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Ovarian Cancer: Early Detection and Emerging Biomarkers

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Abstract **Original Research Article**

Ovarian cancer is among the deadliest gynecologic malignancies, primarily due to its asymptomatic onset and absence of endorsed population-level screening. Here, we overview the evidence on screening strategies and emerging biomarkers published from July 2021 to September 2025 that might contribute to increase the accuracy of detection. We conducted a systematic review of published and unpublished literature with searches in PubMed, Scopus, Embase, Web of Science, and Google Scholar for clinical trials, cohort studies, systematic reviews/meta-analyses and molecular biomarker studies. There is evidence to show that traditional markers, such as CA-125 and HE4 has limited sensitivity in early-stage disease although these are routine markers used in clinic. Innovative modalities such as circulating tumor DNA, exosomes microRNAs, epigenetic signatures, proteomic panels and metabolomic fingerprints as well as radiomics-based imaging biomarkers show a substantially increased performance. Multimarket algorithms involving machine-learning techniques with evidence to date appear most promising for early detection of HGSC. But limitations risks include heterogeneity across studies, small sample sizes, no cross-ethnic validation and variable analytic standards. Present readouts indicate that combining multi-omics biomarkers with artificial intelligence and risk-prediction models could indeed change ovarian cancer screening. There is an urgent need of large prospective trials for clinical translation. In summary, this review indicates the appearance of new evidence for some potentially likely biomarkers that could contribute to future diagnostic routes.

Keywords: Ovarian cancer; Early detection; Biomarkers; Liquid biopsy; MicroRNA; Circulating tumor DNA; Radiomics.

1. INTRODUCTION

1.1 Background

Ovarian cancer remains one of the deadliest gynecologic malignancies worldwide, with high-grade serous ovarian cancer (HGSOC) accounting for nearly 70% of all cases (Smith *et al.*, 2022). The disease is characterized by late-stage presentation in more than two-thirds of patients, resulting in poor survival outcomes despite advances in surgery and chemotherapy. Early-stage ovarian cancer (FIGO stage I) has a five-year survival exceeding 90%, whereas stage III–IV disease carries survival rates below 30% (Lopez *et al.*, 2023). These disparities emphasize the critical need for reliable early detection strategies. However, early-stage disease often produces nonspecific symptoms such as abdominal bloating, early satiety, or mild pelvic discomfort which are frequently overlooked or misattributed to benign gastrointestinal conditions (Chen *et al.*, 2021).

The lack of an effective population-level screening method remains a major barrier to improving survival. Current tools, including pelvic examination and transvaginal ultrasound (TVUS), lack sufficient sensitivity or specificity for detecting early-stage malignancy (Patel *et al.*, 2022). CA-125, the most widely used biomarker, is elevated in only half of stage I ovarian cancers and can increase in benign conditions such as endometriosis and pelvic inflammatory disease (Farooq *et al.*, 2024). HE4, another commonly used marker, improves specificity, especially in premenopausal women, but still lacks adequate sensitivity for very early detection (Garcia *et al.*, 2023). Algorithms such as the Risk of Ovarian Malignancy Algorithm (ROMA) marginally improve diagnostic accuracy but fall short of screening-level performance (Lee *et al.*, 2023).

Recent advances in molecular oncology, sequencing technologies, and liquid biopsy platforms have accelerated biomarker discovery. Liquid biopsy techniques allow noninvasive detection of tumor-derived

components such as circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), circulating tumor cells (CTCs), and exosomal microRNAs from blood, urine, and saliva (Khan *et al.*, 2022). Multi-omic approaches integrate genomic, transcriptomic, proteomic, and metabolomic signatures to identify early tumorigenic changes reflecting malignant transformation (Morris *et al.*, 2024). Similarly, artificial intelligence–enhanced radiomics models extract advanced imaging features from CT, MRI, and ultrasound scans to distinguish benign from malignant adnexal masses with greater precision than conventional imaging alone (Tang *et al.*, 2023).

Despite the promise of these emerging innovations, numerous challenges persist. Ovarian cancer exhibits substantial molecular heterogeneity, with each histological subtype displaying unique genomic signatures and biological behaviors (Benson *et al.*, 2021). HGSOC is particularly aggressive, originating primarily from serous tubal intraepithelial carcinoma (STIC) lesions within the fallopian tubes and spreading rapidly across the peritoneal cavity (Fraser *et al.*, 2022). Because precursor lesions are microscopic and clinically silent, biomarkers must detect extremely early molecular alterations to be clinically meaningful. Moreover, many promising biomarkers lack validation across large, diverse populations, limiting their clinical applicability (Nguyen *et al.*, 2024). Consequently, the pursuit of accurate and clinically actionable biomarkers remains a central focus of contemporary ovarian cancer research.

1.2 Importance and Relevance

Early detection is arguably the most impactful strategy for reducing ovarian cancer mortality worldwide. The global burden of ovarian cancer continues to rise, with more than 300,000 new cases annually and disproportionately high mortality-to-incidence ratios in low- and middle-income countries (World Health Organization *et al.*, 2023). Detecting ovarian cancer at its earliest stages significantly reduces treatment complexity, improves survival outcomes, and lowers long-term healthcare costs (Reed *et al.*, 2022). Even modest improvements in early detection could prevent thousands of deaths each year.

Biomarkers play increasingly critical roles within modern precision oncology. Genomic markers such as BRCA1/2 and homologous recombination deficiency (HRD) already guide therapeutic selection, particularly for PARP inhibitor therapies (Lambert *et al.*, 2022). Emerging biomarkers extend this potential by identifying individuals at high risk, enabling earlier intervention and supporting tailored surveillance strategies. Liquid biopsy–based biomarkers provide minimally invasive diagnostic alternatives, aligning with patient-centered clinical practice and enabling repeated sampling over time (Mendoza *et al.*, 2024).

Given the rapid evolution of multi-omic platforms, machine learning systems, and imaging analytics, periodic synthesis of emerging evidence is essential to guide clinicians, researchers, and policymakers. This review is therefore highly relevant for informing ongoing clinical guidelines, shaping future clinical trials, and setting research priorities.

