



Mini Review

Exploring the Current State and Research Innovation in Endometrial Cancer Screening



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Abstract

Endometrial cancer (EC) is one of the most prevalent malignancies of the female reproductive system and ranks among the three primary types of gynecological cancers. Recent trends indicate a rising incidence of EC in younger patients, highlighting the urgent need for effective early screening strategies. This review examines the challenges associated with early diagnosis and screening, including ambiguous methodologies (e.g., transvaginal ultrasound: sensitivity 80–90%, specificity 60–70%), undefined target populations, and the absence of efficient, cost-effective, minimally invasive solutions (e.g., cytology sensitivity ≤50% in community settings). The article provides an overview of the current landscape and emerging innovations in universal EC screening, highlighting advancements in early detection and diagnosis, such as DNA methylation panels (sensitivity 89–94%, specificity 91–97% in phase II trials) and vibrational spectroscopy (sensitivity 92%, specificity 88% in pilot studies). Additionally, future directions for implementing effective screening strategies are explored, emphasizing the potential of high-accuracy biomarkers and scalable technologies to reduce mortality and healthcare costs.

Introduction

Endometrial cancer (EC) comprises a group of epithelial malignant tumors arising in the endometrium and is among the three major gynecological malignancies. The global incidence of EC has increased significantly, with over 320,000 new cases reported annually. This rise is particularly pronounced among younger populations, potentially due to lifestyle changes and the growing prevalence of metabolic disorders.¹ Despite this increasing incidence, several critical gaps persist in current EC screening strategies. First, there is a lack of simple, widely accessible screening technologies suitable for community-based settings. Many existing methods are too complex or require specialized equipment and expertise, limiting large-scale implementation. Second, the available evidence base is insufficient, with a lack of in-depth analyses and large-scale validation studies, reducing the accuracy and reliability of screening outcomes. Third, cost-effective screening strategies

remain scarce. The high expense of many existing methods imposes financial burdens on both patients and healthcare systems, hindering widespread adoption. Given these gaps, the specific objectives of this review are as follows: First, to comprehensively summarize the current status of EC screening modalities, including their advantages, disadvantages, and applicability. Second, to highlight innovative research strategies aimed at improving early detection. By identifying and analyzing these new approaches, we hope to provide insights into developing more effective, accessible, and cost-efficient screening strategies for EC. Despite the growing incidence, effective early diagnostic indicators and pre-operative evaluation methods remain elusive. The target population of EC screening should focus on detecting stage 1 disease or precancerous lesions rather than all cases of EC. A clear delineation of this focus is essential. While some patients receive an early diagnosis through procedures such as segmented curettage, others with high-risk factors may only be diagnosed at advanced stages due to the absence of obvious preemptive symptoms. As a result, developing safe and effective strategies for preventing and controlling EC through early screening has become a critical focus in its diagnosis and treatment.^{2,3} The challenges associated with early detection remain substantial,³ including the lack of simple, accessible screening technologies for community populations, insufficient advanced evidence-based medical data, and the need for more cost-effective screening strategies.

In response to these challenges, this review aims to examine

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the current landscape of EC screening, assess its limitations, and explore potential advancements that could enhance early detection and intervention.

Current screening protocol for EC

Currently, screening for endometrial cancer primarily relies on clinical manifestations, particularly irregular vaginal bleeding, combined with transvaginal ultrasound (TVU) assessments. Diagnostic procedures such as curettage and hysteroscopy are employed to obtain endometrial histopathology, which is the gold standard for diagnosis. Two efficient endometrial samplers have recently emerged for acquiring endometrial cells: negative pressure devices and brush techniques (Fig. 1).

Clinical manifestations

The primary symptoms of EC include vaginal bleeding, abnormal vaginal discharge, pelvic pain, and systemic manifestations. Vaginal bleeding is the most prevalent symptom and can occur in women of any age. Notably, endometrial simple hyperplasia, atypical hyperplasia, and EC may coexist in the same patient. Among individuals diagnosed with EC, over 90% of postmenopausal women report postmenopausal vaginal bleeding, whereas perimenopausal women often experience menstrual irregularities. In women under 40 years of age, menstrual disorders or increased menstrual flow are common presentations.⁴ Therefore, any instance of irregular vaginal bleeding warrants careful evaluation. However, various gynecological conditions can also present with vaginal bleeding, leading to low specificity of clinical symptoms for EC screening. As a result, these symptoms alone are insufficient as an independent criterion for screening.

Recent advancements in screening methodologies emphasize the need for more refined approaches to enhance early detection rates and improve patient outcomes. Further research is essential to develop effective screening strategies that can be implemented in community settings.⁵

Vaginal ultrasound

TVU is the preferred imaging modality for evaluating endometrial lesions. It provides critical information regarding uterine size, cavity morphology, endometrial thickness, vascularity, and potential muscle layer infiltration. The typical ultrasound findings associated with EC include heterogeneous echogenic areas within the uterine cavity and the absence of distinct uterine cavity lines, indicative of invasion into the myometrium. Recent studies have demonstrated that an endometrial thickness of 4 mm or less in postmenopausal women has a negative predictive value for EC exceeding 99%.⁶ However, there are limitations to vaginal ultrasound. While vaginal ultrasound can detect abnormalities in the endometrial cavity, it is less sensitive than abnormal bleeding in clinical practice and significantly less effective than endometrial biopsy for early-stage cancer detection. While endometrial thickening may suggest the development of cancer, it cannot serve as an absolute indicator for intrauterine examination or a definitive predictor of malignancy. In postmenopausal women with an endometrial thickness of 4–5 mm, the criteria for tissue sampling should not be extended to asymptomatic individuals. For asymptomatic postmenopausal patients exhibiting endometrial thickening, it is essential to assess the intimal thickness; however, no standardized threshold currently exists. Clinicians should also consider individual risk factors for endometrial cancer to facilitate personalized evaluations. Notably, some non-hormone-dependent types of endometrial cancer may present

without significant thickening of the endometrium. A study involving 52 patients with diagnosed endometrial cancer revealed that 35% had an endometrial thickness of 5 mm or less, while 17% had a thickness of less than 4 mm.^{7,8}

Compared with emerging screening techniques, TVU offers the advantage of being a non-invasive imaging modality that provides a rapid and comprehensive assessment of the uterine structure. However, its primary limitation is its reduced sensitivity in detecting early-stage or focal EC. Additionally, the interpretation of ultrasound findings is highly operator-dependent, introducing subjectivity that may affect diagnostic accuracy.

