often observed in perimenopausal middle-aged women and has a well-differentiated histological type. By contrast, type 2 endometrial cancer is more frequent in older women following menopause, is moderately- to poorly-differentiated and has a poor prognosis. It also has four stages; at stage 1, it appears only in the upper part of the uterus. At stage II, it enters into the cervix; at stage III, it spreads into the vagina, nearby tissues, and lymph nodes. At the final stage IV, it moves to the intestine, bladder, and other parts of the body. Various factors cause endometrial cancer including metabolic syndrome, obesity, and consumption of medicines such as tamoxifen and estrogen [152, 153]. Identifying at the earlier stages of endometrial cancer helps to avoid damage of the uterus. Pelvic and transvaginal ultrasound is generally used to identify the endometrial cancer. Also, the endometrial biopsy is an accurate method to identify the endometrial cancer. All these methods are recognized to be expensive and complicated. If the detection method is designed for the biological samples such as urine and blood serum, it will be useful to identify the cancer. Sometimes, the whole blood test is taken to count the blood cells. Due to the overbleeding caused by endometrial cancer, the red blood cell count will be lower in the patient. In this way, they can assume the patient condition but cannot say accurately. Suitable biomarkers with the right probe are necessary to identify endometrial cancer at earlier stages at the lower abundance. All the cancer progressions are varying with the biomarker expression levels. +ese variations are either upregulated or downregulated from their normal level. With the downregulation, there is an expectation of associated target at a lower level [202-210].

❖ Current Biomarkers of Endometrial cancer:

The US National Cancer Institute (NCI) defines a biomarker as ‘a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease’. According to this definition, a biomarker includes not only the proteins normally used as tumor markers, such as CA-125, but also genes and chromosomes. Identifying a suitable biomarker helps to improve the diagnosis method. +e progesterone receptor, estrogen receptor, mutated PTEN, K-ras, p53, oncogenes, and HER2/neu mutation have been found as the potential biomarkers for endometrial cancer. It is found that there is a positive association between the positive estrogen and progesterone with endometrial cancer [194]. Also, PTEN tumor-suppressor gene mutation is found in endometrial cancer [215-216]. At the same time, it is found that K-ras gene is overexpressed but not mutated in endometrial cancer [196]. In addition, oncogene, fibroblast growth factor receptor 2 (FGFR2), P13KCA, and epidermal growth factor receptor (EGFR) are also playing a necessary role in endometrial cancer. FGFR2, a tyrosine kinase receptor, is mainly involved in the process of tissue homeostasis, embryogenesis, and cell proliferation. Mutations in FGFR2 are found (10–12%) in the endometrial cancers [158]. A significant amount of EGFR expression is found in endometrial cancer. p21 and cyclin-dependent kinase inhibitor 2A (CDKN2A) cancer suppressor

genes; the hMLH1, hMSH2, hMSH6, PMS1 and PMS2 mismatch repair genes; Ki-67, an index of cell proliferation; BCL2-associated X protein (Bax), an apoptosis promotor gene; Bcl-2, an apoptosis suppressor; expression levels of estrogen and progesterone receptors; microvascular density (MVD); and vascular endothelial growth factor A (VEGF-A), which are all indices of angiogenesis; expression changes in E/P-cadherin and β-catenin, which are associated with infiltration and metastatic capacity; and ploidy and aneuploidy of DNA [190-201]. The characteristics and functions of each of these biomarkers are described in this review.

Table-5A: Biomarkers of type 1 and type 2 endometrial cancer with expression%.

Target	Function	Change	Type 1 (%)	Type 2 (%)
K-ras	Oncogene	Mutation	13-26	0-10
HER-2/neu	Oncogene	Enhanced expression	Rare	18-80
PIK3CA	Oncogene	Mutation	26-36	26-36
FGFR2	Oncogene	Mutation	12	12
PTEN	Tumor suppressor	Mutation, deletion, methylation	35-55	0-11
p53	Tumor suppressor	Mutation	5-10	80-90
p16	Cancer suppressor	Mutation, methylation, enhanced expression	10	10-40
MLH1	DNA repair	Methylation	20-35	0-10
Bcl-2	Tumor suppressor	Mutation	65	67
Bax	Oncogene	Mutation	48	43
ER, PR	Transcription factor	Enhanced expression	70-73	19-24
β-catenin	Oncogene	Mutation	25-38	0-5
E-cadherin	Tumor suppressor	Mutation, methylation	22-43	57-75
EZH2	Transcription factor	Enhanced expression	16	36
BMI-1	Transcription factor	Enhanced expression	53	62

Table-5A. PIK3CA, phosphatidylinositol 3-kinase catalytic subunit; FGFR2, fibroblast growth factor receptor 2; PTEN, phosphatase and tensin homolog; Bax, BCL2-associated X protein; ER, estrogen receptor; PR, progesterone receptor

Table-5B:. Biomarkers as prognostic predictors in endometrial cancer.

Evidence level	Biomarker
Consistent results obtained in retrospective studies	DNA ploidy *ER/PR* *p53* *Ki-67* *Bcl-2*
Inconsistent results obtained in several studies	*HER-2/neu* *PTEN* *p16* MSI β-catenin *K-ras*
An association with prognosis suggested in a few studies	Angiogenesis markers (MVD, *VEGF-A*, *VPI*, *VMI*, *GMP*) E-cadherin *PI3K* signal activation

Table-5C: Expression and functional characterization of circRNAs in endometrial cancers.

circRNAs	Expression	Binding miRNA	Function	Biomarker	(Refs.)
hsa_circ_0039569	Up	miR-542	NA	Diagnosis	(92)
Circ-ITCH	NA	miRNA-17 miRNA-224	NA	Diagnosis	(95)
circWHSC1	Up	miR-646	Promotes endometrial cancer development	Prognostic biomarker	(97)

Table-6. Genetic characteristics of ovarian and endometrial cancers.

