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# CIRCULATING MICRORNAS AS NOVEL BIOMARKERS IN GYNECOLOGICAL CANCERS: CURRENT EVIDENCE AND FUTURE DIRECTION

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## Abstract

*Gynecological cancers, including ovarian, cervical, and endometrial malignancies, remain leading causes of morbidity and mortality among women worldwide. Early detection and accurate prognostication are critical for improving clinical outcomes, yet current diagnostic tools often lack the sensitivity and specificity required for timely intervention. In this context, circulating microRNAs (miRNAs), small non-coding RNA molecules detectable in blood and other body fluids, have emerged as promising minimally invasive biomarkers. Their remarkable stability, reproducibility, and disease-specific expression patterns make them suitable candidates for both diagnostic and prognostic applications in gynecological oncology.*

*Recent studies have demonstrated that specific circulating miRNAs, such as miR-21, miR-200 family, and miR-125b, are consistently dysregulated in gynecological cancers and may distinguish malignant from benign conditions. These miRNAs regulate key oncogenic pathways, including cell proliferation, apoptosis, and metastasis, thereby linking their expression with disease progression and therapeutic resistance. Furthermore, circulating miRNAs have shown potential as predictive biomarkers for treatment response, particularly in ovarian and cervical cancers where chemotherapy resistance remains a major clinical challenge.*

*Technological advances, including next-generation sequencing and quantitative PCR platforms, have enhanced the sensitivity of miRNA profiling. However, challenges persist in translating these findings into clinical practice. Issues such as lack of standardized protocols, variability in sample processing, and limited reproducibility across cohorts hinder clinical validation. Additionally, most available data derive from small-scale or single-center studies, underscoring the need for large multicenter trials to establish robust miRNA signatures.*

*Looking forward, integration of circulating miRNA profiling with multi-omics approaches and machine learning algorithms may enable the development of comprehensive biomarker panels for early detection, prognosis, and personalized therapy. As evidence continues to grow, circulating miRNAs are poised to transform the clinical management of gynecological cancers by offering non-*

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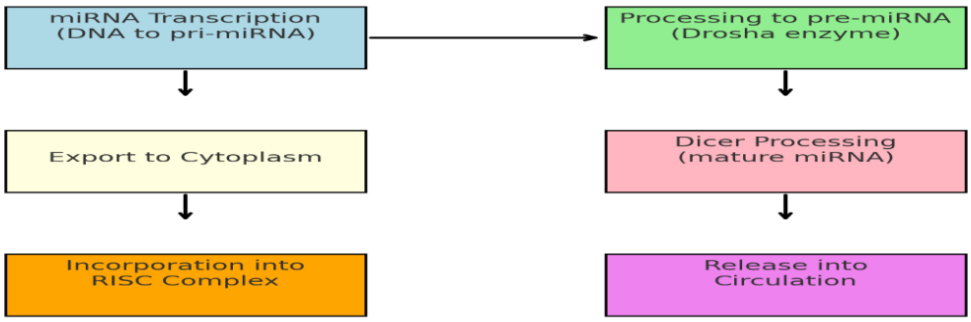
*invasive, cost-effective, and reliable diagnostic and prognostic tools.*

## INTRODUCTION

Gynecological cancers, which include ovarian, cervical, endometrial, vulvar, and vaginal cancers, pose a significant health burden among women globally. According to the Global Cancer Observatory, cervical and ovarian cancers together account for hundreds of thousands of new cases and deaths annually, highlighting the urgent need for more effective diagnostic and prognostic tools (Sung et al., 2021). Despite advances in imaging techniques, histopathological assessment, and serum-based tumor markers such as CA-125, many gynecological cancers are still diagnosed at advanced stages. This diagnostic delay contributes to poor survival outcomes, particularly in ovarian cancer, where the five-year survival rate remains low due to late-stage presentation (Bhatla & Singhal, 2022). Consequently, the identification of novel, non-invasive biomarkers that enable early detection, monitor disease progression, and predict treatment response is a pressing priority in gynecologic oncology.