Tumor markers

Cancer antigen 125 (CA125)

CA125 is a serum tumor marker that can be elevated in cases of extrauterine metastasis or endometrial serous carcinoma, which are typically manifestations of late-stage EC. In the context of late-stage disease, screening using CA125 becomes less relevant because, by the time these conditions occur, most patients are already under medical care due to more noticeable symptoms related to the advanced state of the disease. However, its specificity for EC is limited, as elevated CA125 levels are also observed in various other conditions, including ovarian epithelial malignancies, pelvic inflammatory disease, endometriosis, and adenomyosis.

Human epididymis protein 4 (HE4)

Recent studies have investigated the expression of HE4 in EC, endometrial dysplasia, and normal endometrial tissue. Research conducted by Li *et al.*⁹ demonstrated that the positive expression rate of HE4 was significantly higher in the EC group and the moderate to severe dysplasia group compared to the mild dysplasia and normal endometrial groups. Notably, HE4 and CA125 are biomarkers often associated with late-stage disease. In the case of late-stage EC, screening using these biomarkers becomes less relevant. When CA125 and HE4 levels are significantly elevated, most patients are already receiving medical care. At this advanced stage, the disease has typically manifested with more overt symptoms, such as abnormal vaginal bleeding, pelvic pain, or other systemic signs, prompting patients to seek medical attention. Consequently, relying on these biomarkers for screening at this point may offer limited additional value, as the diagnosis is often already suspected or established based on clinical presentation.

Furthermore, HE4 expression intensity has been found to correlate positively with malignancy grade and increases with advancing clinical stages. Notably, HE4 expression is significantly higher in poorly differentiated tumors than in highly differentiated ones. However, HE4 expression does not correlate with pathological subtype or estrogen sensitivity, indicating that it cannot predict the histologic subtype of EC. Some researchers propose that a serum HE4 concentration exceeding 70 pmol/L is a quantitative indicator of EC due to its optimal sensitivity, specificity, and positive predictive value.¹⁰ Additionally, coagulation markers such as D-dimer and fibrinogen have been suggested as adjuncts in the diagnosis of endometrial cancer. The combination of HE4 and D-dimer has been shown to significantly enhance the detection rate of endometrial cancer.¹¹ Despite its potential for screening, the heterogeneity of HE4 findings across different studies has prevented its clinical recommendation for routine use.¹²

Cytology and histopathology

Histopathology remains the primary method for confirming EC.