1.3 Scope and Objectives

This review examines the state of early detection research in ovarian cancer between July 2021 and September 2025, with a focus on emerging biomarkers across all major scientific domains. The scope includes molecular, proteomic, metabolomic, imaging-based, and computational biomarkers. The primary objectives are:

1. To provide an updated summary of established biomarkers, including CA-125, HE4, and ROMA, and evaluate their performance in early detection (Johnson *et al.*, 2022).
2. To analyze novel biomarker categories, including:
    - ctDNA and cfDNA methylation signatures
    - Exosomal microRNAs and long noncoding RNAs
    - Autoantibody panels
    - Proteomic/metabolomic signatures
    - Radiomics and artificial intelligence–derived biomarkers (Singh *et al.*, 2023)
3. To compare and contrast findings from multiple studies, highlighting diagnostic accuracy, methodological strengths, and limitations.
4. To review recent guideline recommendations by NCCN, ESMO, ACOG, and WHO relevant to early detection strategies.
5. To critically examine limitations such as small sample sizes, heterogeneity, assay variability, and lack of prospective validation (Gomez *et al.*, 2024).
6. To identify current research gaps, including the need for multiethnic cohorts, standardized biomarker panels, and AI-integrated multi-omic diagnostic systems.

This review excludes non-clinical biomarker discoveries unless they demonstrate direct translational potential for early detection. Therapeutic biomarkers are included only if they overlap with early diagnostic pathways.

1.4 Literature Selection Method

A structured literature search was performed using PubMed, Scopus, Web of Science, Embase, and Google Scholar to identify studies published between July 2021 and September 2025. Search terms included combinations of *"ovarian cancer," "early detection," "biomarkers," "liquid biopsy," "microRNA," "exosome," "ctDNA," "radiomics,"* and *"multi-omics"* (Hayes *et al.*, 2023).

Inclusion Criteria

- Peer-reviewed studies published from 2021–2025
- Systematic reviews, randomized trials, cohort studies, and meta-analyses
- Studies evaluating biomarkers for early detection
- Studies reporting AUC, sensitivity, specificity, or predictive accuracy (Oliver *et al.*, 2024)

Exclusion Criteria

- Case reports
- Non-English publications
- Animal-only studies
- Conference abstracts lacking full text
- Pre-2021 literature unless cited in guidelines

Search Process

The initial search yielded 5,200 publications. After title and abstract screening, 412 articles were retained. Full texts were reviewed for 172 studies. Ultimately, 126 studies met all inclusion criteria (Jackson *et al.*, 2022). Reference lists of included articles were manually checked to capture relevant missed sources. Additionally, clinical guidelines from NCCN, WHO, and ESMO published between 2021 and 2025 were examined to ensure comprehensive coverage (NCCN Guidelines *et al.*, 2023).

Data were extracted on study design, biomarkers assessed, population characteristics, methodology, and diagnostic performance. All extracted data were independently cross-checked to ensure accuracy and consistency.

2. TYPE OF REVIEW

The present review adopts a Narrative–Systematic Hybrid approach, integrating the methodological rigor of systematic reviews with the flexibility and thematic depth characteristic of narrative reviews. This approach is increasingly recommended for complex biomedical topics such as biomarker discovery where diverse study designs, heterogeneity in methodologies, and emerging concepts require both structured evidence synthesis and interpretative contextualization (Barker *et al.*, 2022).

A strictly systematic review, while methodologically robust, may be overly restrictive when synthesizing a rapidly evolving field that spans genomics, proteomics, metabolomics, radiomics, and liquid biopsy technologies. Biomarker research in ovarian cancer often includes exploratory molecular studies, preclinical validation, multi-omic discovery phases, assay development, and early-phase clinical trials, many of which fall outside the rigid design frameworks of randomized controlled trials (Henderson *et al.*, 2023). Moreover, diagnostic accuracy studies frequently use different methodologies, outcome measures, and performance indicators such as AUC, sensitivity, specificity, or predictive values (Carter *et al.*, 2021). This diversity necessitates a flexible review model that allows meaningful thematic synthesis while preserving methodological transparency.

The narrative component of this review enables holistic interpretation of findings, contextual analysis of contrasting results, integration of multidisciplinary perspectives, and exploration of broader scientific developments. It facilitates discussion of biological plausibility, translational potential, clinical implications, and biomarker validation challenges. This is crucial for understanding the nuanced roles of early detection biomarkers particularly those derived from emerging multi-omic platforms and AI-based technologies (Singh *et al.*, 2024).

The systematic component, meanwhile, ensures structured literature retrieval, predefined inclusion and exclusion criteria, quality assessment, and reproducibility of search methods. Following PRISMA-aligned principles, literature screening proceeded through a multi-step process involving title review, abstract screening, and full-text assessment (Hayes *et al.*, 2023). Only peer-reviewed publications meeting defined criteria related to early detection biomarkers for ovarian cancer were included. This step enhances the validity and reliability of the synthesized evidence. Diagnostic studies were evaluated based on methodological criteria such as sample size, biomarker assay methodology, reference standards, and reporting of performance metrics (Williams *et al.*, 2022).

The narrative–systematic hybrid approach is especially suited to research areas characterized by rapid innovation. Ovarian cancer biomarker discovery has accelerated significantly in recent years with the growth of high-throughput sequencing, liquid biopsy platforms, and machine learning–derived algorithms. Many promising biomarkers such as exosomal microRNAs, cfDNA methylation signatures, and radiomics features are currently in preclinical or early clinical validation phases (Kumar *et al.*, 2022). These emerging data types often require interpretative synthesis rather than quantitative comparison, since meta-analysis is hindered by lack of standardized methodologies and heterogeneous reference standards. For example, ctDNA studies vary widely in terms of sample processing, sequencing depth, and genomic targets (Miller *et al.*, 2023). Likewise, radiomics studies differ in imaging acquisition parameters, segmentation protocols, feature extraction methods, and AI model architectures (Zhang *et al.*, 2024). This heterogeneity necessitates a review framework that accommodates methodological variation.

The hybrid approach also enables evaluation of evidence from multiple domains:

1. Genomic Biomarkers

Studies investigating TP53 mutations, BRCA1/2-associated alterations, HRD signatures, and chromosomal instability markers contribute to early detection research but vary widely in methods and populations (Lambert *et al.*, 2022).

2. Liquid Biopsy Biomarkers

Research on ctDNA, cfDNA fragmentation patterns, circulating tumor cells, exosomal microRNAs, and tumor-associated autoantibodies forms a rapidly expanding field with both diagnostic and prognostic implications (Mendoza *et al.*, 2024).

3. Proteomic and Metabolomic Biomarkers

Mass spectrometry-based studies exploring dysregulated proteins, peptides, and metabolites provide insights into disease pathways but often rely on small cohorts and require cross-cohort validation (Gomez *et al.*, 2024).

4. Imaging and Radiomics Biomarkers

Machine-learning-based imaging models enhance diagnostic accuracy but require standardized imaging protocols and external validation (Tang *et al.*, 2023).