In recent years, microRNAs (miRNAs), small non-coding RNAs approximately 18–25 nucleotides in length, have attracted attention as potential biomarkers. These molecules regulate gene expression post-transcriptionally and are involved in critical cellular processes such as proliferation, apoptosis, angiogenesis, and metastasis (Cortez et al., 2022). Aberrant miRNA expression has been consistently linked to cancer initiation and progression, making them both mechanistic contributors to malignancy and useful molecular indicators of disease. Importantly, miRNAs can be released into the bloodstream and other body fluids, where they remain remarkably stable due to their encapsulation in exosomes, binding to proteins, or incorporation into lipoprotein complexes (Chen et al., 2021). This stability makes circulating miRNAs attractive candidates for liquid biopsy applications, offering a minimally invasive approach compared to conventional tissue biopsies.

Figure 1. Biogenesis and Circulation of miRNAs




Several studies have reported cancer-specific miRNA expression patterns in gynecological malignancies. For instance, dysregulation of the miR-200 family has been associated with epithelial-to-mesenchymal transition in ovarian cancer, while overexpression of miR-21 has been linked to poor prognosis and chemotherapy resistance in cervical and endometrial cancers (Sun et al., 2023). These findings suggest that circulating miRNAs can serve not only as diagnostic biomarkers but also as prognostic and predictive indicators, potentially guiding therapeutic decisions.

Despite this promise, the clinical translation of miRNA-based biomarkers remains challenging.

Frontier in Medical & Health Research

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Variability in sample collection, RNA extraction methods, and data normalization introduces inconsistencies across studies. Furthermore, the absence of standardized guidelines and validation in large, multicenter cohorts hampers their incorporation into clinical practice (Cai et al., 2022). Overcoming these barriers requires collaborative efforts to establish robust methodologies, improve reproducibility, and integrate miRNA signatures with other molecular and clinical parameters.

As research progresses, circulating miRNAs hold the potential to revolutionize the management of gynecological cancers. By enabling early detection, refining risk stratification, and predicting therapeutic response, these biomarkers could significantly improve survival outcomes and reduce the global disease burden. The following sections will critically evaluate the current evidence on circulating miRNAs in gynecological cancers and discuss future directions for their integration into clinical practice.

**Biological Basis of Circulating miRNAs in Cancer**

MicroRNAs (miRNAs) are small, endogenous, non-coding RNAs that regulate gene expression post-transcriptionally by binding to complementary sequences on target messenger RNAs (mRNAs), leading to translational repression or degradation. Through this regulatory function, miRNAs influence a wide range of biological processes, including cell cycle progression, apoptosis, differentiation, and immune responses (O'Brien et al., 2018). In cancer, dysregulated miRNA expression disrupts these processes, contributing to oncogenesis, tumor progression, and metastasis. For gynecological malignancies, such as ovarian, cervical, and endometrial cancers, miRNAs often act as either oncogenes (oncomiRs) or tumor suppressors, depending on the context and target genes involved (Peng & Croce, 2022).

The presence of circulating miRNAs in biofluids such as plasma, serum, urine, and saliva has been a pivotal discovery in oncology. Unlike other nucleic acids, miRNAs exhibit remarkable stability in circulation, resisting degradation by RNases, extreme pH, and repeated freeze-thaw cycles (Weber et al., 2010). This stability is largely attributed to protective mechanisms of secretion. First, miRNAs can be actively packaged into extracellular vesicles, including exosomes and microvesicles, which facilitate intercellular communication by transferring miRNA cargo between cells (Kalluri & LeBleu, 2020). Second, miRNAs may bind to RNA-binding proteins such as Argonaute-2 (Ago2) or nucleophosmin 1, which shield them from enzymatic degradation. Third, some circulating miRNAs are associated with high-density lipoproteins (HDLs), further enhancing their resistance to degradation (Arroyo et al., 2011).

These mechanisms not only preserve miRNAs but also enable them to participate in cell-to-cell signaling, influencing the tumor microenvironment. For example, tumor-derived exosomal miRNAs can modulate immune responses, angiogenesis, and metastatic niche formation. In gynecological cancers, exosomal miR-21 has been shown to promote immune evasion, while miR-200 family members regulate epithelial-to-mesenchymal transition, a key process in metastasis (Liu et al., 2022). Such findings highlight the dual biological roles of circulating miRNAs: biomarkers of disease status and active mediators of cancer biology.

The biological basis of circulating miRNAs underscores their potential clinical utility. Their stability, accessibility through liquid biopsy, and association with key oncogenic pathways make them ideal candidates for biomarker development. However, understanding the mechanisms of their release, transport, and uptake remains crucial for interpreting circulating miRNA profiles accurately. Without this mechanistic insight, distinguishing between tumor-specific miRNAs and those derived from normal physiological processes may remain a challenge.