Tissue	Type	Subtype	Somatically mutated genes (frequency)	Reference
Endometrial	Type I: endometrioid	Endometrioid	*PTEN* (64%)	
			PIK3CA (59%)	(29)
			ARID1A (55%)	(29)
			CTNNB1 (32%)	(29)
			MLL2 (32%)	(29)
			FBXW7 (27%)	(29)
			RNF43 (27%)	(32)
			APC (23%)	(32)
			FGFR2 (18%)	(32)
			KRAS (9%)	(32)
			PIK3R1 (9%)	(32)
			EGFR (14%)	(32)
			AKT1 (5%)	(32)
			NRAS (5%)	(32)
			TP53 (5%)	(32)
	Type II: non-endometrioid	Papillary serous	*TP53* (82%)	(30)
			PIK3CA (24%)	(30)
			FBXW7 (20%)	(30)
			PPP2R1A (18%)	(30)
		Clear cell	*TP53* (45%)	(30)
			PPP2R1A (33%)	(31)
			PIK3CA (29%)	(31)
			PTEN (13%)	(31)
			PIK3R1 (9%)	(32)
			KRAS (5%)	(32)
Ovarian	Epithelial	High-grade serous	*TP53* (96%)	(29)
			CSMD3 (6%)	(29)
			FAT3 (6%)	(29)
			BRCA1 (3%)	(29)
			BRCA2 (3%)	(29)
		Endometrioid	*TP53* (68%)	(32)
			ARID1A (30%)	(32)
			CTNNB1 (26%)	(32)
			PTEN (17%)	(32)
			PIK3CA (15%)	(32)
			KRAS (10%)	(32)
			PPP2R1A (11%)	(32)
			CDKN2A (12%)	(32)
			BRAF (8%)	(32)
		Clear cell	*ARID1A* (57%)	(30)
			PIK3CA (40%)	(30)
			PPP2R1A (7%)	(30)
			KRAS (4.7%)	(30)
		Low-grade serous	*BRAF* (38%)	(31)
			KRAS (19%)	(31)
		Mucinous	*TP53* (56%)	(32)
			KRAS (40%)	(32)
			PPP2R1A (33%)	(32)
			CDKN2A (16%)	(32)
			PTEN (11%)	(32)

- Cervical cancer (CC):

It is a major public health concern worldwide, ranking 4th in terms of incidence and mortality among cancers affecting women.Human papillomavirus (HPV) infection is the primary cause of CC; however, smoking, age, and low socioeconomic

status have been linked to the disease development [200- 203]. Diagnostic tests such as Pap smears and viral DNA analysis, as well as the development of vaccines against different HPV genotypes, have all contributed significantly to reducing CC incidence [204]. Despite advancements in screening and treatment, this cancer remains a major public health issue, particularly in lowand middle-income countries where access to cervical cancer screening is limited [205- 2011]. Researchers are actively characterizing new molecular biomarkers that hold potential for aiding in disease detection, risk assessment, treatment monitoring, and survival prognosis.

Figure-9:. Multiple risk factors leading to cervical cancer.

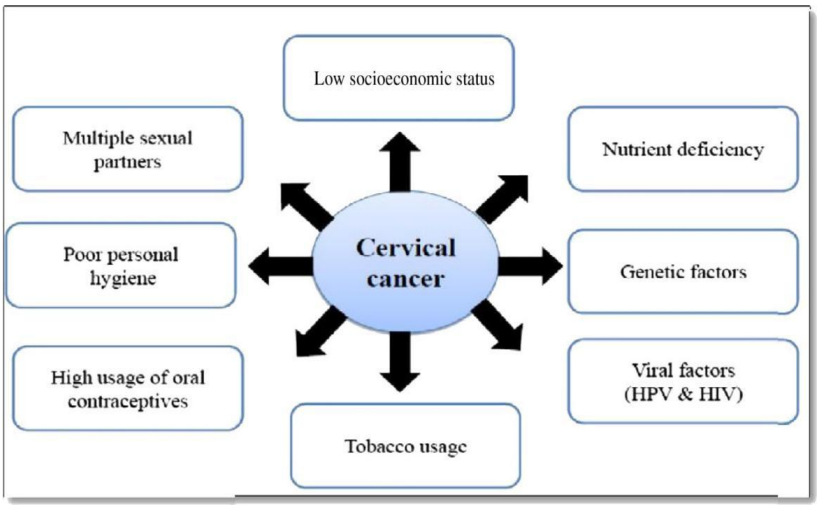


Figure-10: Promising predictive molecular biomarkers for cervical cancer. [Lizano M. et al. IJMM, 2024;53: 50].

