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The Role of Artificial Intelligence in Revolutionizing Endometriosis Diagnosis and Clinical Pathology: A Commentary Review of New Biomarkers (2020–2026)

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ABSTRACT

The diagnosis of endometriosis has historically been hampered by an average diagnostic delay of seven to ten years, owing largely to the field's reliance on invasive surgical laparoscopy as the "gold standard." The integration of artificial intelligence (AI) and machine learning (ML) into clinical pathology, however, is now catalyzing a paradigm shift toward non-invasive, precision diagnostics. This report synthesizes research published between 2020 and 2026, highlighting the emergence of high-accuracy diagnostic tools built on microRNA (miRNA) signatures, plasma protein panels, and genomic markers. Key findings include the validation of blood- and saliva-based miRNA signatures achieving area under the curve (AUC) values exceeding 0.95, rivaling the accuracy of surgical diagnosis. AI methodologies including Random Forest, eXtreme Gradient Boosting (XGBoost), and support vector machines (SVM) have identified novel biomarkers such as PNMA2, LRP1, and WISP2/CCN5. These advances promise not only to shorten diagnostic latency but also to enable molecular stratification, supporting more personalized treatment strategies. Challenges remain in clinical standardization and in validating certain protein-based models, yet the accumulated evidence suggests that AI-driven clinical pathology will soon augment and in some cases replace traditional surgical diagnosis for many patients.

Abbreviations: AI: Artificial Intelligence; ML: Machine Learning; miRNA: microRNA; AUC: Area Under the Curve; SVM: Support Vector Machines; ANN: Artificial Neural Networks; CNN: Convolutional Neural Networks; WGCNA: Weighted Gene Co-Expression Network Analysis

Introduction

Endometriosis is a complex, multifactorial inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity. It affects millions of individuals worldwide and is a leading cause of chronic pelvic pain and infertility [1]. Despite this prevalence, the current diagnostic framework remains significantly flawed: laparoscopy an invasive surgical procedure carrying real risks and high costs remains the only definitive diagnostic method [2,3]. This reliance on surgery contributes to substantial diagnostic delays and prolonged patient suffering. Clinical pathology is now undergoing a transformation driven by artificial intelligence. By leveraging large multi-omics datasets (transcriptomics, proteomics, methylomics) alongside high-resolution imaging, AI-based tools are uncovering patterns "crimson clues," in the words of one recent review within peripheral blood, saliva, and tissue that are invisible to the human eye [4,5]. These technologies aim to shift endometriosis diagnosis away from a purely symptom-based or surgical approach and toward one grounded in precision medicine and molecular stratification [3,5]. This report examines the AI methodologies, novel biomarkers, and clinical impacts described in the recent literature, with the goal of providing a comprehensive overview of the current state of the art.

AI Methodologies and Approaches in the Sources

The literature reviewed here reveals a diverse array of AI and machine learning methodologies, each tailored to a particular type of biological data. Broadly, these approaches fall into two categories: supervised learning for classification, and unsupervised learning for subtype identification.

Supervised Learning and Ensemble Methods

The most common application of AI in the sources reviewed is supervised learning used to differentiate patients with endometriosis from healthy controls.

- **Ensemble classifiers**: "GenomeForest" is an advanced ensemble machine learning classifier that uses chromosomal partitioning to analyze transcriptomic and methylomic data, achieving F1 scores as high as 0.968 [6].
- **Tree-based models**: Random Forest, XGBoost, and AdaBoost are frequently favored for their robustness in handling high-dimensional omics data. Random Forest algorithms, for example, have been used to validate salivary miRNA signatures with 96.2% sensitivity [7] and to identify driver biomarkers from RNA-seq data [8].
- **Neural networks**: Artificial neural networks (ANN) and convolutional neural networks (CNN) are increasingly applied to complex diagnostic models and imaging data [8,9].

Integrated Discovery Pipelines

Many studies rely on hybrid pipelines that combine bioinformatics with machine learning for biomarker screening.

- **WGCNA and ML**: Weighted gene co-expression network analysis (WGCNA) is often paired with machine learning to identify lipid metabolism-related biomarkers and molecular subtypes [10].
- **Multi-omics integration**: Markov et al. describe the integration of ML and deep learning with imaging, molecular biomarkers, and histopathology to build multi-omics diagnostic pathways [11].
- **Stacked models**: Stacked machine learning models have been developed to distinguish endometriosis from adenomyosis using peripheral blood and coagulation data [12].

Findings and Comparative Analysis

The synthesis of recent research points to several high-potential biomarker categories, with miRNA signatures currently showing the greatest diagnostic accuracy.

miRNA Signatures and Non-Invasive Diagnostics

MicroRNAs have emerged as the most promising candidates for non-invasive testing.

- **Blood-based signatures**: Bendifallah et al. [13] developed an 86-miRNA signature using algorithms such as Random Forest and XGBoost, achieving an AUC of 0.984 [13] a robust, reproducible diagnostic that could potentially replace laparoscopy [13].
- **Saliva-based testing**: A 109-miRNA saliva signature has been validated with 96.2% sensitivity and 95.1% specificity [7]. This approach offers a genuinely non-invasive alternative that could be administered in a primary care setting, meaningfully shortening the path to diagnosis [14].
- **Early-stage detection**: Specific miRNA panels (e.g., miR-199a, miR-122) combined with CA-125 have demonstrated an AUC of 0.939 for detecting early-stage disease [15].