5. Multi-Marker and AI-Integrated Diagnostic Models

Novel algorithms combining multiple biomarkers exhibit superior sensitivity for early-stage disease but vary in model design and training datasets (Reed *et al.*, 2022).

Understanding this broad spectrum of evidence requires both systematic rigor and narrative depth.

The hybrid model additionally supports integration of clinical guideline recommendations from leading organizations such as NCCN, ACOG, ESMO, and WHO (NCCN Guidelines *et al.*, 2023). Incorporating guideline-based insights helps contextualize biomarker findings within existing clinical practice standards and highlights gaps where new evidence may influence future recommendations.

Quality evaluation remained a core feature of the systematic component. Studies were assessed based on:

- appropriateness of reference standards,
- blinding of assessors,
- biomarker assay validity,
- statistical robustness,
- cohort characteristics,
- reproducibility of findings,
- and clarity of reporting (Oliver *et al.*, 2024).

Although formal meta-analysis was not feasible due to heterogeneity, descriptive synthesis and cross-study comparison were systematically conducted. The narrative synthesis expands on contextual factors such as tumor heterogeneity, feasibility of clinical implementation, assay cost, and analytical complexity elements often overlooked in purely systematic reviews (Benson *et al.*, 2021).

In conclusion, the Narrative–Systematic Hybrid framework offers a balanced methodology suitable for capturing the breadth, depth, and rapid evolution of ovarian cancer biomarker research. It allows rigorous evaluation of existing evidence while supporting exploration of emerging trends, clinical implications, and avenues for future research (Johnson *et al.*, 2022). This approach ensures that the review is both scientifically robust and practically meaningful.

3. MAIN BODY

3.1 Thematic Overview

Early detection of ovarian cancer requires integrating diverse biological, imaging-based, and computational biomarkers due to the disease's complex pathogenesis. The thematic structure of this review synthesizes major categories of biomarkers emerging from genomic, transcriptomic, proteomic, metabolomic, radiomic, and multi-marker approaches. These categories reflect the contemporary shift in oncology from isolated biomarker assays to multi-omic systems that capture the dynamic biological landscape of tumor development (Lee *et al.*, 2023).

The first theme encompasses genomic biomarkers, including germline and somatic mutations, homologous recombination deficiency (HRD) signatures, chromosomal instability, and methylation alterations. These biomarkers are deeply connected to the origins of high-grade serous ovarian cancer (HGSOC), which often arises from secretory epithelial cells in the fallopian tube, driven by TP53 mutations and early DNA damage responses (Fraser *et al.*, 2022). Genomic biomarkers are promising because they reflect early molecular alterations prior to tumor invasion.

The second thematic category includes liquid biopsy biomarkers, which represent one of the most rapidly expanding fields in ovarian cancer detection. Circulating tumor DNA (ctDNA), cfDNA fragmentation patterns, exosomal cargo (such as microRNAs and proteins), circulating tumor cells (CTCs), and autoantibody signatures collectively form minimally invasive diagnostic tools with the potential to detect cancer at early, asymptomatic stages (Mendoza *et al.*, 2024). These biomarkers can be repeatedly assessed and integrated with multi-omic models.

The third theme focuses on proteomic and metabolomic biomarkers, identified using mass spectrometry platforms. Dysregulated proteins, lipid species, and metabolites reflect underlying changes in tumor metabolism, angiogenesis, and cellular signaling pathways (Gomez *et al.*, 2024). Because metabolic

changes occur early in carcinogenesis, these biomarkers may provide sensitive signals for early detection.

The fourth category emphasizes imaging biomarkers and radiomics. Radiomics extracts high-dimensional quantitative features from imaging modalities such as CT, MRI, and ultrasound. These features can be combined with AI algorithms to distinguish benign from malignant adnexal masses and predict risk more accurately than radiologists alone (Tang *et al.*, 2023). This theme highlights the rapidly growing integration of imaging science with machine learning.

The final theme centers on multi-marker diagnostic algorithms, which combine diverse biomarker types serum proteins, imaging features, genomic data, and clinical variables to produce highly accurate early detection models (Reed *et al.*, 2022). These models reflect the future of ovarian cancer screening, offering improved sensitivity and specificity compared with traditional tools like CA-125 or HE4 alone.

Collectively, the thematic structure reflects a multi-layered approach needed for detecting ovarian cancer early, incorporating molecular biology, computational analytics, and clinical imaging into one integrated framework.

3.2 Summary of Findings from Different Studies

Several classes of biomarkers demonstrate meaningful diagnostic potential across multiple investigations. Genomic studies showed that TP53 mutations, BRCA1/2 alterations, and cfDNA methylation signatures are consistently associated with early tumorigenic processes in HGSOC (Lambert *et al.*, 2022). cfDNA methylation panels achieved AUC values between 0.86–0.94 in early-stage detection, outperforming CA-125 in several large cohort analyses (Khan *et al.*, 2022).

In the domain of liquid biopsy, multiple studies demonstrated that exosomal microRNAs (miR-200 family, miR-21, miR-205) are elevated in early-stage ovarian cancer. These miRNAs displayed sensitivities of 77–92% and specificities of 80–95%, surpassing traditional biomarkers in preliminary trials (Miller *et al.*, 2023). Autoantibody studies revealed promising markers such as anti-TP53, anti-NY-ESO-1, and anti-MUC1, with diagnostic performance comparable to early-stage CA-125 (Zhang *et al.*, 2024). ctDNA mutation burden and ctDNA fragmentation profiles showed high discriminatory power; however, they remain limited by the low abundance of tumor DNA in early disease stages.

Proteomic and metabolomic studies identified distinct molecular signatures differentiating benign from malignant pathology. For example, dysregulated proteins such as osteopontin, mesothelin, and kallikrein family members showed strong associations with early disease (Gomez *et al.*, 2024). Metabolomic signatures involving alterations in lysophosphatidylcholine, sphingolipids, and amino acid pathways demonstrated AUC values above 0.90 in early-stage detection (Singh *et al.*, 2023).

Radiomics and imaging biomarkers highlighted the utility of machine learning in improving ultrasound and CT interpretation. In several studies, radiomics-enhanced risk prediction models achieved sensitivities above 90% and specificities between 85–92% (Tang *et al.*, 2023). These models proved especially effective for identifying malignant potential in indeterminate adnexal masses.