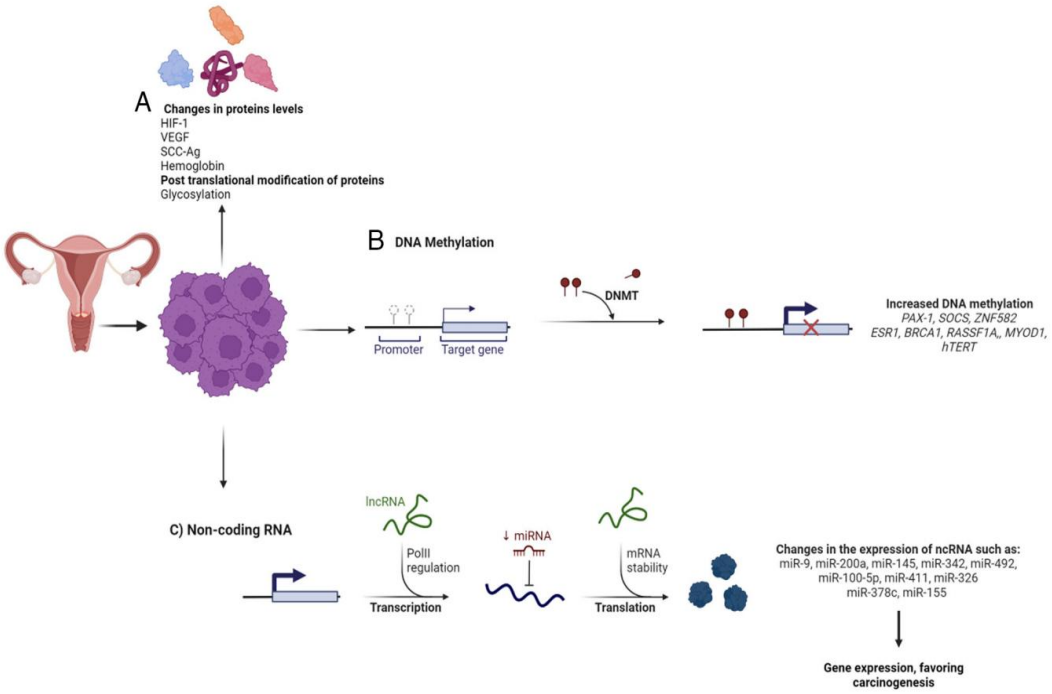


Figure-10, Illustrating that (A) candidate protein biomarkers. The predictive value of protein biomarkers is mainly based on their abnormal expression levels and aberrant glycosylation; this is the case of VEGF, HIF-1, hemoglobin and Scc-Ag, which have shown that alterations in their levels are related to the clinical response. (B) Possible methylation-based biomarkers. Modifications in DNA methylation patterns, are present in cervical cancer, mainly hypermethylation in several genes including PAX-1, ZNF582, ESR1, MYOd1, BRcA1, RASSF1A and hTERT, favoring decreased gene expression. Some of these genes have been evaluated to identify new predictive biomarkers. (c) Potential role of non-coding RNAs as predictive biomarkers. miRNAs are implicated in post-transcriptional regulation of gene expression. Profiles of aberrantly expressed miR, such as miR-9, miR-200a, miR-145, miR-342, miR-492, miR-100-5p, miR-411, miR-326, miR-378c and miR-155,

have been associated with treatment response in cervical cancer; also long non-coding RNAs and circular RNAs have been associated with clinical response; however, the involved molecular mechanisms have not yet been elucidated and are subject of further investigation. VEGF, vascular endothelial growth factor; HIF-1, hypoxia-inducible factor; Scc-Ag, squamous cell carcinoma antigen; PAX-1, paired-box transcription factor 1; ZNF582, zinc finger protein 582; ESR1, estrogen receptor 1; MYOD1, myogenic differentiation 1; BRCA1, breast cancer gene 1; RASSF1A, Ras association domain family member 1A; hTERT, human telomerase reverse transcriptase; miRNA/miR, microRNA

Table-7: Major Genes Involved in Cervical Malignancies: [4-101].

S. No	Genes	Chromosome Location	Total Exons	Protein (Amino Acids)	Function	References
1.	Tumor protein (*TP53*)	17p13.1	11	393	Controls the activity of cell cycle pro- gression and apoptosis	26,27,45
2.	Phosphatidyl inositol-4, 5-bisphosphate 3-kinase (*PIK3CA*)	3q26.3	21	1068	An oncogene that plays major role in the PIK-AKT signaling pathway	29,30,45
3.	Serine/ Threonine Kinase 11 (*STK11*)	19p13.3	10	433	Controls the cell and DNA damage response	31,45
4.	Kirsten Rat Sarcoma Viral Oncogene Homolog (*KRAS*)	12p12.1	05	188	An oncogene involved in regulation of cell division	32,33,45
5.	Epidermal Growth Factor Receptor (*EGFR*)	7p11.2	28	1210	An oncogene involved in regulation of cell division	34,45
6.	Nucleolar Protein (*NOL7*)	6p21.3	08	257	A tumor suppressor gene that plays a role in the cell cycle	37,45
7.	Cyclin- dependent Kinase Inhibitor 2A (*CDKN2A*)	9p21.3	03	156	Encode for tumor suppressor protein; plays a significant role in the regulation of the cell cycle	38,45
8.	Phosphatase and Tensin Homolog (*PTEN*)	10q23.3	09	403	Main function is to regulate the cell cycle	39,45
9.	Binding Protein p300(*EP300*)	7p11.2	31	2414	Regulates cell growth, assumes speci- alized functions	29,45

Table-8: Biomarkers for investigation of carcinogenesis, precancerous lesions and cervical carcinoma [102-181].

Croups of Markers	Markers	References
Biomarkers of HPV infection and carcinogenesis	HPV DNA, E6/E7 mRNA p53, Rb, p16INK4a, telomerase RNA gene (TERC), serum SCC-Ag, OCVA1	[8,10–13,15,20–26]
Markers of cell cycle and proliferation	Ki-67, cyclin D1, p53, p63	[12,26–36]
Markers of apoptosis	P53, BCL-2, BCL-XL, BAX	[10,27,37–44]
Expression of cytokeratins–markers of differentiation	CK7, CK8, CK17, CK19	[27,36,37,45–49]
Markers of cell adhesion, invasion and metastasis	E-cadherin, P-cadherin, CD44, ADAM9, MT1-MMP, TIMP-1, TIMP-2, MT1-MMP, MMP-2, MMP-1, MMP-9, MMP-14, proMMP-14 furin, gelatinase, TIMP-1 and TIMP-2	[27,50–55]
Biomarkers of cancer stem cells	Nanog, nucleostemin (NS), musashi1 (Msi1), SOX2, KLF4, CD133, Cd44, ALDH1, CD49f, ABCG2, BMI1, PIWIL2, LGR5, OCT4, CD117	[48,56–64]
Markers of angiogenesis	VEGF, podoplanin (PDPN), thrombospondin-1 (TSP-1, antiangiogenesis factor), CD31 (a nonspecific endothelial marker), CD34, CD105 (a tumor-specific endothelial marker)	[27,65–71]
Vaginal microbiome, inflammation and immune homeostasis	Evaluation of the diversity of cervicovaginal microbiome	[56,72–81]

Table-9: Cervical cancer biomarkers identified in different biological samples through proteomics analysis [199-215].