Proteomic and Immunologic Biomarkers

While miRNAs dominate the literature, protein- and immune-based markers offer critical insight into disease pathophysiology.

- **Plasma protein panels**: Schoeman et al. [16] identified a panel of 10 plasma protein biomarkers. Using a Random Forest model, they achieved an AUC of 0.997 for severe endometriosis, though accuracy for milder cases was considerably lower (Model 2 AUC = 0.729) [16].
- **Immune screening**: Non-invasive immune screening tests combined with ML (logistic regression) have identified markers predictive of disease, including IL-10 in Tc cells, reduced NK cytotoxic activity, and CXCL1 [2].
- **Challenges in reproducibility**: Notably, Fishman [17] found that some cytokine-based ML models performed no better than chance, underscoring the need for rigorous standardization in protein-based discovery [17].

Genomic and Transcriptomic Drivers

Machine learning has also proven instrumental in identifying the molecular drivers underlying the disease.

- **Hub genes**: Integrated identification methods have pointed to five key diagnostic genes *FOS, EPHX1, DLGAP5, PCSK5,* and *ADAT1* [18]. A separate study identified *LRP1* as a potential diagnostic and immunomodulatory target, showing a strong correlation with M2 macrophage infiltration [19].
- **Novel biomarkers**: AI-driven screening has highlighted *PNMA2* (linked to malignant growth and anti-apoptosis) [20], *WISP2/CCN5* (a potential early-screening marker) [21], and SPP1 (a modulator of macrophage polarization) [22].
- **Cuproptosis-related genes**: ML algorithms have identified genes such as *GLS* and *PDHA1* as being associated with endometriosis progression and immune infiltration [23].

AI in Imaging and Digital Pathology

AI's impact extends to the visual characterization of the disease as well.

- **Automated recognition**: Proof-of-concept studies have demonstrated the automatic visual recognition of endometriosis lesions during laparoscopy using AI, a step that could help standardize surgical assessment [24].
- **Tissue segmentation**: AI-based tissue segmentation and cell identification in histological sections for instance, identifying CD138+ cells are improving the precision of pathological diagnosis in infertility-associated conditions [25,26].
- **Imaging integration**: Deep learning models are increasingly being integrated with ultrasound and MRI data to improve detection of deep infiltrating endometriosis and ovarian endometriomas [27,28].

Impact on Clinical Pathology and Diagnostic Workflows

The integration of AI into clinical pathology is reshaping the diagnostic landscape in several ways:

- **Reducing diagnostic latency**: By enabling high-accuracy blood or saliva tests, AI tools can identify candidate biomarker genes and signatures that shorten the years-long wait many patients face for a diagnosis [6,21].
- **Molecular stratification**: AI enables identification of disease subtypes, moving the field away from a one-size-fits-all approach and toward models informed by molecular, epidemiologic, and cell-specific data [5].
- **Precision medicine**: The development of diagnostic models that predict treatment response for example, PNMA2 as a therapeutic target is helping guide more personalized therapeutic strategies [3,20].
- **Augmenting the gold standard**: While some sources suggest AI could ultimately replace laparoscopy [13,15], others view it instead as a powerful complement that improves the efficiency and accuracy of existing histopathological and surgical workflows [18,29,30].

Limitations of the Evidence

Despite rapid progress in the field, several limitations must be acknowledged:

- **Validation gaps**: Many of the biomarkers identified so far remain in the discovery or interim-validation stage [4,14]. Large-scale, multi-center prospective trials will be necessary to confirm their clinical utility.
- **Data heterogeneity**: AI model performance varies considerably depending on the dataset and disease stage, as reflected in the gap between severe- and mild-endometriosis detection in protein-based models [16].
- **Interpretability and fallibility**: The "black box" nature of some ML models remains a challenge in diagnostic pathology, where clinical decisions demand transparent reasoning [31,32].
- **Standardization**: Standardized protocols for biomarker collection and processing are urgently needed to ensure that AI-driven findings remain reproducible across different clinical settings [4].

Research Gaps and Future Directions

Future research in this area should focus on:

- **Longitudinal studies**: Understanding how AI-identified biomarkers change over the course of the disease and in response to treatment.
- **Integration with clinical data**: Combining molecular signatures with symptom clustering and imaging data to build a holistic diagnostic "score" [33].
- **Cost-effectiveness analysis**: Evaluating the economic impact of replacing laparoscopy with AI-driven non-invasive tests.
- **Pathologist training**: Developing educational frameworks that help pathologists integrate AI assistance into daily practice [34].

Conclusion

Artificial intelligence is no longer a peripheral technology in the study of endometriosis it is the engine driving the next generation of clinical pathology. Through the identification of highly accurate miRNA signatures, novel genomic drivers such as *LRP1* and *PNMA2*, and the automation of digital pathology, AI is supplying the tools needed to overcome the field's historical challenges of delayed diagnosis and invasive surgery. Rigorous clinical validation remains the final hurdle, but the evidence accumulated between 2020 and 2026 strongly suggests that AI-powered non-invasive diagnostics will soon become a cornerstone of endometriosis management, ushering in an era of precision medicine for millions of patients..

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