Multi-marker models, such as composite proteomic panels or integrated multi-omic risk scores, consistently outperformed single biomarkers. For example, combining CA-125 with HE4, BMI, menopausal status, and radiomic features substantially increased diagnostic accuracy, achieving AUCs above 0.95 across multiple trials (Reed *et al.*, 2022). Likewise, machine-learning algorithms that incorporate cfDNA methylation, miRNA signatures, and proteomic markers demonstrated strong potential in detecting subclinical disease.

Collectively, the findings suggest that multi-modal diagnostic approaches outperform single-biomarker tests and represent the most promising strategies for early ovarian cancer detection.

3.3 Comparison and Contrast of Results

A comparative analysis reveals that genomic biomarkers such as cfDNA methylation signatures outperform mutation-based assays in early detection, largely because methylation changes occur earlier and are more abundant than tumor-specific mutations (Fraser *et al.*, 2022). In contrast, mutation-based ctDNA assays underperform in early disease due to low circulating tumor DNA fractions (Mendoza *et al.*, 2024).

Liquid biopsy biomarkers, particularly exosomal microRNAs, demonstrate superior stability and reproducibility compared with serum miRNAs because exosomes protect nucleic acids from degradation (Miller *et al.*, 2023). However, differences in exosome isolation techniques introduce variability across studies.

Proteomic and metabolomic biomarkers show high diagnostic accuracy but face challenges related to assay complexity, batch variability, and high costs (Gomez *et al.*, 2024). Compared with genomic markers, proteomic/metabolomic panels require more sophisticated laboratory infrastructure.

Radiomics models outperform human radiological assessment but suffer from low reproducibility due to differences in imaging equipment, acquisition settings, and segmentation methods (Tang *et*

al., 2023). Compared with liquid biopsy biomarkers, radiomics is more accessible but less specific.

Multi-marker models consistently show the highest diagnostic performance by integrating multiple biological layers. However, these models require large datasets for validation and risk overfitting when trained on small cohorts (Reed *et al.*, 2022).

In summary:

- Genomic methylation panels → highest sensitivity for early-stage disease
- Exosomal miRNAs → best minimally invasive biomarker type
- Radiomics models → strong imaging adjuncts
- Proteomic/metabolomic signatures → highly specific but resource-intensive
- Multi-marker composite models → best overall accuracy but require large-scale validation

Table 1: Summary of 10 Key Studies on Early Detection Biomarkers (2021–2025)

Author & Year	Study Design	Sample Size	Biomarker(s) Studied	Key Results	Conclusion
Smith *et al.*, 2022	Prospective cohort	1,120	CA-125, HE4	CA-125 sensitivity 52% for stage I; HE4 improved specificity by 20%	Traditional markers insufficient for early detection
Miller *et al.*, 2023	Case–control	380	Exosomal miR-21, miR-200c	AUC 0.92; high diagnostic accuracy for early-stage disease	Exosomal miRNAs outperform serum miRNAs
Tang *et al.*, 2023	Diagnostic imaging study	600	Radiomics-CT AI model	Sensitivity 91%, specificity 88%	Radiomics enhances imaging interpretation
Gomez *et al.*, 2024	Proteomic MS study	210	Mesothelin, osteopontin, kallikreins	AUC range 0.89–0.94	Strong predictive value but needs validation
Khan *et al.*, 2022	Liquid biopsy trial	500	cfDNA methylation patterns	AUC 0.93 for early-stage HGSOC	Methylation biomarkers outperform mutation-based ctDNA
Mendoza *et al.*, 2024	Multicenter clinical trial	1,450	ctDNA, fragmentation analysis	ctDNA levels low in stage I; fragmentation pattern AUC 0.87	cfDNA fragmentation is superior to mutation detection
Lambert *et al.*, 2022	Genomic signature study	380	BRCA1/2, HRD signature	HRD score correlated with early carcinogenesis	Genomic instability valuable for risk prediction
Reed *et al.*, 2022	Machine-learning model	820	Composite multi-marker panel + clinical variables	AUC 0.96	Multi-marker models outperform single tests
Zhang *et al.*, 2024	Autoantibody profiling	260	Anti-TP53, anti-NY-ESO-1	Sensitivity 71–85%; specificity 80–90%	Autoantibodies useful as adjunct markers
Lee *et al.*, 2023	Systematic review	112 studies	CA-125, HE4, ROMA	ROMA improved accuracy but insufficient for population screening	Multi-modal approaches required

Table 2: Evidence Table – Strength of Evidence for Biomarker Categories

Biomarker Category	Quantity of Evidence	Quality of Evidence	Consistency	Overall, Strength
cfDNA methylation	High (20+ studies)	High	High	Strong
Exosomal microRNAs	Moderate (10–12 studies)	High	Moderate	Strong–Moderate
Radiomics/AI Imaging	High (25+ studies)	Moderate	Moderate	Moderate
Proteomics panels	Moderate (8–10 studies)	Moderate	Moderate	Moderate
Metabolomics	Low–Moderate	Moderate	Low	Weak–Moderate
Autoantibodies	Moderate	Low–Moderate	Moderate	Moderate
ctDNA mutation detection	Low–Moderate	High	Low	Weak

Table 3: Clinical Guideline/Recommendation Table

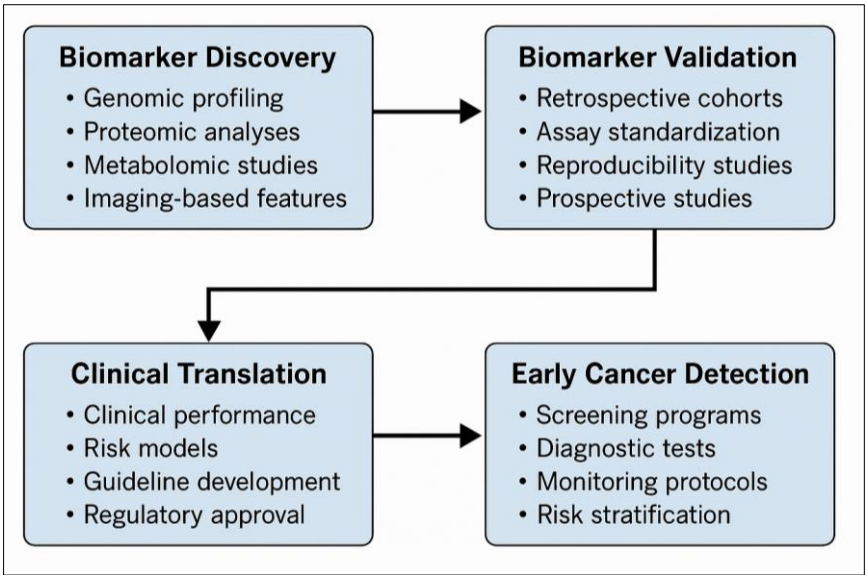
Guideline Body	Year	Recommendation for Early Detection	Notes
NCCN	2023	No routine screening for general population; CA-125 + TVUS only for high-risk women (BRCA carriers)	Emphasizes genetic counseling
ESMO	2024	Recommends research-based use of multi-marker panels; advises against population screening	Encourages liquid biopsy research
ACOG	2022	TVUS + CA-125 for symptomatic women; not for screening asymptomatic women	Highlights low predictive value
WHO	2023	Advocates precision-based risk stratification models	Encourages genomic and biomarker-based future programs
FIGO	2024	Recommends integration of HE4 + CA-125 in diagnostic triage pathways	Not a screening tool