BioMarkers	Samples	Assay/ Technique	Conclusion	Ref.
ATP6AP1, CIRBP, CYR61, CCPG1, IGFBP7, LGMN, MTR, PTP4A1, SLC38A2, TGF-1, TRIM26,	HeLa, SiHa	iTRAQ-MS, WB	Possible therapeutic target	(58)
CLPTM1, CKAP5, FAM120A, TMX2	HeLa, SiHa, C33A	LC-MS/MS	Possible therapeutic target	(53)
TIMP1, ADAM10, FUCA1, SOD2, NEU1	HeLa, SiHa, C33A	LC/MS-MS, WB, MRM	Possible therapeutic target	(67)
Cornulin	Tissue	2D, MALDI-TOF-MS, IHC		(40)
AIF-1, ALP-2, B-FABP, CDK4, ICA69, NCK-1, PRSS1,	Tissue	ESI-MALDI-TOF/MS, WB, RT-PCR IHC	Diagnostic marker	(44)
S100A9, eEF1A1, PKM2	Tissue	2D, MALDI-TOF-MS WB/IHC		(68)
FABP5, HspB1, MnSOD	Tissue	2D-DIGE MALDI-TOF/TOF MS	Diagnostic, prognostic marker	(46)
G6PD	Tissue	iTRAQ NanoLC-MS/MS qRT-PCR. WB Microrray	Possible therapeutic target,	(69)
VEGF, VEGF-C	Serum, tissue	IHC, ELISA	Prognostic marker	(70)
TKT, APOA, FGA	Serum	LC-ESI-MS/MS, ELISA	Prognostic marker	(71)
AACT, A1AT, TRFE, FETUA, KNG1, VTDB	Serum	iTRAQ- LC-MS/MS	Diagnostic marker	(72)
SCC-Ag, hs-CRP, CA-125	Serum	ELISA	Prognostic marker	(73)

APOA4, APOA1, APOE), EPPK1, CFHR1, CP, F2, MASP2, CLU	Plasma	2D-DIGE MALDI-TOF/TOF MS ELISA	Diagnostic, Possible therapeutic target	(48)
APOA1, mTOR	Plasma	2D HPLC, LTQ MS/MS	Potential biomarker	(74)
ASAH1, CYC, DDX5, ENO1, PCBP2, TYPH	CVF	iTRAQ-MS	Diagnostic, Prognostic marker	(75)
ACTN4, VTN, ANXA1, CAP1, ANXA2, MUC5B	CVF	LC-MS/MS	Potential biomarker	(76)
ACTN4	CVF	ELISA	Potential biomarker	(77)
CD44, LRG1, MMRN1, S100A8, SERPINB3,	Urine	LC-MS/MS WB	Diagnostic marker	(78)
APOA1, MPO	cervical mucus	LC-MS/MS	Diagnostic marker	(59)

Table-10: Expression and functional characterization of circRNAs in cervical cancers [48-62].

circRNAs	Expression	Binding miRNA	Function	Biomarker	(Refs.)
Circ_0067934	Up	miR-545	Promotes cervical cancer progression	Metastasis(+)	(48)
circ-ATP8A2	Up	miR-433	Promotes cell progression and suppressing the expression of epidermal growth factor receptor	Lymph node invasion and FIGO stage(+)	(49)
circ-0000745	Up	NA	Acts as a tumor promoter	Vascular/lymphatic invasion(+)	(45)
circ_0005576	Up	miR-153-3p	Promotes cervical cancer progression	Pathological stage and lymph node metastasis(+)	(50)
circRNA_101308	Down	miR-26a-5p, miR-196a-5p, miR-196b-5p, miR-335-3p, and miR-1307-3p	Tumor suppressor	Deep myometrial invasion and lymph node metastasis(-)	(51)
circSLC26A4	Up	miR-1287-5p	Facilitates cancer progression	Poor prognosis	(52)
Circ_0018289	Up	miR-497	Promotes tumorigenesis	Poor prognosis	(53)
hsa_circ_0023404	Up	miR-136	Promotes tumorigenesis	Poor prognosis	(54)
circ-ITCH	Down	miR-93-5p	Suppresses proliferation and metastasis	NA	(61)
hsa_circ_0000263	Up	miR-150-5p	NA	NA	(62)

- Vulvar Cancer:

Vulvar cancer (VC) is a rare malignancy accounting for about 5% of cancers of the female genital tract and most often occurs in older women [33]. About 90% of vulvar carcinomas are squamous cell cancers and lesions are multifocal in about 5% of cases. The labia majora are involved in about 50% of cases followed by labia minor, mons pubis, clitoris, Bartholin glands, and perineum [4]. The overall incidence of vulvar cancer has risen over the last decade, probably because of an increase in human papilloma virus (HPV) infections [202-216]. Few biological markers have demonstrated clinical value for the management of vulvar cancer. Previous studies demonstrated that HPV and the surrogate biomarker p16 are associated with a less aggressive behaviour of vulvar cancer., while p53 positivity seems to be related with poor prognosis and significantly increased recurrence [212-215] .

- TECHNOLOGIES USED IN THE DETECTION OF TUMOR BIOMARKERS:

Multiple technologies have been developed for the detection of tumor biomarkers as follows (Fig-11). In the past decades, various immunoassay methods have played crucial roles in the discovery of tumor biomarkers. Meanwhile, molecular hybridization technology and gene amplification detection technology further broaden the horizon of the application of tumor biomarkers in clinical practice. Immunohistochemistry (IHC) brings about the original distribution of biomarkers in fixed tissue. Furthermore, rapidly developed DNA sequencing and gene-editing technologies accelerate the speed and numbers of digging out prognostic and predictive tumor biomarkers. Other technologies, such as liquid biopsy and different microscopy technologies, as well as single-cell sequencing analysis,[89-101] also provide tremendous convenience in cancer therapy