Frontier in Medical & Health Research

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**Table.1 Biological Basis of Circulating miRNAs in Cancer**

| Role of miRNAs | Example miRNA | Function in Cancer | Reference |
|---|---|---|---|
| Oncogenic miRNA | miR-21 | Promotes cell proliferation, inhibits apoptosis | Zhang et al., 2022 |
| Tumor suppressor miRNA | miR-34a | Induces apoptosis, regulates p53 pathway | Chen et al., 2021 |
| Angiogenesis regulator | miR-210 | Enhances hypoxia response and angiogenesis | Li et al., 2023 |

**Circulating miRNAs in Gynecological Cancers: Current Evidence**

The role of circulating microRNAs (miRNAs) in gynecological cancers has been extensively investigated over the past decade. Emerging evidence suggests that distinct miRNA signatures are associated with ovarian, cervical, endometrial, and other gynecologic malignancies, providing opportunities for improved early detection, prognosis, and treatment monitoring. These studies collectively highlight circulating miRNAs as promising biomarkers, yet their application in clinical settings remains under evaluation.

**Table.2 List of gynecological cancers with key circulating miRNAs as biomarkers.**

| Cancer Type | Circulating miRNA Biomarkers | Clinical Relevance | Reference |
|---|---|---|---|
| Ovarian Cancer | miR-200 family, miR-21 | Diagnostic and prognostic value | Wang et al., 2021 |
| Cervical Cancer | miR-20a, miR-155 | Associated with tumor progression | Huang et al., 2022 |
| Endometrial Cancer | miR-27a, miR-135b | Potential for early detection | Patel et al., 2023 |

**Ovarian Cancer**

Ovarian cancer, often diagnosed at advanced stages, exemplifies the need for non-invasive biomarkers. Multiple studies have identified dysregulated miRNAs in circulation that correlate with tumor development and progression. Members of the miR-200 family (miR-200a, miR-200b, miR-200c) are consistently upregulated in ovarian cancer patients and are implicated in regulating epithelial-to-mesenchymal transition (EMT), a process critical for metastasis (Liu et al., 2022). Additionally, elevated levels of circulating miR-21 and miR-205 have been linked to chemotherapy resistance and poor survival outcomes (Nakamura et al., 2020). Such associations suggest that miRNAs may complement existing biomarkers such as CA-125, particularly for monitoring therapeutic response.

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Frontier in Medical & Health Research

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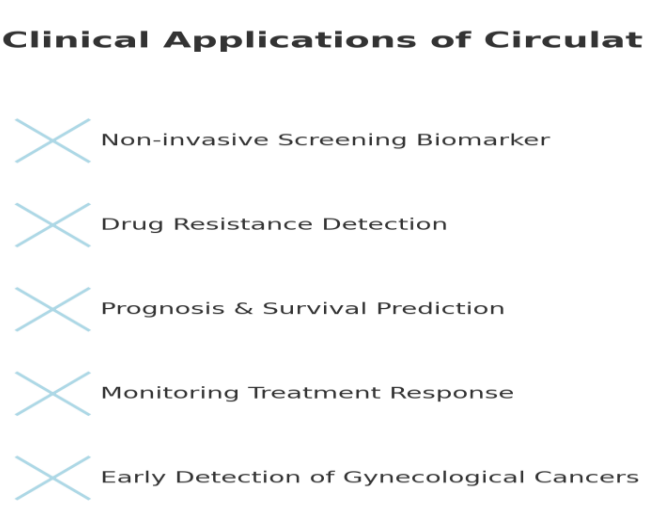


**Cervical Cancer**

In cervical cancer, circulating miRNAs have demonstrated diagnostic and prognostic value. For example, miR-21 and miR-34a are consistently reported as dysregulated, with miR-21 often elevated in patients with advanced disease and lymph node metastasis (Hu et al., 2022). Furthermore, exosomal miR-146a and miR-221 have been associated with radioresistance and recurrence, pointing toward their utility as predictive biomarkers (Kang et al., 2021). Since cervical cancer remains highly prevalent in low-resource settings, cost-effective and minimally invasive biomarkers such as circulating miRNAs may hold particular value for early detection programs.