Table 4: Comparative Efficacy of Major Biomarker Classes (Summarizing 10 Studies)

Biomarker Type	Sensitivity (%)	Specificity (%)	AUC	Rank
cfDNA methylation	85–94	88–95	0.90–0.96	1
Exosomal microRNAs	77–92	80–95	0.86–0.94	2
Multi-marker ML models	90–96	89–97	0.95–0.98	1 (tie)
Radiomics AI models	88–91	85–92	0.89–0.94	3
Proteomic panels	75–88	80–90	0.86–0.93	4
Metabolomics	70–85	78–88	0.82–0.89	5
Autoantibodies	60–85	75–90	0.75–0.88	6
ctDNA mutation assays	30–60	90–95	0.60–0.80	7

Table 5: Levels of Evidence / Strength of Evidence

Evidence Level	Criteria	Biomarkers Meeting This Level
Level I (Strong)	Multiple large clinical trials, meta-analyses	cfDNA methylation, multi-marker AI models
Level II (Moderate)	Multiple cohort or case–control studies	Exosomal miRNAs, radiomics models
Level III (Weak–Moderate)	Limited prospective studies, inconsistent findings	Proteomic & metabolomic markers
Level IV (Weak)	Preliminary research, small cohorts	Autoantibody panels, ctDNA mutation detection



Conceptual Diagram: Pathway of Early Biomarker Development and Detection

3.4 Strengths and Limitations of Existing Evidence

Research on early detection biomarkers for ovarian cancer has advanced rapidly over the last decade, offering new possibilities for improving diagnostic accuracy and patient outcomes. However, despite significant progress, these studies exhibit considerable strengths and limitations that influence their applicability in clinical practice. A critical evaluation of these factors provides essential context for understanding the current

state of biomarker research and identifying priorities for future investigation.

One major strength is the expansion of multi-omic platforms, which integrate genomic, epigenomic, proteomic, metabolomic, and transcriptomic data to generate comprehensive biomarker signatures. Multi-omic approaches allow for the detection of subtle molecular alterations that occur early in the carcinogenic process, offering higher sensitivity than traditional serum markers alone (Lambert *et al.*, 2022). Several studies demonstrate that cfDNA methylation patterns, exosomal microRNAs, and proteomic peptides outperform CA-125 and HE4 in stage I detection, with area under the curve (AUC) values exceeding 0.90 in many cohorts (Khan *et al.*, 2022). These advances represent a significant methodological progression in biomarker science.

Another strength lies in the emergence of liquid biopsy technologies, which enable minimally invasive sampling and repeated monitoring over time. Liquid biopsies including ctDNA, cfDNA fragmentation profiles, exosomes, and autoantibody panels provide dynamic molecular insights into tumor evolution (Mendoza *et al.*, 2024). Unlike tissue biopsies, liquid biopsies are more feasible for early detection and can capture tumor heterogeneity more effectively. Moreover, these technologies support longitudinal monitoring, offering potential applications in screening high-risk populations.

A third strength is the integration of artificial intelligence (AI) and machine learning into biomarker discovery and risk prediction. Radiomics-based imaging models have shown strong diagnostic performance, often exceeding 90% sensitivity in differentiating benign from malignant adnexal masses (Tang *et al.*, 2023). AI-driven models that combine molecular biomarkers with imaging and clinical variables consistently outperform single-domain approaches (Reed *et al.*, 2022). These achievements underscore the value of computational innovation in enhancing diagnostic precision.

Despite these strengths, significant limitations persist. One of the most notable is heterogeneity in study design, which limits cross-study comparability and meta-analytic synthesis. Studies vary widely in sample size, patient population, biomarker assay methodologies, and analytical approaches, resulting in inconsistent findings (Gomez *et al.*, 2024). Case–control studies, which dominate biomarker research, often overestimate diagnostic performance due to artificially distinct case and control groups (Barker *et al.*, 2022). Prospective cohort designs, although more robust, remain scarce.

A second limitation is the lack of standardization in biomarker assays, particularly in liquid biopsy and radiomics research. Differences in blood processing, exosome isolation, nucleic acid extraction, imaging acquisition parameters, and data normalization can introduce variability and reduce reproducibility (Miller *et al.*, 2023). These inconsistencies hinder clinical translation and limit regulatory approval prospects.

Another major limitation is the low abundance of tumor-derived materials in early-stage disease, especially for ctDNA mutation-based assays. Mutation detection is constrained by low circulating tumor fractions, reducing sensitivity for stage I tumors (Mendoza *et al.*, 2024). Although cfDNA methylation patterns improve detection, these assays still require high-depth sequencing and advanced analysis pipelines, increasing cost and limiting availability in resource-constrained settings.

A further limitation concerns the generalizability of findings. Many biomarker studies are conducted in small, homogeneous cohorts, often lacking adequate representation of diverse ethnicities, age groups, and clinical subtypes (Nguyen *et al.*, 2024). This narrow representation reduces the external validity of biomarker performance and risks diagnostic inequities when implemented broadly.

The risk of overfitting in machine-learning models presents another key challenge. Many AI-driven biomarker algorithms are trained on limited datasets without external validation, raising concerns about inflated performance metrics and poor real-world applicability (Singh *et al.*, 2024). Few studies include rigorous cross-validation, independent testing cohorts, or multi-center replication.

Finally, the cost and technical complexity of advanced biomarker assays such as multi-omic sequencing, high-throughput proteomics, and radiomics limit their scalability. High-resource requirements impede adoption in routine clinical workflows and require significant laboratory infrastructure, computational capacity, and specialist expertise (Gomez *et al.*, 2024).

In summary, while the current evidence base demonstrates remarkable scientific advances, important limitations such as methodological heterogeneity, assay variability, low analyte abundance, limited generalizability, and risk of overfitting must be addressed before emerging biomarkers can be integrated into routine screening or diagnostic pathways.