Figure-11: Technologies for the detection of tumor biomarkers

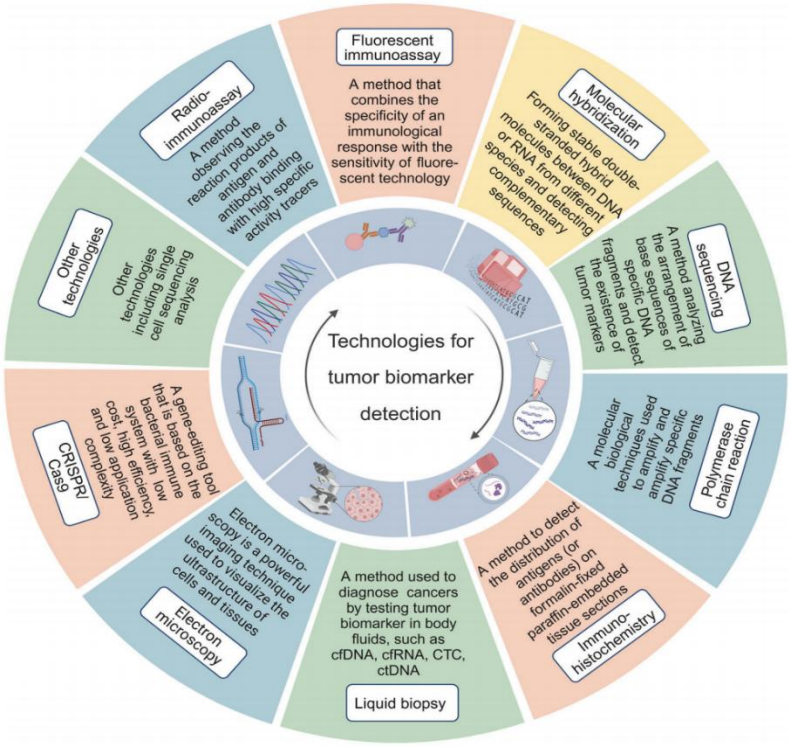


Figure-12: Overview of human tumor biomarkers:[187-201]

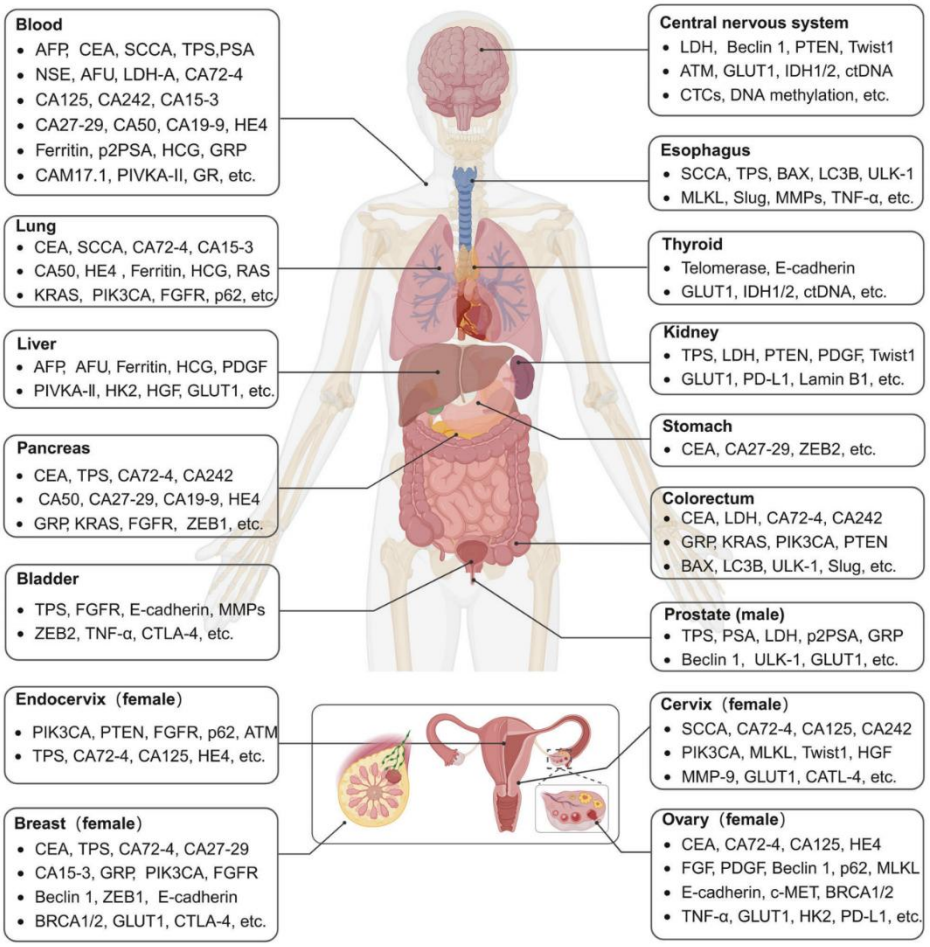


Table- 13: List of biomarkers and methods for gynecological cancer:

Category	Biomarker	Method
Viral markers		
Molecular (DNA)	HR-HPV DNA	PCR, signal amplification, and probe amplification
Molecular (DNA)	HPV genotype	PCR
Molecular (DNA)	Viral load	PCR
Molecular (mRNA)	Viral E6/E7 mRNA	PCR
Protein	E6/E7 oncoprotein	Immunohistochemistry
Protein	E4 protein*	Immunohistochemistry
Host/cellular biomarker		
Protein	P16INK4A/KI67	Immunohistochemistry
Protein	MCM5*	Immunohistochemistry
Protein	TOP2A*	Immunohistochemistry
Immunoprotein	PDL-1*	Immunohistochemistry
Molecular	miRNA*	RT-PCR
Molecular	Methylation markers*	Quantitative methylation specific-PCR
Circulating biomarkers		
Serum biomarker	SCC-Ag	ELISA
Serum biomarker	CEA	ELISA
Liquid biopsy	cfHPV DNA*	qPCR, ddPCR, NGS