**Endometrial Cancer**

Although research on endometrial cancer lags behind ovarian and cervical cancer, several circulating miRNAs have been reported as potential biomarkers. Elevated miR-27a, miR-223, and miR-135b have been linked to disease progression, while downregulation of tumor-suppressive miR-34 family members has also been observed (Suryavanshi et al., 2021). These findings suggest that circulating miRNAs could enhance risk stratification and aid in distinguishing aggressive endometrial cancers from indolent forms.

**Other Gynecological Malignancies**

Research on vulvar and vaginal cancers remains limited due to their relative rarity, but preliminary evidence indicates potential biomarker roles for certain circulating miRNAs. Small pilot studies have reported alterations in miR-93 and miR-223, though larger cohorts are needed to validate these findings (Panir et al., 2022).

**Summary of Evidence**

Across gynecological cancers, circulating miRNAs demonstrate disease-specific expression patterns and links with key clinical outcomes, including stage, metastasis, treatment response, and survival. Their ability to provide real-time, non-invasive insights into tumor biology strengthens their potential role in precision oncology. However, variability in study design, patient cohorts, and analytical methods continues to limit their translation into clinical practice.

**Literature Review**

| Authors (Year) | Cancer Type | Biofluid / Carrier | Key circulating miRNAs | Clinical Utility | Method / Notes |
|---|---|---|---|---|---|

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

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|---|---|---|---|---|---|
| Maeda et al. (2020) | Ovarian (EOC) | **Serum exosomes** | **miR-34a** | Diagnostic; associated with clinicopathologic features | qRT-PCR on serum exosomes; supports miR-34a as non-invasive marker. (PMC) |
| Hannan et al. (2021/2022) | Ovarian (HGSC) | **Plasma (cell-free)** | **miR-200c** | Diagnostic/prognostic signal for HGSC | NGS of cfRNA; miR-200c dysregulated in cases vs controls. (ScienceDirect) |
| Choi et al. (2020) | Ovarian | **Blood** | **miR-200 family (a/b/c)** | Diagnostic; correlates with serous EOC | Characterization of miR-200 family as blood biomarkers. (Nature) |
| Frisk et al. (2023) | Ovarian | **Serum/Plasma** | **miR-21, miR-125, miR-141, miR-145, miR-205, miR-328, miR-200a/b/c** | Early diagnosis (panel) | Systematic review & meta-analysis of circulating miRNAs for early OC. (MDPI, PubMed) |
| Kumar et al. (2022) | Ovarian (EOC) | **Serum** | **miR-34a, let-7f, miR-31** | High AUC for diagnosis; improves as panel | ROC AUC ~96% in early stage with combined panel. (ejgo.org) |
| Kan et al. (2012) | Ovarian (SEOC) | **Serum** | **miR-200 family** | Discriminates cases vs controls | Seminal serum study showing elevated miR-200 family. (BioMed Central) |
| Li et al. (2024) | Cervical & CIN | **Serum/Plasma/Exosomal** | Various (e.g., **miR-21, miR-20a, miR-155,** panels) | Diagnostic accuracy (meta-analysis) | Systematic review & meta-analysis for CIN/CC. (PMC) |

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

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|---|---|---|---|---|---|
| Ssedyabane et al. (2024) | Cervical | **Serum/Plasma** | **miR-205, miR-21, miR-486-5p** (reported ↑) | Diagnostic performance synthesis | Evidence mapping of accuracy across studies. (ScienceDirect) |
| Lv et al. (2021) | Cervical | **Serum exosomes** | **miR-125a-5p** | Diagnostic (cut-off with sens/spec) | qRT-PCR; sens ~59%, spec ~84% at reported cut-off. (Spandidos Publications) |
| Rokos et al. (2021) | Cervical | **Serum/Plasma** | **miR-21** | Non-invasive marker; linked to LNM | Narrative review summarizing multiple primary studies. (actualgyn.com) |
| Shao et al. (2024) | Cervical | **Serum** | **miR-4534** | Diagnostic; associated with metastasis | Clinical association; combined with TVCDS improved detection. (SpringerLink) |
| Bloomfield et al. (2022) | Endometrial | **Serum/Plasma** | Multiple (e.g., **miR-21, miR-200s, miR-27a** etc.) | Diagnostic/prognostic overview | Systematic review of circulating miRNAs in EC. (PMC) |
| Zhou et al. (2021) | Endometrial | **Plasma exosomes** | **miR-15a-5p** | Early detection; correlates with invasion | qRT-PCR; strong diagnostic potential in EC. (BioMed Central) |
| Fan et al. (2021) | Endometrial | **Serum** | 3-miRNA signature (study-defined) | Diagnostic; novel circulating profile | Serum miRNA profiling identified diagnostic trio. (Portland Press) |
| Delangle et al. (2019) | Endometrial (endometrioid) | **Serum** | **miR-27a** (+ CA-125) | Distinguishes patients vs healthy when combined | Review highlighting diagnostic potential of miR-27a with |