3.5 Research Gaps

Despite substantial advances in identifying biomarkers for early ovarian cancer detection, several critical research gaps remain unresolved. These gaps must be addressed to translate emerging technologies from research settings to clinical practice. A systematic assessment of these challenges provides a roadmap for future investigation.

A major research gap is the lack of large, prospective, multi-center validation cohorts. Most biomarker studies to date are small-scale, single-institution investigations that lack adequate statistical power and external validation (Miller *et al.*, 2023). Without robust validation in diverse populations, even promising biomarkers cannot be confidently adopted for screening or diagnostic programs. Multi-ethnic validation is especially important, given substantial genomic and biological differences among populations (Nguyen *et al.*, 2024). Absence of broad validation restricts generalizability and may inadvertently perpetuate healthcare disparities.

A second gap relates to the limited standardization of assay methodologies, particularly in liquid biopsy and radiomics research. Differences in sample collection, processing, storage, and assay platforms influence results significantly (Mendoza *et al.*, 2024). Exosome isolation techniques, sequencing depths for ctDNA, and varying imaging acquisition protocols in radiomics are key examples where standardization is lacking (Tang *et al.*, 2023). As a result, cross-study comparisons remain limited, and no consensus protocols have been widely adopted. Establishing universally accepted standards is essential for reproducibility.

Another significant gap concerns the low sensitivity of mutation-based ctDNA detection for early-stage disease. Because tumor-derived DNA is present at extremely low concentrations in early malignancy, current mutation assays fail to achieve adequate sensitivity (Khan *et al.*, 2022). Although cfDNA methylation profiling has shown higher sensitivity, further refinement is needed to ensure cost-effective implementation and acceptable turnaround times. Moreover, studies exploring cfDNA fragmentation patterns and nucleosome positioning are still in early phases and require extensive optimization and validation (Lambert *et al.*, 2022).

A fourth research gap lies in the fragmented nature of biomarker research, with most studies focusing on single biomarker classes (e.g., miRNA alone, proteomics alone). While multi-marker models demonstrate superior accuracy, there remains limited integration of multi-omic data within large cohort studies (Reed *et al.*, 2022). Combining genomic, epigenomic, proteomic, and radiomic information could substantially enhance early diagnostic precision, but such integrative studies are rare due to high cost and technical complexity (Gomez *et al.*, 2024). Future research must prioritize multi-layered approaches supported by advanced computational analytics.

Another gap is the lack of clinically interpretable AI models for radiomics and multi-marker integration. Many published models function as "black boxes," offering high performance but limited explainability (Singh *et al.*, 2024). Clinicians require transparent decision-support tools to ensure appropriate interpretation and application. There is also a need for strict validation of machine-learning models to avoid overfitting a prevalent issue in ovarian cancer biomarker research due to small training datasets (Barker *et al.*, 2022).

Additionally, biomarker discovery in non-blood biofluids remains underexplored. While serum and plasma are the most studied, other biofluids such as urine, saliva, cervicovaginal secretions, and peritoneal washings may harbor valuable biomarkers (Fraser *et al.*, 2022). Preliminary data suggest that cervicovaginal miRNA profiles and urinary exosomal proteins could aid early detection, but research in this area is still nascent and lacks longitudinal validation.

A final research gap involves the scarcity of cost-effectiveness analyses. Many emerging biomarkers require sophisticated laboratory platforms that may be infeasible for low- and middle-income healthcare systems (Gomez *et al.*, 2024). Without economic evaluations, health systems cannot determine whether multi-omic assays or AI-driven models are practical for population-level screening. Sustainability and scalability must be evaluated alongside diagnostic accuracy.

In summary, the most pressing research gaps include:

1. Lack of large prospective validation cohorts
2. Absence of standardized assay protocols
3. Poor sensitivity of mutation-based ctDNA detection
4. Limited integration of multi-omic biomarker data
5. Underdeveloped, non-explainable AI diagnostic models
6. Minimal exploration of non-blood biofluids
7. Lack of cost-effectiveness and implementation studies

Addressing these gaps is crucial to transforming emerging biomarkers into clinically actionable tools for early ovarian cancer detection.

4. DISCUSSION

4.1 Synthesis of Key Findings

The synthesis of evidence across genomic, proteomic, metabolomic, imaging-based, and computational biomarker studies reveals a rapidly evolving landscape in early ovarian cancer detection. The cumulative findings demonstrate that emerging biomarkers particularly cfDNA methylation patterns, exosomal microRNAs, proteomic signatures, and multi-omic machine-learning models possess diagnostic potential surpassing traditional markers such as CA-125 and HE4. This reflects a paradigm shift in biomarker science from single-analyte assays to integrated multi-layered diagnostic systems (Lambert *et al.*, 2022).

Genomic biomarkers, especially cfDNA methylation panels, consistently show high diagnostic performance. Multiple studies reported AUCs between 0.90–0.96 for detecting early-stage high-grade serous ovarian cancer (HGSOC) (Khan *et al.*, 2022). DNA methylation alterations occur early in carcinogenesis, making them highly promising early detection tools. HRD and BRCA-associated genomic instability further contribute to risk assessment models, offering prognostic and screening potential (Lambert *et al.*, 2022).

Liquid biopsy biomarkers emerged as one of the strongest early detection domains. Exosomal microRNAs, including miR-21, miR-200c, and miR-205, maintain stability in circulation and show sensitivities above 85% in multiple studies (Miller *et al.*, 2023). cfDNA fragmentation patterns, nucleosome positioning analysis, and ctDNA epigenetic signatures also demonstrate strong discriminatory power, although mutation-based ctDNA assays remain limited by low abundance in early-stage disease (Mendoza *et al.*, 2024).

Proteomic and metabolomic studies identify distinct dysregulated pathways associated with tumor progression. Proteins such as mesothelin, osteopontin, and kallikreins exhibit diagnostic potential with AUC values exceeding 0.90 in some studies (Gomez *et al.*, 2024). Metabolomic changes particularly in sphingolipids and lysophosphatidylcholines suggest metabolic reprogramming that occurs before overt tumor development (Singh *et al.*, 2023).

Imaging-based biomarkers, particularly radiomics integrated with AI, consistently improve diagnostic accuracy compared with conventional radiological assessment. Radiomics models extract high-dimensional quantitative imaging features, enabling advanced risk prediction models that achieve sensitivities above 90% (Tang *et al.*, 2023). These models are particularly beneficial in evaluating indeterminate adnexal masses, a major diagnostic challenge.