- Biomarkers for Prognosis and Treatment of Gynecological Cancer:

Many retrospective studies have examined the effects of molecular markers on prognosis[73-79]. Several studies have shown an association of aneuploidy with poor prognosis [79-78]., while the expression of steroid receptors is associated with higher survival rates and better treatment response [79-88].). Among oncogenes, the overexpression of HER-2 is associated with a reduced survival rate, but the clinical meaning and the predictability of treatment response are not fully understood [62-72]. The overexpression of p53 has also been associated with a poor prognosis by a plurality of retrospective studies and the loss of expression of p16 is similarly linked to a poor prognosis [83-103]. The effect of the mutation of PTEN remains controversial, since this has been found to be positively associated with prognosis, whereas the loss of expression and methylation of PTEN are negatively associated with prognosis [99-130]. A high proliferative activity of tumor cells based on Ki-67 expression and the number of mitoses is associated with a poor prognosis in endometrial cancer; however, the multivariate survival analyses do not show concordant results, which may be due to technical differences in measuring Ki-67 [85-156]. The loss of expression of Bcl-2 and the resultant reduced apoptosis are also associated with a poor prognosis [79-87]. Drugs for molecularly targeted treatment are being explored for endometrial cancer. The biomarkers described in the previous sections are not necessarily the targets, but a number of biomarkers are under study as potential therapeutic targets, including aromatase, hormone receptors, EGFR tyrosine kinases, the VGFR family, PTEN as a downstream molecule in the PI3K pathway and mTOR. Abnormalities in the PI3K pathway are common in endometrial cancer and theuse of analogs of wortmannin, a PI3K inhibitor, as drugs is being examined. A number of mTOR inhibitors, including temsirolimus, are being tested in phase 2 trials in the US [88]. The efficacy and safety of cetuximab, gefitinib, erlotinib, lapatinib and trastuzumab (EGFR inhibitors) and aflibercept and bevacizumab (VGFR inhibitors) are also being examined in phase 2 trials [89]. circRNAs play an important role in the regulation of cellular proliferation, migration and invasiveness in cervical, ovarian and endometrial cancer, primarily via the miRNA sponging mechanism. Due to the stability of circRNAs, they possess great potential in tumor diagnosis and treatment. Furthermore, circRNAs can regulate gynecological tumors through a variety of molecular mechanisms, and blocking these pathways may represent novel therapeutic methodologies. Although sequencing techniques have identified a growing number of circRNAs, their functions in gynecological cancer are still largely unclear. Moreover, the sample populations of recent studies have been relatively small and from a single study center, thus the reliability of the results cannot be fully guaranteed. Therefore, the introduction of more clinically available sample types, such as serum and urine, would improve study convenience. In addition, current research is primarily focused on the sponging function of circRNAs, with limited research into other functions [200-216].

- New Biomarker Discovery and Development:

- Although few new markers have reached the clinic in recent years, several reported cancer biomarkers have been found to have low sensitivity [200].

- In future the clinical cancer management belongs to prognostic and predictive markers of cancer, they are important as they

will be used to make clinical decisions that may save lives [121].

- Biomarkers that correctly predict the outcome in a specific disease and allow physicians and patients to make informed decisions for treatment need to be developed [212].

- It should be concerned as whether the tools available are well suited to provide the technological support to meet demands of new biomarker development [119].

- The discovery of biomarkers has been a slow approach to identify proteins that are dysregulated as a sequence of disease and shed into body fluids, such as serum, saliva, urine [213].

- The recent advancements in genomic technologies improved new mass spectrometric technologies with advanced bioinformatic tools. Those shows great promise of meeting demand for a variety of new biomarkers discovery [214, 215].

- The combined use of genomics, proteomics and bioinformatics tools may hold promise for early detection of disease by proteomic patterns [214].

- Diagnosis based on proteomic signatures as a compliment to histopathology [26].

- Individualized selection of therapeutic combinations that targets the entire disease specific protein network, rational modulation of therapy based on changes in diseased protein associated with drug resistance and understanding of carcinogenesis [215].

Challenges in biomarker development:

- A number of challenges can be occurred in biomarker discovery to development.

- Oncologists and scientists are aware that validation and implementation in clinic biomarkers is long and complicated [127, 128].

The main challenges included are as follows: [129, 130]

- Failure of validation protocols

- Wrong targets

- False discoveries

- Unstable nature of biomarkers

- No more clinical requirements

- False positivity and false negativity

- Small sample size

- Inadequate controls

In conclusion, gynecological cancer is a global reproductive health issue among only in women which requires more effective and control strategies

7. DISCUSSION

The WHO recommends the use of HPV DNA testing with/without cytology as the part of cervical cancer screening programs.[117]. -risk HPV genotyping and viral load assessment are proposed as triage markers for women with positive HPV DNA test results or negative cytological findings, providing additional benefit in risk categorization.[20,30-34]. E6/E7 mRNA-based assays have shown higher specificity, potentially complementing traditional screening methods for borderline/low grade lesions such as ASCUS/LSIL.[19,40-43]. Triage and risk assessment offers great advantage in clinical settings leading to more personalized treatment. Dual staining by P16/Ki-67 has proven useful for diagnosing cervical dysplasia and cancerous lesions, distinguishing them from histological mimics [151]. New biomarkers, such as MCM5/TOP2A, offer maximum specificity for CIN 2 and CIN 3 lesions when used in combination with p16/ Ki67.[156]. SCC-Ag is a prognostic and predictive biomarker for poor survival rates, particularly useful in economically weak countries due to its cost-effectiveness.[61-64]. MiRNAs have gained importance due to their implications in gene silencing and carcinogenesis, providing prognostic information and insights into patient responses to treatment modalities.[58-60]. However, their use is limited in clinical settings due to liquid biopsy is an alternative, minimally invasive modality for cancer management, detecting cell-free HPV DNA in cervical cancer patients to monitor the treatment response and diagnose early tumor recurrence.[171-174]. PD-1/PD-L1 inhibitors have been found to be valuable in treating advanced or recurrent cancer, and their detection may be of value in managing advanced stage cervical cancer.[166,168]. Furthermore, current therapeutic options for cervical cancer are associated with debilitating side effects and tumour drug resistance, and despite considerable advancement with the use of combination therapies to improve the efficacy of single-agent treatments, new and improved therapies to treat cervical cancer are still urgently needed. The concept of stages of cervical carcinogenesis was originally