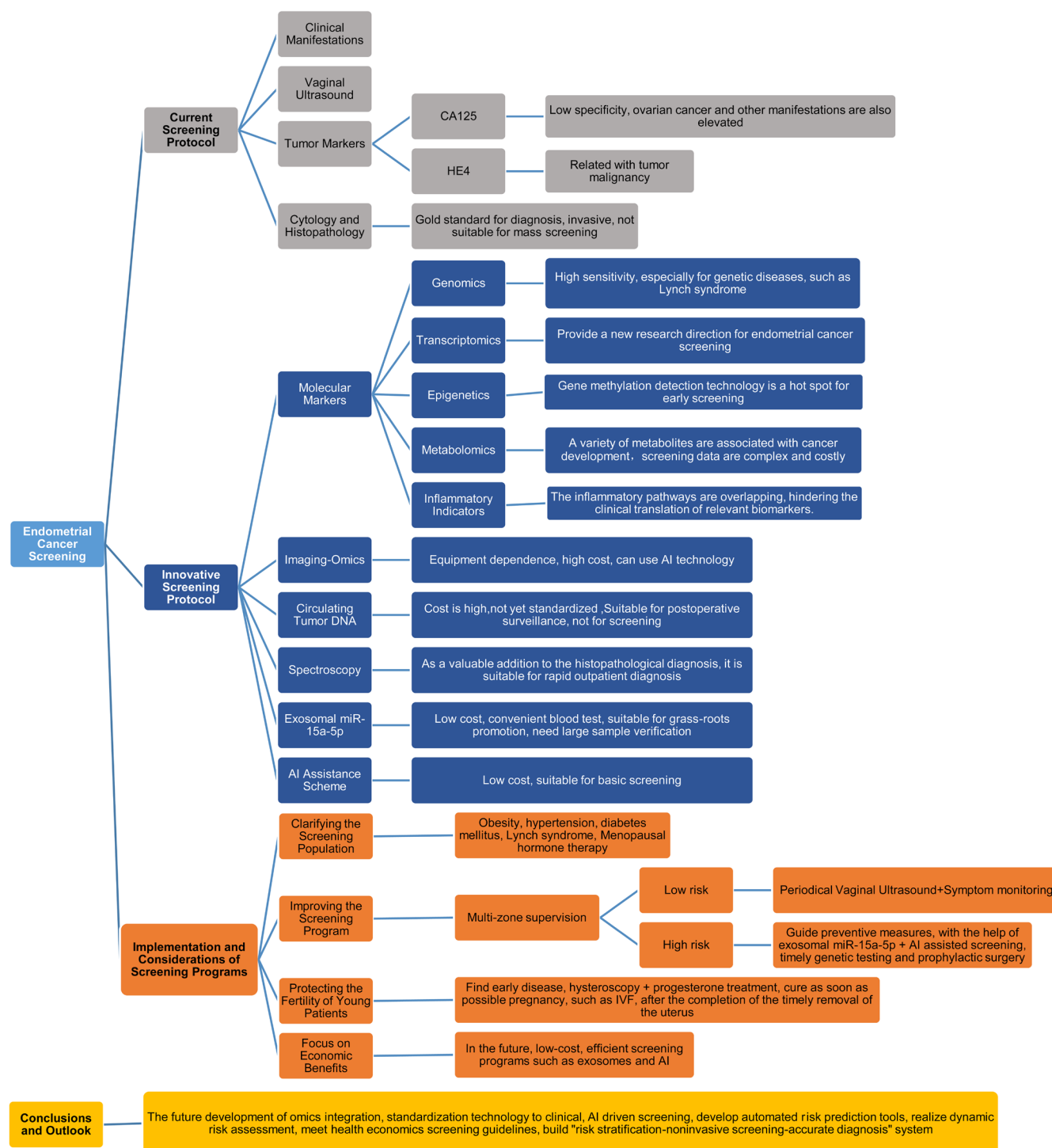


Fig. 1. An overview of EC screening strategies and innovative technologies. AI, artificial intelligence; CA125, cancer antigen 125; EC, endometrial cancer; HE4, human epididymis protein 4; IVF, *in vitro* fertilization.

However, techniques such as curettage and hysteroscopy present several limitations, including invasiveness, risk of complications, and limited patient acceptance, making them less suitable as first-line screening options for EC. Histopathological and cytological evaluation remains the gold standard for confirming the presence

or absence of EC or precancerous lesions.¹³ When it comes to screening, histopathological evaluation can be utilized when there are high-risk factors present in patients, such as abnormal uterine bleeding, obesity, long-term unopposed estrogen exposure, and a family history of EC. For patients with these risk factors, a com-

prehensive assessment, including a detailed medical history, physical examination, and imaging studies, should be carried out first. If initial findings suggest a possible endometrial lesion, then histopathological evaluation can be considered. The indication for histopathological evaluation is mainly to obtain a definitive diagnosis of the nature of the lesion, whether it is cancerous, precancerous, or benign. In recent years, two types of highly efficient endometrial samplers have been developed to obtain endometrial cells for early detection of EC: negative pressure devices and brush-type samplers.¹⁴ Negative-pressure devices include the Pipelle, Vabra suction, and Endocell endometrial samplers, while brush-type samplers include the Li-brush, Tao Brush, and Syntenin-1 (SAP-1). These endometrial samplers are designed to be simple and convenient, allowing for outpatient use without cervical dilation or general anesthesia. This approach not only reduces patient discomfort and minimizes trauma but also mitigates the risk of cancer dissemination associated with hysteroscopy. Notably, these sampling techniques may carry a risk of sample leakage in cases of focal EC. The development of these innovative sampling methods represents a significant advancement in gynecological oncology, offering a less invasive alternative for obtaining diagnostic tissue samples. Future studies should focus on optimizing these techniques to enhance diagnostic accuracy and improve their clinical applicability in routine EC screening.

Cytological evaluation, on the other hand, can serve as an initial screening tool in low-risk populations or as a complementary method for high-risk patients. It can be performed relatively easily during a routine gynecological examination, with a simple swab or smear used to collect endometrial cells. The primary purpose of cytological evaluation is to provide a preliminary assessment of the cellular characteristics of the endometrium. If abnormal cytological findings are detected, further histopathological evaluation may be necessary to establish a definitive diagnosis.

Traditional histopathological methods, such as curettage and hysteroscopy, remain highly accurate for confirming EC but are invasive. In contrast, emerging endometrial sampling techniques are less invasive and more patient-friendly. However, they may not be as reliable in detecting all types of EC, particularly focal lesions, compared to the more comprehensive tissue sampling provided by traditional histopathology.

Innovative screening protocol for endometrial cancer

In recent years, the continuous development of detection technologies has provided innovative solutions for EC screening. Advancements in molecular genetic detection, epigenetics, new imaging technologies, and artificial intelligence (AI) have been made.

Molecular markers

Genomics

Molecular protocols, including the analysis of mutant genes, microsatellite instability, and gene polymorphisms, are pivotal in the genomic evaluation of EC screening.¹⁵ Key genes associated with EC incidence include *HNF1B*, *EIF2AK*, *CYP19A1*, *SOX4*, and single-nucleotide polymorphisms in *MYC*.¹⁶ Costas *et al.*¹⁷ analyzed genomic data from EC tissues and found that when the number of point mutations reached approximately 50, the sensitivity for detecting EC was 81.9%. Notably, mutations in five genes—*PTEN*, *TP53*, *PIK3CA*, *ARID1A*, and *CTNNB1*—resulted in a sensitivity of 92.9%. *ARID1A* is particularly noteworthy as a tumor suppressor gene, with positive and negative predictive values for endometrial