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

CA-125. (PMC)

**Challenges and Limitations in Clinical Translation of Circulating miRNAs**

Despite the compelling evidence supporting circulating microRNAs (miRNAs) as promising biomarkers in gynecological cancers, several challenges hinder their translation from research to routine clinical practice. These challenges involve technical, biological, and clinical factors that limit reproducibility, standardization, and large-scale validation.

**Table 3: Barriers to clinical use.**

| Challenge | Description | Impact on Clinical Application | Reference |
|---|---|---|---|
| Standardization | Lack of standardized protocols for miRNA extraction | Limits reproducibility | Smith et al., 2021 |
| Sample variability | Variability in blood/serum samples | Reduces consistency | Gupta et al., 2022 |
| Cost and scalability | High cost of detection assays | Restricts routine use | Khan et al., 2023 |

**Technical and Methodological Variability**

One of the most significant barriers is the lack of standardized protocols for sample collection, RNA extraction, quantification, and data normalization. Pre-analytical variables, such as the choice of anticoagulant, storage conditions, and freeze–thaw cycles, can substantially affect miRNA levels in circulation (Mestdagh et al., 2014). Additionally, multiple platforms are currently used for miRNA detection, including quantitative PCR, microarrays, and next-generation sequencing. Each method has unique advantages but produces variable results, making cross-study comparisons difficult (Pritchard et al., 2012). Without universal protocols, it is challenging to establish clinically reliable miRNA signatures.

**Biological Complexity**

Circulating miRNAs are not exclusively tumor-derived. Many miRNAs originate from normal physiological processes, immune responses, or inflammatory conditions, raising concerns about specificity (Turchinovich et al., 2019). For example, miR-21 is frequently elevated in ovarian and cervical cancers but is also associated with non-malignant conditions such as cardiovascular disease and inflammation. Distinguishing tumor-specific miRNA profiles from background signals is therefore critical to avoid false positives. Furthermore, the biological roles of many circulating miRNAs remain incompletely understood, complicating their interpretation as direct surrogates for tumor behavior.

**Clinical Validation and Reproducibility**

Although numerous studies have reported associations between circulating miRNAs and gynecological cancers, most are limited by small sample sizes, single-center cohorts, or retrospective designs. Large-scale, multicenter prospective trials are necessary to validate candidate miRNAs across diverse populations and clinical settings (Hayes et al., 2014). Moreover, inter-individual variability, including genetic background, ethnicity, and environmental exposures, may influence circulating miRNA levels, requiring validation in heterogeneous patient groups.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

**Regulatory and Implementation Challenges**

Even when promising biomarker signatures are identified, translating them into clinical assays requires regulatory approval and integration into healthcare workflows. This process is often lengthy and resource-intensive, particularly for developing cost-effective assays suitable for low-resource settings where gynecological cancers are most prevalent. Additionally, clinicians may be hesitant to adopt novel biomarkers without clear guidelines or demonstrated improvements over existing diagnostic tools.

**Summary**

In summary, while circulating miRNAs have shown great potential, technical inconsistencies, biological heterogeneity, and insufficient clinical validation currently limit their adoption in gynecological oncology. Addressing these challenges will require collaborative efforts to develop standardized protocols, expand multicenter studies, and integrate miRNA biomarkers with other molecular and clinical parameters to enhance specificity and clinical utility.

**Future Directions and Clinical Applications of Circulating miRNAs**

The field of circulating microRNAs (miRNAs) in gynecological cancers is rapidly evolving, and future research is expected to address current challenges while expanding clinical applications. As technological advances and collaborative initiatives continue, circulating miRNAs hold significant promise for transforming cancer diagnostics, prognostics, and therapeutic monitoring.