based on pathomorphological changes; it was confirmed by studies using genome-wide screening of molecular disorders at different phases of cervical cancer development. Each molecular profile (genome, transcriptome, proteome, etc.) in the dynamics of the development of the disease progression gradually accumulates multiple aberrations and thus contributes to the development of the tumor [181]. Despite the large number of publications dedicated to various aspects of cervical carcinogenesis, pathologists still play an important role in the development of diagnostic approaches and targeted therapies aimed at tumors characterized by a certain phenotype and the presence of biomarkers that allow the response to targeted therapy to be predicted, enabling the monitoring of response to treatment [92]. It should be emphasized the high importance of modern screening studies in various countries aimed at detecting neoplasms of the cervix using such well-known markers as P16 and Ki-67 [93–96]. Immunohistochemistry is used to study both the various stages of carcinogenesis, but also to search for effective prognostic and predictive factors. Thus, immunohistochemical markers of apoptosis p53 and human epidermal growth factor receptor 2 protein levels were evaluated by as potential prognostic factors in cervical cancer associated with a poor prognosis [197]. At present, molecular, biochemical and genetic aspects of cervical carcinogenesis continue to be investigated [198,199]. PI3K/Akt, Wnt/β-catenin, ERK/MAPK, NF-κB, YY1, AP-1, JAK/STAT and CXCL12/CXCR4 signaling pathways have a significant role in the cervical cancerogenesis in HPV-infected individuals [198]. The modern methods are used to search for serum markers in cervical cancer by mean of perspective technologies such as magnetic bead-based weak cation—exchange chromatography fractionation combined with matrix-assisted laser desorption / ionization-time of flight mass spectrometry [200], the multiplex proximity extension assay is used [201]. Some examples of alternative therapies that have been explored in cervical cancer include immunotherapy, targeted therapy, and genetic approaches such as CRISPR/Cas9 and RNAi. While these therapies shown increasing promise in treatment outcomes, many of them remain investigational and are expensive alternatives [201-216]. An approach that may lead to rapid and cost-effective drugs is to identify commercially available non-cancer drugs that target the host factors that co-operate with the HPV oncoproteins, particularly E6 and E7, that drive cervical cancer progression [178-193].

A significant amount of modern research of cervical neoplasia is aimed at identifying genetic, epigenetic changes, revealing the possible role of long non-coding RNAs and circular RNAs in cervical carcinogenesis [102–107]. Modern tendencies in the problem of cervical neoplasia include research on immune factors and the vaginal microbiome [208–210]. Thus, to study various aspects of cervical carcinogenesis, various methods are currently used, both traditional cytological and modern immunohistochemical, molecular, genetic and others; multidisciplinary approaches seem to be promising.

This review also highlights the significant advances in non-invasive diagnostic methods for the early detection of endometrial cancer (EC), focusing on novel biomarkers and liquid biopsy techniques. Conventional diagnostic methods such as transvaginal ultrasound and endometrial biopsy, while effective, are often uncomfortable for patients and limited in early detection. New approaches using liquid biopsies—such as DNA methylation, circulating tumor DNA (ctDNA), and microRNA biomarkers—offer promising alternatives for high-risk populations. Studies show that specific methylation markers (e.g., ZSCAN12, GYPC, and OXT) and circulating miRNAs have high diagnostic accuracy in detecting earlystage EC, potentially allowing these techniques to be seamlessly integrated into routine cervical screening. These innovative biomarkers not only increase diagnostic sensitivity and specificity but also improve accessibility and convenience for patients by reducing the need for invasive procedures. In the future, these minimally invasive approaches could revolutionize cervical cancer screening and early diagnosis, ultimately contributing to a more efficient and individualized diagnosis for at-risk patients. In addition, longitudinal studies are essential to assess the predictive capacity of these biomarkers for cancer development in high-risk groups [73-81].

This review overviewed the advancements in identifying biomarkers and high-affinity aptamers, Liquid biopsy based biomarkers, DNA/ RNA/ Protein biomarkers for gynecologic cancers diagnosis and therapy, which includes cervical, uterus and endometrial cancers. Special focus has been given to aptamers/ liquid biopsy/ protein/ RNA selected against a wide range of biomarkers for gynecologic cancers. For the past few decades, aptamers are replacing other probes due to their uniqueness such as amenability to the chemical modifications to yield the stability under the stringent conditions. +e detection of HPV with aptamer shows the higher performance than the detection by using the commercial kits because methods with aptamers are more sensitive and selective to the target [178-193].

The best biological diagnostic tool today seems to be a combination of CA125 and HE4 levels in order to predict the risk of ovarian cancer in patients with suspected benign ovarian tumors. If the level of CA125 is increased as well as that of HE4, it is necessary to evoke a malignant lesion and therefore to envisage a surgical treatment for an anatomopathological examination. On the other hand, if one of the markers was above the cut-off as long as the other was below the cut-off specified, a simple ultrasound or biological monitoring may be considered. As the HE4 levels increase with advancing age, it might be interesting to establish algorithms which take into account the patients' age and not her menopausal status. The previously published algorithms (CHP-I or ROMA P) have not proved to be valuable compared to RMI or ROMA algorithms. Serum HE4 levels vary in smokers and in hormonal contraceptive users, thus it seems relevant that this information should always be included in the patient's clinical history. Nonetheless, since CA125 levels are independent from these variables, the simultaneous measure of these two markers allows the correction of any possible variations in such specific cases [133-149].