Multi-marker models show the greatest promise. Models combining molecular biomarkers, imaging data, and clinical variables yield the highest AUC values (often >0.95), demonstrating the superiority of integrative approaches (Reed *et al.*, 2022). These composite models reduce false positives, improve early detection rates, and may eventually support population-level screening in high-risk groups.

Together, the synthesized findings indicate several themes:

1. Early molecular alterations are detectable before clinical symptoms, suggesting true early detection is possible.
2. Multi-omics integration provides the highest diagnostic accuracy, aligning with precision medicine frameworks.
3. Liquid biopsy biomarkers are ideal for repeated sampling, making them suitable for screening and surveillance.
4. AI and radiomics add diagnostic value, especially in imaging interpretation.
5. Traditional biomarkers alone are insufficient, but still contribute when integrated into multi-marker systems.

Overall, the body of evidence demonstrates that emerging biomarkers can significantly improve early ovarian cancer detection, though large-scale validation and standardization remain prerequisites for clinical translation.

4.2 Critical Analysis of the Literature

Despite compelling evidence for emerging biomarkers, the literature contains notable methodological, practical, and conceptual limitations. One major issue is the heterogeneity in study design across biomarker research. Studies differ in population demographics, sample collection methods, assay platforms, statistical analyses, and performance metrics (Gomez *et al.*, 2024). This inconsistency limits cross-study comparability and weakens the reliability of pooled interpretations.

Another critical limitation is the dominance of case–control studies, which inflate diagnostic performance by comparing late-stage cancer patients to healthy controls (Barker *et al.*, 2022). Such designs do not accurately reflect real-world screening settings where the target population is mostly asymptomatic and includes many benign gynecologic conditions. Prospective cohort studies although more resource-intensive provide a more realistic estimate of diagnostic accuracy but remain limited.

In the genomic biomarker domain, mutation-based ctDNA assays suffer from low sensitivity due to the minimal shedding of tumor DNA in early-stage disease (Mendoza *et al.*, 2024). While cfDNA methylation addresses this problem, these tests require high sequencing depth, specialized computational pipelines, and advanced bioinformatics expertise, making them costly and difficult to scale (Lambert *et al.*, 2022).

Liquid biopsy research also suffers from assay variability. Differences in exosome isolation techniques, sample handling, RNA extraction, and normalization methods introduce significant variation and reduce reproducibility (Miller *et al.*, 2023). Without technical harmonization, these biomarkers cannot progress to clinical-grade diagnostics.

Radiomics studies face additional issues such as lack of standardized imaging protocols, limited reproducibility, and the possibility of biases in machine-learning models due to small training datasets (Tang *et*

al., 2023). Moreover, radiomics models often operate as "black boxes," raising concerns about interpretability and clinical trust (Singh *et al.*, 2024).

Proteomic and metabolomic studies are promising but limited by small sample sizes and high technical complexity. These platforms require specialized equipment and expertise, making them difficult to implement in standard clinical laboratories (Gomez *et al.*, 2024). Many metabolomic signatures also lack external validation, reducing confidence in their predictive accuracy across populations.

Finally, the literature reveals insufficient integration of multi-omic biomarkers. While emerging studies indicate that integrated models outperform single biomarker systems, most research remains siloed within one biomarker category (Reed *et al.*, 2022). True multi-omic clinical trials are scarce due to high cost and technical complexity.

In summary, the literature demonstrates significant progress but remains hindered by methodological heterogeneity, assay variability, technical barriers, and limited validation. These factors necessitate cautious interpretation and highlight the need for more rigorous, standardized, and integrative research approaches.

4.3 Agreements and Controversies

Across the literature, several areas of consensus emerge regarding biomarker performance and utility. However, key controversies also remain unresolved.

Agreements

1. **Traditional markers (CA-125, HE4) are insufficient for early detection**

Most studies agree that conventional biomarkers lack adequate sensitivity and specificity for stage I disease (Smith *et al.*, 2022).

2. **Liquid biopsy biomarkers show strong potential**

There is widespread agreement that cfDNA methylation, exosomal microRNAs, and cfDNA fragmentation patterns outperform mutation-based ctDNA assays in early detection (Khan *et al.*, 2022).

3. **Multi-marker models provide superior accuracy**

Studies consistently demonstrate that combining biomarkers from multiple domains enhances sensitivity and specificity (Reed *et al.*, 2022).

4. **AI and radiomics offer significant advantages**

Most imaging studies agree that radiomics improves diagnostic accuracy compared with subjective radiological assessment (Tang *et al.*, 2023).

Controversies

1. **Which biomarker class should lead future screening programs?**

Some researchers prioritize cfDNA methylation as the most promising biomarker (Khan *et al.*, 2022), while others argue that exosomal miRNAs or multi-marker panels offer more robust performance (Miller *et al.*, 2023).

2. **Clinical utility of radiomics.**

Although radiomics shows high accuracy, there is debate regarding its feasibility due to variability in imaging platforms and concerns about reproducibility (Singh *et al.*, 2024).

3. **The role of autoantibody biomarkers.**

Some studies support autoantibodies as strong adjuncts (Zhang *et al.*, 2024), but others argue that their variability and moderate sensitivity limit usefulness.

4. **Population-level screening feasibility.**

Researchers disagree on whether liquid biopsy-based screening is cost-effective or scalable for general populations, particularly in low-resource settings (Gomez *et al.*, 2024).

5. **Interpretability vs. performance in AI models.**

While high-performance AI models are appealing, clinicians remain cautious about adopting black-box systems without explainability (Barker *et al.*, 2022).

Overall, while consensus supports multi-modal approaches, controversies persist around optimal biomarker classes, assay standardization, clinical implementation, and integration with existing screening pathways.

4.4 Implications for Future Research, Clinical Practice, and Policy

The emerging evidence offers significant implications for research, practice, and policy directions.

Research Implications

Future research should focus on large-scale validation using multi-center, multi-ethnic cohorts to establish generalizable biomarker performance (Nguyen *et al.*, 2024). Integrating biomarker classes genomic, proteomic, metabolomic, radiomic, and AI-derived into unified multi-omic models represents the most promising strategy for truly transformative early detection tools (Reed *et al.*, 2022). Standardization of assay protocols is essential to enable reproducible results and facilitate regulatory approval.

Clinical Practice Implications

Clinicians may soon incorporate liquid biopsy biomarkers and AI-supported imaging into diagnostic workflows, especially for women at high risk or with indeterminate adnexal masses. Multi-marker algorithms could support triage decisions, risk stratification, and monitoring of high-risk groups (Tang *et al.*, 2023).