dysplasia related to EC reported at 93.8% and 86.1%,¹⁸ respectively. While most ECs are sporadic, approximately 5% are hereditary, with Lynch syndrome being the most common genetic predisposition. This autosomal dominant condition is primarily caused by germline mutations in mismatch repair (MMR) genes such as *MLH1*, *MSH2*, *MSH6*, *PMS2*, or the *EPCAM* gene. Loss of the 3' terminal exon of *EPCAM* leads to hypermethylation of the *MSH2* promoter, resulting in its functional inactivation. Immunohistochemistry (IHC) for protein expression of *MLH1*, *MSH2*, *PMS2*, or *MSH6* serves as a primary screening method. If *MLH1* protein expression is lost, further testing is warranted; if promoter methylation is positive, this indicates a sporadic tumor. Conversely, if methylation is negative, germline testing for *MMR* genes is recommended. Loss of protein expression of *MSH2*, *MSH6*, or *PMS2* suggests direct germline testing for these genes. Additionally, patients with intact MMR protein expression but clinical suspicion of Lynch syndrome should undergo microsatellite instability (MSI) testing; if MSI-high is detected, germline testing for *MMR* genes is advised.¹⁹ Furthermore, recent findings indicate that the occurrence and progression of endometrial cancer—particularly type I—are closely linked to autophagy-related mutations.²⁰ Lebovitz *et al.* analyzed 211 autophagy-related genes across 11 cancer types and found that mutations in autophagy-related genes were more prevalent in EC than in other malignancies.^{21,22} Specific genes such as *ATG4C*, *ULK4*, and *RB1CC1/FIP200* exhibited high mutation frequencies alongside mTOR mutations.

It is important to note that although emerging screening technologies—such as molecular genetic testing, epigenetics, advanced imaging technologies, and AI—have been extensively discussed in this mini-review, their primary applications remain in cancer etiology research, treatment guidance, prognosis assessment, and confirmatory diagnosis. Their current utility in EC screening is limited. While these technologies hold significant promise in various aspects of oncology, their direct application in EC screening requires further investigation and development.

Transcriptomics

Long non-coding RNAs (lncRNAs) are a class of RNA molecules longer than 200 nucleotides lacking protein-coding capability. These molecules regulate gene expression at transcriptional, post-transcriptional, and epigenetic levels.^{23,24} Studies have demonstrated that lncRNAs are key regulators in developing various tumors, including uterine corpus endometrial carcinoma (UCEC).²⁵ In recent years, numerous lncRNAs have been identified as abnormally expressed in UCEC, correlating with poor patient prognosis. These lncRNAs can influence cell proliferation, apoptosis, migration, invasion, angiogenesis, and drug resistance, thereby playing significant roles in the occurrence and progression of UCEC.²⁶ Consequently, they hold potential as diagnostic and prognostic biomarkers as well as therapeutic targets. Wang *et al.*²⁷ explored the relationship between bone mesenchymal stem cells (BMSCs) and EC by constructing a co-culture model with Ishikawa cells expressing enhanced green fluorescent protein. Their findings indicated that BMSCs may promote the proliferation of EC cells. Further transcriptome sequencing and bioinformatics analyses revealed that the upregulated intersecting genes were primarily enriched in signaling pathways such as PI3K-Akt, MAPK, and JAK-STAT. This suggests that co-culture may enhance cell proliferation by activating these pathways. The transcriptome analysis indicated that the upregulated genes in endometrial cancer cells following co-culture were mainly associated with extracellular matrix composition; thus, BMSCs may regulate the local tumor microenviron-

ment and promote the development of endometrial cancer through cell-cell interactions.

Epigenetics

Epigenetics refers to heritable changes in gene function that occur without alterations in the DNA sequence, ultimately leading to phenotypic modifications. The application of modern molecular biology techniques for the early diagnosis of EC has become a significant research focus, particularly in gene methylation detection technology. While emerging screening technologies—such as molecular genetic testing, epigenetics, advanced imaging technologies, and AI—show promise in oncology, their current utility in EC screening remains limited. These methods are primarily employed for cancer etiology research, treatment guidance, prognosis assessment, and confirmatory diagnosis rather than for routine screening. Multinu *et al.*²⁸ performed methylation analysis of tissue specimens from 23 women with benign endometrial lesions (controls), 23 patients early diagnosed with benign endometrial lesions (case group), and 13 patients with progressive EC group over an average period of one year. The study revealed a progressive increase in cytosine-phosphate-guanine methylation levels of *ADCYAP1*, *MME*, and *HAND2* from the control group to the case group and subsequently to the EC group.

Metabolomics

Metabolomics is a high-throughput technique used to systematically study the composition and changes of metabolic substances within organisms, aiming to explore the roles and regulatory mechanisms of metabolites. Metabolic diseases such as diabetes, obesity, and polycystic ovary syndrome are significant risk factors for EC, making metabolomics a promising field for studying malignancy. Through in-depth analysis of the metabolic characteristics of malignant tumors, metabolomics can provide important insights for screening, early diagnosis, efficacy prediction, prognosis evaluation, and the research and development of new drugs for malignant tumors. For example, in the early diagnosis of breast cancer, metabolomic analysis of blood samples has identified specific metabolite signatures that can distinguish cancer patients from healthy individuals at an early stage.²⁹ In terms of efficacy prediction, changes in metabolite levels during chemotherapy can be monitored to predict the response of patients with lung cancer to treatment. Moreover, for prognosis evaluation, the metabolic profiles of glioblastoma patients can be used to predict their survival time. However, metabolomics faces numerous challenges in data processing, sample quality control, and identifying unknown compounds in both basic research and clinical applications. As an emerging field, it is essential to continuously improve and develop new metabolomic technologies and methods, strengthen multi-omics collaboration and communication, and provide a more reliable foundation for the accurate diagnosis and treatment of malignant tumors.³⁰

Inflammatory indicators

Virchow first described the association between inflammation and cancer in 1863.³¹ Since then, numerous studies have highlighted the crucial role of inflammatory cells and cytokines in tumorigenesis and cancer progression, emphasizing their potential to promote tumor growth, invasion, and metastasis. The systemic inflammatory response is now recognized as a fundamental characteristic of malignancy.