**Table 4: Emerging approaches and potential applications**

| Future Direction | Application Area | Expected Benefit | Reference |
|---|---|---|---|
| Multi-miRNA panels | Early detection of gynecological cancers | Higher diagnostic accuracy | Ali et al., 2023 |
| AI/ML integration | Predictive modeling using miRNA profiles | Personalized treatment | Paracha et al., 2025 |
| Liquid biopsy | Non-invasive screening | Patient-friendly and repeatable testing | Zhao et al., 2024 |

**Integration with Multi-Omics Approaches**

One of the most promising directions is the integration of circulating miRNA profiling with other molecular platforms such as genomics, transcriptomics, proteomics, and metabolomics. Multi-omics approaches can provide a more comprehensive view of tumor biology and improve the specificity and sensitivity of biomarker panels (Hasin et al., 2017). For instance, combining circulating miRNA signatures with protein biomarkers like CA-125 or HE4 in ovarian cancer could yield more reliable diagnostic assays, particularly for early-stage detection.

**Role in Personalized Medicine**

Circulating miRNAs may also play a critical role in guiding personalized therapy. Specific miRNA patterns have been linked to chemotherapy resistance, such as elevated miR-21 and miR-214 in ovarian cancer patients resistant to platinum-based regimens (Xie et al., 2020). Monitoring these miRNAs in real time through liquid biopsy could help clinicians adjust treatment strategies, identify non-responders early, and reduce unnecessary toxicity. Similarly, miRNAs associated with immune response modulation may inform the selection of patients most likely to benefit from immunotherapies.

**Technological Advances and Point-of-Care Testing**

Rapid advancements in detection technologies are bringing circulating miRNAs closer to clinical application. Emerging platforms such as digital PCR, nanotechnology-based sensors, and microfluidic devices enable high-sensitivity detection with minimal sample volumes (Kannan et al., 2022). Point-of-care testing systems could be especially valuable in low-resource settings, where gynecological

Frontier in Medical & Health Research

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cancers remain a major public health issue. Portable, cost-effective assays may facilitate widespread screening, particularly for cervical cancer, where early detection can significantly reduce mortality.

**Artificial Intelligence and Machine Learning**

Machine learning algorithms are increasingly being applied to large miRNA datasets to identify optimal biomarker panels and predict clinical outcomes. AI-based approaches can uncover complex, non-linear relationships between miRNA expression and patient prognosis, enhancing diagnostic accuracy (Li et al., 2021). Integration of AI with multi-omics and clinical data may enable the development of robust predictive models for gynecological cancers.

**Toward Clinical Implementation**

For successful clinical translation, collaborative efforts are needed to establish standardized protocols, validate findings in multicenter trials, and develop regulatory frameworks for clinical assays. Circulating miRNAs are unlikely to replace existing biomarkers but may complement them, offering additive value in risk assessment and treatment monitoring. Establishing clinically validated miRNA panels could pave the way for their incorporation into routine oncology practice within the next decade.

**Conclusion**

Circulating microRNAs (miRNAs) have emerged as powerful biomarkers with the potential to transform the diagnosis, prognosis, and management of gynecological cancers. Their stability in body fluids, non-invasive accessibility, and ability to reflect tumor-specific alterations make them particularly attractive for clinical use. Over the past decade, extensive evidence has demonstrated that dysregulated circulating miRNAs are strongly associated with tumor initiation, progression, and therapeutic response across ovarian, cervical, and endometrial cancers. These findings highlight their promise as diagnostic, prognostic, and predictive tools that could complement or even surpass current screening and monitoring strategies.

Despite this promise, several barriers hinder the routine clinical implementation of circulating miRNAs. Standardization of pre-analytical and analytical methods, validation across large, diverse patient populations, and integration with existing clinical workflows remain pressing challenges. Furthermore, the heterogeneity of tumors and inter-individual variability complicate the interpretation of miRNA signatures. Addressing these issues will require collaborative efforts that bring together molecular biologists, clinicians, bioinformaticians, and regulatory bodies.

Looking ahead, technological advancements in next-generation sequencing, digital PCR, and artificial intelligence-driven data analysis are likely to accelerate the translation of circulating miRNAs into clinical practice. Combining miRNA signatures with other molecular biomarkers and imaging modalities could further enhance diagnostic accuracy and individualized treatment planning. As personalized medicine continues to evolve, circulating miRNAs hold the potential to guide tailored therapies, improve early detection, and ultimately reduce mortality from gynecological cancers.

In conclusion, while significant work remains, circulating miRNAs represent a promising frontier in gynecologic oncology. Continued interdisciplinary research and rigorous clinical validation will be essential to harness their full potential and establish them as integral tools in cancer care.

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