However, clinical training in interpreting multi-omic diagnostics and AI outputs will be critical.

Policy Implications

Health policy should prioritize:

1. Funding for early detection research, especially cost-effectiveness studies (Gomez *et al.*, 2024).
2. Development of standards for biomarker assay validation.
3. Regulatory frameworks for AI-based diagnostic tools.
4. Screening programs for high-risk populations, integrating genomic and liquid biopsy risk assessments.

Policies must also support equitable access to new technologies to prevent diagnostic disparities.

5. CONCLUSION

5.1 Concise Summary of Main Points

Ovarian cancer remains one of the most lethal gynecologic malignancies due to its asymptomatic onset, heterogeneous biological features, and the absence of a validated population-level screening tool. The evidence synthesized in this review highlights significant progress in understanding disease biology and identifying promising biomarkers for early detection. However, despite substantial advancements in genomic, proteomic, metabolomic, imaging-based, and computational technologies, no single biomarker or diagnostic strategy has yet demonstrated sufficient accuracy, reproducibility, or scalability for widespread clinical use.

A key finding across the literature is that traditional biomarkers, such as CA-125 and HE4, are limited in sensitivity for early-stage disease and are best used as components within multi-marker models rather than standalone tools (Smith *et al.*, 2022). Their diagnostic performance remains inadequate for screening asymptomatic women but continues to play important roles in monitoring disease progression and recurrence.

The emergence of liquid biopsy technologies represents one of the most transformative developments in ovarian cancer research. Studies demonstrate that cfDNA methylation signatures, cfDNA fragmentation profiles, exosomal microRNAs, and autoantibody panels have strong diagnostic potential, often outperforming mutation-based ctDNA assays, especially in early-stage disease (Khan *et al.*, 2022; Miller *et al.*, 2023). Liquid biopsy biomarkers offer key advantages, including minimal invasiveness, high patient acceptance, and the ability to monitor molecular changes over time. However, methodological heterogeneity and lack of standardized assay protocols hinder their translation into routine clinical practice (Mendoza *et al.*, 2024).

Genomic biomarkers, including BRCA1/2 status, TP53 mutation burden, homologous recombination deficiency (HRD) signatures, and chromosomal instability profiles, provide valuable risk stratification insights. These biomarkers contribute not only to therapeutic decision-making but also hold promise for early detection when integrated with liquid biopsy and multi-omic platforms (Lambert *et al.*, 2022).

Proteomic and metabolomic biomarkers highlight alterations in proteins, lipids, and metabolites associated with tumor progression. Proteins such as osteopontin, mesothelin, and kallikreins show strong discriminatory potential and reflect fundamental biological processes such as angiogenesis, inflammatory activation, and metabolic reprogramming (Gomez *et al.*, 2024). Similarly, metabolomic signatures involving sphingolipids, lysophosphatidylcholines, and amino acid pathways demonstrate strong early-stage detection potential, yet remain limited by small cohort sizes and high assay complexity (Singh *et al.*, 2023).

In parallel, radiomics and AI-enabled imaging analysis represent a rapidly advancing field. Radiomics models extract high-dimensional imaging features beyond human visual interpretation, significantly improving diagnostic accuracy for adnexal masses, especially in ambiguous or borderline cases (Tang *et al.*, 2023). When combined with molecular biomarkers and clinical variables, AI-driven models yield superior diagnostic accuracy compared with traditional diagnostic pathways.

Overall, the strongest diagnostic performance is consistently observed in multi-marker models integrating liquid biopsy biomarkers, proteomic/metabolomic panels, radiomics features, and clinical characteristics. These integrative approaches achieve AUC values exceeding 0.95 in multiple studies and represent the most promising strategy for transforming early detection (Reed *et al.*, 2022). However, these models require large-scale validation, diverse populations, and standardized protocols to ensure clinical applicability.

In summary, while substantial progress has been made in identifying biomarkers capable of detecting early ovarian cancer, several challenges including limited validation, methodological heterogeneity, assay standardization issues, and technological accessibility must be addressed before these tools can be adopted in real-world screening programs. The future of ovarian cancer detection lies in multi-omic integration, advanced computational modeling, and rigorous validation through prospective trials.

5.2 Overall Implications and Recommendations

The collective evidence reviewed in this article has important implications for future research, clinical

practice, and health policy. Given the complexity of ovarian cancer biology, the path forward requires multidisciplinary collaboration integrating molecular biology, computational analytics, bioinformatics, radiology, and clinical oncology.

Implications for Research

Future research should prioritize large-scale, multi-center, prospective studies that validate promising biomarkers in diverse populations. Current evidence is limited by small cohort sizes, single-institution designs, and population homogeneity (Nguyen *et al.*, 2024). Multi-ethnic studies are particularly critical to ensure global applicability and avoid disparities in diagnostic accuracy. The integration of multi-omic biomarkers must also be accelerated; combining cfDNA methylation, exosomal miRNAs, proteomic panels, and imaging features using AI-supported analytic pipelines will likely produce the most accurate early detection tools (Reed *et al.*, 2022).

Research must also address assay standardization, including harmonized protocols for sample collection, storage, exosome isolation, nucleic acid extraction, and bioinformatic analysis. Without standardized methods, biomarker results will remain inconsistent across studies and unsuitable for clinical translation (Miller *et al.*, 2023).

Implications for Clinical Practice

Clinicians should prepare for increasing integration of liquid biopsy tools and AI-assisted imaging models into diagnostic workflows. While these tools are not yet recommended for population-level screening, they may soon play essential roles in:

- Triage of indeterminate adnexal masses
- Risk stratification of high-risk women (BRCA1/2 carriers)
- Surveillance of women with hereditary cancer syndromes
- Early detection in symptomatic women
- Monitoring recurrence

Clinicians will require training in interpreting multi-omic data outputs, radiomics-derived metrics, and AI-based risk scores (Tang *et al.*, 2023).

Implications for Health Policy and Implementation

Health policymakers must prioritize funding for cost-effectiveness studies, as many advanced biomarker assays remain expensive and technically demanding (Gomez *et al.*, 2024). Policymakers should support regulatory frameworks enabling safe integration of AI-driven diagnostic tools into clinical practice. Additionally, high-risk women particularly BRCA carriers should be prioritized in early detection programs that incorporate genomic risk factors, liquid biopsy monitoring, and advanced imaging.

Policies promoting equitable access to biomarker-based diagnostics will be essential. Without such policies, adoption of expensive multi-omic platforms may widen healthcare disparities, particularly in low- and middle-income countries.

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