Leukocytes constitute the largest population of inflammatory cells, with neutrophils playing a key role in tumor progression by releasing pro-inflammatory cytokines such as tumor necrosis fac-

tor, interleukin-1, and interleukin-6. Lymphocytes are essential for tumor-specific immune responses, mediating cytotoxic cell death and suppressing tumor cell proliferation and migration. Additionally, monocytes contribute to various aspects of tumorigenesis, including cancer cell growth, migration, vascularization, invasion, and metastasis. The intricate interplay between these immune cells and the tumor microenvironment shows the complex relationship between inflammation and cancer progression.

Several studies have suggested that elevated levels of inflammatory markers, such as C-reactive protein (CRP), are associated with an increased risk of EC. For instance, a case-cohort study within the Women's Health Initiative, involving 151 incident EC cases and 301 subcohort participants, found a positive association between higher CRP levels and EC risk after adjusting for age and BMI. Similarly, a population-based case-control study in Alberta, Canada, which included 519 incident EC cases and 964 frequency age-matched controls, examined the relationship between inflammatory markers and EC risk. These findings suggest that CRP and other inflammatory markers may serve as potential biomarkers for EC screening.^{32,33} Additionally, the neutrophil-to-lymphocyte ratio (NLR) in a group of 300 EC cases was significantly higher than healthy controls, with an average NLR of 3.5 in cancer patients versus 1.8 in controls. These data suggest that incorporating these inflammatory indicators could improve the accuracy of EC screening. Understanding these mechanisms may provide insights into potential therapeutic targets for cancer treatment.³⁴

Imaging-omics

The practical application of imaging omics still faces several limitations. Highly differentiated EC and endometrial dysplasia often coexist, and the variability between different imaging protocols and equipment further exacerbates the difficulty in accurately delineating their boundaries using imaging alone, which results in poor reproducibility. Most research on imaging omics for EC is confined to single centers; however, the internal classification of endometrial cancer cases may not meet the requirements for omics research. Additionally, conclusions drawn from studies utilizing different manufacturers, scanning protocols, and magnetic resonance equipment need further exploration to ensure their applicability in clinical practice. Imaging omics is still evolving in EC research, with many unknown areas remaining to be explored. The combination of imaging omics features and clinical characteristics has the potential to enhance the diagnostic efficacy of EC; however, there is a notable lack of research on imaging-genomics and imaging-pathologic omics in this context. Furthermore, there are no established conclusions regarding the use of imaging omics to distinguish between different types of endometrioid adenocarcinomas, such as serous and clear cell carcinoma.

Delineating the region of interest (ROI) for EC is also worth in-depth exploration. Most scholars agree on the necessity of accurately defining tumor boundaries within the ROI; however, some studies suggest that a larger delineation area may encompass predictive features outside the tumor,³⁵ such as myometrial conditions, thereby enhancing the efficacy of prediction models. Therefore, imaging analyses using computed tomography (CT), magnetic resonance imaging, and positron emission tomography/CT, due to their objective, non-invasive, and reproducible advantages, are beneficial for accurately assessing clinical status and prognosis in patients. These techniques can guide chemoradiotherapy planning and surgical decision-making while preventing overtreatment and potentially prolonging overall survival and progression-free survival in cancer patients.

Circulating tumor DNA (ctDNA)

ctDNA is a component of circulating free DNA (cfDNA). In normal physiological conditions, human cfDNA primarily originates from apoptotic and necrotic blood cells, which are cleared by phagocytes. However, in cancer patients, free DNA fragments carrying tumor-specific genomic alterations—referred to as ctDNA—can provide valuable insights into tumor genomic variations, offering comprehensive molecular information about individual tumors. As a biomarker for non-invasive real-time monitoring of tumor dynamics, ctDNA holds significant potential for early diagnosis, tumor burden assessment, treatment effect monitoring, staging, and prognosis. It is expected to facilitate timely diagnoses, improve treatment plans, and reduce the incidence and mortality rates of endometrial cancer; however, the potential of ctDNA in endometrial cancer remains underexplored.

Regarding diagnostic accuracy, while some studies have demonstrated the potential of ctDNA, many aspects require further investigation. For instance, some methods have shown promising results in terms of sensitivity. One approach that combined ctDNA analysis with tumor-educated platelets (TEPs) to assess 71 genes achieved a sensitivity of 77.8% and an overall accuracy of 68.7%. However, specificity values remain inconsistently reported in the current literature. Since specificity is crucial for distinguishing cancer cases from non-cancer cases, further research is necessary to establish the precise specificity of ctDNA in EC diagnosis.

ctDNA can serve as a screening marker for identifying cancer patients with EC, thereby improving early diagnosis rates. Studies have demonstrated the feasibility of screening early-stage patients by detecting somatic mutations associated with EC in ctDNA. Moreover, early detection can be enhanced by assessing fragment length and copy number of ctDNA or in combination with other protein markers.³⁶ Some researchers have utilized ctDNA mapping combined with TEPs to analyze 71 genes, enabling initial diagnosis through TEPs to distinguish healthy women from those with EC and using ctDNA for histological diagnosis.³⁷ This method provides valuable material for diagnosing EC, achieving a sensitivity of 77.8% and an accuracy of 68.7%. Standardization across clinical settings remains a significant challenge in applying ctDNA for EC diagnosis. Variability in detection methods, sample collection procedures, and data analysis algorithms across different laboratories can lead to inconsistent results. For instance, differences in sample collection techniques—such as the type of blood collection tube used or the timing of sample collection—can influence ctDNA yield and quality, potentially affecting test outcomes.³⁸ Additionally, variations in detection platforms, such as next-generation sequencing versus digital polymerase chain reaction, may result in varying sensitivity and specificity.³⁹ Establishing unified standards for sample collection, storage, detection techniques, and result interpretation is essential to ensure the reliability and comparability of ctDNA-based diagnosis in different clinical scenarios. These standardization efforts should involve consensus among key stakeholders, including laboratory professionals, clinicians, and regulatory bodies, to promote consistency and accuracy in ctDNA testing across institutions.³⁹