Modern screening studies in various countries which emphasized the early diagnosis of neoplasms of the cervix using biomarkers as P16 and Ki-67 [93–96]. Immunohistochemistry was used to study both the various stages of carcinogenesis, but also to search for effective prognostic and predictive factors. Thus, immunohistochemical markers of apoptosis p53 and human epidermal growth factor receptor 2 protein levels were evaluated by as potential prognostic factors in cervical cancer associated with a poor prognosis [197]. At present, molecular, biochemical and genetic aspects of cervical carcinogenesis continue to be investigated [198,199]. PI3K/Akt, Wnt/β-catenin, ERK/MAPK, NF-κB, YY1, AP-1, JAK/STAT and CXCL12/CXCR4 signaling pathways have a significant role in the cervical cancerogenesis in HPV-infected individuals [98]. The modern methods are used to search for serum markers in cervical cancer by mean of perspective technologies such as magnetic bead-based weak cation—exchange chromatography fractionation combined with matrix-assisted laser desorption / ionization-time of flight mass spectrometry [200], the multiplex proximity extension assay is used [201]. A significant amount of modern research of cervical neoplasia is aimed at identifying genetic, epigenetic changes, revealing the possible role of long non-coding RNAs and circular RNAs in cervical carcinogenesis [202–207].

Developing a joint screening program for cervical, endometrial, and ovarian cancers would be a groundbreaking step in gynecological health but requires careful planning, significant investment, and collaboration across medical and policy domains. Based on the existing technologies and present understanding of the diagnostics targets (i.e. HPV, plasma proteins, and possibly circulating tumor DNA [ctDNA]), integrating multiple targets into a single assay would be feasible, given that the detection of both HPV DNA (and possibly also other DNA targets) and plasma proteins using the Proximity Extension Assay (PEA) can all be achieved using a single readout technology, such as real-time PCR. The fact that the screening would target several cancers might increase motivation for women to participate. The pros of such a joint screening program for cervical, endometrial, and ovarian cancers include 1) integrated prevention, potentially reducing morbidity and mortality, 2) early detection of cancers that currently lack screening programs, 3) efficient use of existing infrastructure, and 4) multiple cancer screening might encourage higher participation. However, here are also a number of cons to consider, 1) challenges in integrating different test modalities, 2) screening for multiple cancers may lead to overdiagnosis and overtreatment, 3) balancing sensitivity and specificity for three cancers is complex, and 4) different cancers may require separate sample types complicating implementation [33-56].

Despite the potential of cancer biomarkers, their translation into clinical application has progressed relatively slow. The process requires an extensive foundation of clinical samples as the basis and involves repeated design and validation. Translational research has been suggested as a means to bridge the gap between the results of basic research on biomarker discovery and clinical practice [98]. However, strengthening the process of translational research on biomarkers for clinical application remains an area that requires further exploration [99-104].

8. CONCLUSIONS

The generalization and individualization of treatment are significant factors in cancer therapy. Biomarkers, including tumor markers such as CA19-9 and neuron-specific enolase (NSE), are currently used clinically as diagnostic clues. Biomarkers including p53, PTEN, HER2, Ki-67, kras, MSI, VEGF and HE4 collectively offer a comprehensive profile for diagnosing and monitoring uterine cancers. These biomarkers provide valuable insights into tumor characteristics, molecular pathways, and prognosis, aiding in personalized treatment strategies and improving patient outcomes. The emerging biomarkers L1CAM, MMR proteins and CTCs integrating into clinical practice holds potential for improving early detection, risk stratification, and therapeutic decision-making in uterine cancers.

Liquid biopsy has emerged as a pivotal, noninvasive tool for the detection and monitoring of gynecological cancers, offering real-time insights into tumor biology that complement standard tissue-based approaches, but it has not yet been entered into routine clinical practice in gynecological oncology. Ultimately, ongoing interdisciplinary efforts, larger prospective trials, cost-effectiveness analyses, and meticulous follow-up will be essential for resolving these gaps and ensuring that promising laboratory data translate into meaningful, patient-centered outcomes in gynecologic oncology.

Proteomics-based approaches have played a crucial role in the discovery of biomarkers for the diagnosis, prognosis, and treatment of GC. As opposed to currently employed techniques like Pap smears and HPV testing, the introduction of proteomic biomarkers may allow for earlier detection and better management of GC. Several proteins in CVL samples (e.g., an immune checkpoint protein, TIM-3, growth factors, VEGF, TGF-α, and an anti-inflammatory cytokine, IL-10) discriminated EC from benign conditions, particularly, when tested in combinations with CA19–9, CA125, eotaxin, G-CSF, IL-6, MCP-1, MDC, MCP-3 and TRAIL, specific biomarkers (e.g., TIM-3, VEGF, TGF-α, TRAIL, MCP-3, IL-15, PD-L2, SCF) associated with histopathological tumor characteristics, including histological type and grade, tumor size, presence and depth of myometrial invasion or mis- match repair protein status, implying their potential utility for disease prognosis or monitoring therapies. Mass spectrometry-based techniques, coupled with advanced data analysis algorithms, allow for the high-throughput screening of large numbers of samples, facilitating the discovery of novel biomarkers with high sensitivity and specificity. Proteomic profiling can also reveal alterations in protein expression and modifications that can aid in patient stratification, disease classification, prognosis prediction, and personalized treatment strategies. Personalized risk assessment, early detection, and patient-tailored drug selection are just a few of the ways in which proteomics-based-

biomarkers testing has the potential to dramatically improve GC management.

Despite extensive research in recent decades on the possible role of biological molecules such as proteins, dNA and non-coding RNA as predictive biomarkers, the identification of valid and reproducible response marker treatment is neither concise nor clear in gynecological cancer. A comprehensive understanding of each biomarker will be important to efficiently diagnose the disease and to provide direction in selecting the appropriate therapeutic alternatives.

Therefore, clinical studies with a larger number of patients and with clearly defined inclusion criteria are required to facilitate the integration of the information generated in each investigation. Moreover, the relevant findings must also be made accessible to the majority of patients.

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