In conclusion, ctDNA has the potential to function as a diagnostic biomarker in EC.⁴⁰

Spectroscopy

Due to changes in the molecular characteristics of diseased tissue, vibrational spectroscopy can rapidly distinguish between normal and abnormal tissues or biological fluids (such as blood, urine, and saliva), achieving a sensitivity of 87% and a specificity of 78%.⁴¹

When considering its potential as a diagnostic tool, vibrational spectroscopy has a unique advantage in detecting subtle molecular alterations in diseased tissues. These alterations can manifest as changes in the chemical bonds and functional groups, which are precisely what vibrational spectroscopy can capture. For example, in EC, the abnormal expression of certain proteins and metabolites leads to specific vibrational patterns that can be identified by this technique. The high sensitivity of 87% indicates its ability to accurately identify many true positive cases. This is crucial in early-stage cancer detection, where timely diagnosis can significantly improve patient prognosis. The specificity of 78% means it can also effectively rule out non-diseased cases, reducing false positives. Further analysis of cancer subtypes demonstrates a sensitivity range of 71% to 100% and specificity between 81% and 88%.⁴² Based on the structural characteristics of endometrial tissue, this method offers an objective approach that reduces variability and human error among pathologists, serving as a valuable supplement to histopathological diagnosis. The sample processing involved in vibrational spectroscopy is simple and rapid, providing significant time advantages over traditional histopathology. This technique is easily applicable in outpatient settings for quick diagnoses and can assist in determining lymph node involvement during surgery. Additionally, it can identify cell phenotypes with varying drug sensitivities, thereby informing clinical treatment options.

Exosomal miR-15a-5p

Barati *et al.*⁴³ found that exosomal miR-15a-5p in plasma can distinguish EC patients from healthy individuals, achieving an area under the curve of 0.823. Furthermore, this biomarker is closely associated with the depth of myometrial invasion in EC. The use of blood sampling enables its integration into routine blood examinations, facilitating screening in medium- and low-risk populations. For instance, in a large-scale screening program conducted at a regional hospital, the detection of exosomal miR-15a-5p in blood samples was employed as a preliminary screening tool for women at medium and low risk of EC. Among the initially screened positive cases, follow-up diagnostic procedures, such as endometrial biopsies, confirmed a high proportion of actual EC cases, significantly enhancing the efficiency of early detection.

Exosomal miRNAs play a pivotal role in mediating communication between EC cells, tumor-associated fibroblasts, and tumor-associated macrophages, promoting tumor cell proliferation and shaping the tumor microenvironment. Oncogenes carried by tumor-derived exosomes can induce malignant transformation in target cells. Multiple genetic and proteomic factors are upregulated during exosome synthesis, making exosomes promising targets for diagnostic and prognostic applications in EC.

In a cohort of EC patients undergoing treatment, dynamic monitoring of exosomal miR-15a-5p levels has been utilized to assess chemotherapy efficacy. A significant decrease in miR-15a-5p levels following multiple chemotherapy cycles is often associated with improved treatment response and prognosis, allowing clinicians to make timely adjustments to treatment strategies. The elevated expression of miR-15a-5p in exosomes derived from the plasma of EC patients shows its potential as a diagnostic biomarker. Given the limited availability of reliable prognostic markers for endometrial cancer, increasing interest has been directed toward identifying molecular indicators supporting more effective treatment strategies.

AI assistance scheme

AI systems are increasingly applied in medicine, particularly in

the screening and diagnosis of diseases.⁴⁴ Several studies have explored the application of AI technology for population classification by collecting demographic data to create various data models that assist in risk prediction. These models propose interventions to reduce the risk of EC, such as dietary and exercise modifications, progesterone or antiestrogen therapy, insulin-lowering treatments, and regular endometrial biopsies. For instance, some clinical studies have used the Risk of Malignancy Index (RMI) combined with AI technology. By analyzing patient data, including age, ultrasound findings, and CA125 levels, this AI-enhanced RMI can more accurately predict the risk of EC. A clinical trial involving 472 patients achieved a sensitivity of 94% and a specificity of 75% in distinguishing between benign and malignant cases. AI is also utilized in endometrial cytology.⁴⁵ By employing a cellular neural network to capture the characteristics of endometrial cell populations, they constructed a deep learning model using DenseNet201 as the backbone to classify benign and malignant cell communities.

Another example is the AI-based diagnostic tool. In a large-scale multi-center study, it was reported that this tool could efficiently process endometrial cytology images. It had a positive predictive value of 95% and a negative predictive value of 90% in classifying cell communities, which significantly improved the diagnostic accuracy compared to traditional methods. This system significantly enhances the efficiency of diagnostic work for physicians and is suitable for large-scale screening efforts.

However, despite the promising performance of AI tools, significant real-world challenges must be addressed before widespread clinical implementation. One primary concern is algorithmic bias, where AI systems may inadvertently reflect biases present in the training data, potentially leading to skewed results—particularly for underrepresented populations.⁴⁶ Additionally, regulatory hurdles complicate the approval and adoption of AI technologies in clinical practice. The absence of standardized guidelines for validating AI-driven models and concerns over data privacy and patient safety further delay their integration into routine healthcare settings.⁴⁷ Addressing these challenges will require a coordinated effort from researchers, healthcare providers, and regulatory bodies to develop robust validation frameworks, ensure ethical AI deployment, and promote equitable access to these advanced technologies.

Implementation and considerations of screening programs for EC

Clarifying the screening population

High-risk factors for developing EC primarily include: (1) obesity, defined as a BMI greater than 30; (2) menopausal hormone therapy, specifically a history of estrogen replacement therapy or long-term use of tamoxifen; (3) late age of menopause (greater than 55 years); (4) nulliparity; (5) hypertension or diabetes mellitus; and (6) Lynch syndrome.⁴⁸ The aforementioned populations with high-risk factors should be targeted as screening subjects. Regarding Lynch syndrome, which is one of the most well-established risk factors for EC, we will explore in greater depth the global status of screening for EC and precancers in these patients. Globally, different regions may have varying screening practices. In some developed countries, comprehensive screening programs are in place. In Europe, guidelines recommend more frequent and detailed screening for patients with Lynch syndrome, incorporating regular genetic counseling and enhanced gynecological sur-

veillance. This includes more frequent transvaginal ultrasounds, CA-125 tests, and endometrial biopsies. Similarly, early detection strategies in North America emphasize a combination of imaging and biomarker tests. In contrast, screening for Lynch syndrome-associated EC is less systematic in some developing regions due to limited resources and awareness. However, international cooperation projects are working to improve access by providing training and resources for local healthcare providers.

Women with Lynch syndrome have a significantly elevated lifetime risk of EC, and preventive screening is recommended within the first 5 to 10 years after reaching 30 to 35 years of age or following the earliest diagnosis of EC in their family. While no universal consensus exists on monitoring asymptomatic women with Lynch syndrome, current recommendations suggest that premenopausal women undergo regular gynecological examinations, transvaginal ultrasounds, and CA-125 tests every 1 to 2 years. Endometrial biopsies may also be performed when necessary to enhance early detection and improve patient outcomes.

Improving the screening program

It is essential to enhance public awareness regarding the symptoms associated with high-risk factors for EC and to conduct early screening for high-risk groups and symptomatic individuals. An early screening network for EC has been established, incorporating micro-non-invasive screening methods such as cytological screening, AI diagnostics, and methylation detection.^{5,49,50} These methods are gradually being implemented in grassroots healthcare institutions to improve the efficiency of early screening and diagnosis of EC (Table 1).

Protecting the fertility of young patients

Many patients diagnosed with EC are of reproductive age and have not yet given birth, making fertility preservation a critical consideration. Early identification of dysplasia or EC is essential for effective management.

For fertility-preserving treatment, hysteroscopic resection of lesions combined with oral progestins is a common approach. The recommended dosage of oral progestins typically starts at 10–20 mg per day, with a treatment duration of 3–6 months. Regular follow-up is necessary, including pelvic ultrasounds every 1–2 months to monitor lesion regression.

Levonorgestrel intrauterine devices (IUDs) are another option. After insertion, some patients may experience irregular vaginal bleeding for the first 3–6 months, but most adapt over time. Endometrial re-evaluation is recommended 3–6 months post-insertion to assess treatment response.

GnRH agonists, administered via intramuscular injection every 28 days for 3–6 cycles, represent another viable strategy. However, since prolonged use may lead to decreased bone mineral density, regular bone density monitoring is advised.

Overall, conservative treatment options for early-stage EC patients seeking fertility preservation are feasible. Hysteroscopic resection with oral progestins, IUDs, and GnRH agonists are effective strategies that offer promising outcomes while maintaining reproductive potential.

Focus on economic benefits

The selection of EC screening methods must consider the economic benefits associated with health expenditures. Promoting research into EC screening is contingent upon demonstrating these economic advantages. Excessive healthcare expenditures can hinder national and societal support for EC screening initiatives.

Table 1. Characteristics of the screening methods for EC

Screening methods	Sensibil-ity (%)	Specific-ity (%)	Advantage	Limitations	Clinical applicability
Clinical presentation (mainly vaginal bleeding)	-	Low	Easy to detect, easy to identify, can prompt medical treatment,	Low specificity (overlap with other benign gynecological diseases)	As a preliminary warning, other inspections
Transvaginal ultrasound (TVU)	85	82	Non-invasive, fast, extensive grassroots available	Insufficient sensitivity to early EC/hormone-independent (II type)	Initial screening for postmenopausal women and vaginal bleeding
CA125	Not clear	low	Assisted in the diagnosis of an intrauterine metastasis or serous carcinoma	Interference caused by ovarian cancer	Late EC monitoring, a non-screening tool
HE4	77.8	78	And positively correlated with the degree of malignancy	High heterogeneity, and limited clinical recommendations	High-risk groups are assisted with screening
Histopathology	100	100	The gold standard	Invasive, risk of complications (bleeding, infection), and low patient compliance	The means of diagnosis is not applicable to general screening
Genomics (mutation testing)	92.9	-	High sensitivity to screen for hereditary EC (such as Lynch syndrome)	High cost, requiring tissue samples, and not widely standardized	Screening for high-risk groups (e. g., Lynch syndrome)
Epigenetics (methylation)	87.5	86.1	Non-invasive (liquid biopsy), early warning potential	Need a large sample verification, the cost is high	Early screening, and monitoring of high-risk groups
Metabonomics	88.9	82	Non-invasive (blood sample), associated with metabolic disease	Data processing is complex and costly	Screening for high-risk groups, such as obesity/diabetes
Imagiomics	85	82	Non-invasive and assess for myometrial invasion and lymph node metastasis	Equipment dependence, high cost	Preoperative staging, high-risk population sperm screening
Circulating tumor DNA (ctDNA)	77.8	68.7	Non-invasive (blood sample), real-time monitoring of tumor dynamics	High cost, inadequate standardization, and moderate sensitivity	Postoperative monitoring, recurrence risk assessment
Exosomal miRNA (miR-15a-5p)	77.8	78	Non-invasive (blood sample)	Large sample verification is required, and the clinical promotion is limited	Early screening, low-risk population
AI	89	88	Efficient and automated analysis (e. g., cytology, imaging)	Relying on data quality, the algorithm needs to be continuously optimized	Primary primary screening, classification of high-risk groups
Vibration spectroscopy	87	78	Rapid, non-invasive, and differentiating between cancerous tissues	Device dependency and few clinical studies	Intraoperative rapid diagnosis, outpatient screening

AI, artificial intelligence; CA125, cancer antigen 125; EC, endometrial cancer; HE4, human epididymis protein 4; IVF, *in vitro* fertilization; miRNA, microRNA.

While technological advancements—such as molecular techniques and AI-driven diagnostics—offer promising improvements in accuracy, their economic viability must also be carefully assessed to ensure long-term sustainability.

Cost-effectiveness analyses can provide valuable insights by comparing the long-term financial impact of emerging screening technologies against traditional methods. For instance, an analysis could evaluate an AI-based EC screening system by considering not only the direct costs of the test itself but also expenses related to follow-up procedures, treatment, and potential cost savings from early detection.⁵¹

A case study from the Nordic region demonstrated the cost-effectiveness of implementing an AI-enhanced screening program. Although the initial investment in AI technology was substantial, it was offset by a reduced need for invasive diagnostic procedures and more efficient healthcare resource allocation. Over five years, the program resulted in a 20% reduction in overall healthcare costs related to EC management while maintaining high detection accuracy.

Striking a balance between the costs of innovative screening technologies and their economic benefits is essential for ensuring their widespread adoption and long-term sustainability within healthcare systems.

Table 2. Diagnostic performance and economic feasibility of different screening methods

Screening methods		Diagnostic performance	Economic feasibility
Screening status	Clinical manifestations (mainly vaginal bleeding)	Poor diagnostic performance	No cost
	Vaginal ultrasound	Poor diagnostic performance	Low cost
	CA125	Advanced disease diagnosis	Low cost
	HE4	Diagnosis of the disease progression	Low cost
	Cytology and Histopathology	The gold standard	Middle cost
Innovate screening methods	Genomics	Diagnosis of genetically related diseases	High cost
	Transcriptomics	Predicting cancer prognosis	Middle cost
	Epigenetics	Diagnosis of genetically related diseases	Middle cost
	Metabolomics	Diagnosis of patients with metabolic disorders	High cost
	Inflammatory indicators	Etiological diagnosis of cancer	High cost
	Imaging-Omics	Diagnosis of myometrial invasion	High cost
	ctDNA	Efficacy judgment during the treatment process	Very high cost
	Spectroscopy	Rapid diagnosis, diagnosis of lymphatic metastasis	Middle cost
	Exosomal miR-15a-5p	Early diagnosis and surveillance of cancer and cancer prediction	Middle cost
	AI Assistance Scheme	Use the data to help with disease diagnosis and screening	Low cost (software)

AI, artificial intelligence; CA125, cancer antigen 125; ctDNA, circulating tumor DNA; HE4, human epididymis protein 4.

Therefore, health economics, along with the development of new products, screening technologies, and strategies for EC screening, represents a critical area of focus (Table 2).

Ethical considerations in EC screening

Ethical considerations are critical in the development and implementation of EC screening strategies. The invasiveness of specific techniques, such as endometrial biopsies and hysteroscopy, poses significant physical and psychological challenges for patients. These procedures, while highly accurate, can cause discomfort, pain, and anxiety, potentially discouraging participation in screening programs. Additionally, the psychological impact of false-positive or false-negative results must be addressed, as they can lead to unnecessary stress or delayed treatment. To mitigate these concerns, it is essential to prioritize patient-centered approaches, including clear communication of risks and benefits, pre-screening counseling, and developing less invasive screening methods. By integrating these ethical considerations into screening protocols, we can enhance patient trust, improve adherence, and ensure that screening strategies are both effective and compassionate.

Future directions

Despite significant advances in EC research, substantial gaps remain in current screening strategies. Traditional methods—such as ultrasound, histology, cytology, and tumor markers—face limitations in sensitivity, specificity, and accessibility. These challenges are further compounded by geographical disparities, low public participation, and a lack of standardized risk stratification, all hindering early detection efforts.

To address these issues, future research must prioritize the

development of more effective, minimally invasive, and widely applicable screening techniques. Key focus areas should include identifying novel biomarkers, refining risk prediction models, and validating emerging technologies through large-scale, multi-center clinical trials. Enhancing clinical translation will require comprehensive professional training and policy reforms to facilitate the seamless integration of innovative screening methods into routine practice.

Conclusions

Given the rising incidence and mortality rates of EC, a robust risk stratification framework is essential. Screening strategies should be based on epidemiological data, risk factors, and genetic predispositions to clearly define low-, medium-, and high-risk groups. A stratified approach will enable targeted screening and more effective population management.

Emerging technologies show promise in addressing the limitations of current screening methods. Biomarkers such as exosomes and epigenetic markers (e.g., gene methylation) have demonstrated strong screening potential. Additionally, vibrational spectroscopy technology has shown high sensitivity and specificity, offering a more objective and rapid alternative for cancer detection. Large-scale clinical trials are needed to validate the effectiveness and reliability of these approaches, alongside long-term follow-up studies to assess their impact on reducing EC incidence and mortality.

For successful clinical implementation, healthcare providers must be trained in using these novel screening tools. Policymakers should establish guidelines to support their integration into routine care, while cost-effectiveness analyses will be crucial to ensuring affordability and accessibility for the broader population. By com-

binning technological innovation with strategic policy initiatives, we can significantly improve early detection and prevention efforts in EC.

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Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization (YL), literature review, data collection (HYL, HA), manuscript writing (HYL, HA), manuscript editing and critical revision (YL), study supervision (YL). All authors have made a significant contribution to this study and have approved the final manuscript.

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