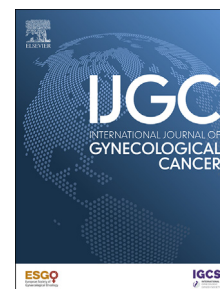


Current challenges and emerging tools in endometrial cancer diagnosis

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ABSTRACT

The diagnostic process of endometrial cancer includes imaging methods such as trans-vaginal ultrasound, along with procedures to obtain endometrial tissue for histologic evaluation. Common techniques for tissue sampling include Pipelle endometrial biopsy, hysteroscopy, and dilation and curettage, which are used to confirm the diagnosis, determine tumor histology, grade, and molecular profile. However, diagnostic algorithms for endometrial cancer differ significantly across countries, influenced by local resources, protocols, and the availability of diagnostic methods. These variations include differences in the endometrial thickness threshold for recommending a biopsy and the choice of the initial diagnostic test. Moreover, patients often have multiple tests and appointments before a definitive diagnosis, although only 5%-10% of women with post-menopausal bleeding are diagnosed with endometrial cancer. Current diagnostic techniques have limitations. Pipelle endometrial biopsy has a significant false-negative rate (10%-20%) and may fail to provide adequate diagnostic material in up to 30% of cases. Hysteroscopy, while useful, is associated with pain in up to 65% of patients and can delay diagnosis because of limited availability. Dilation and curettage is an invasive procedure requiring general anesthesia and has a higher complication rate. In response to these challenges, there is growing interest in developing new diagnostic tools that are less invasive and provide 1-step diagnoses, including liquid biopsies from urine, blood, cervico-vaginal and endometrial fluid samples by means of genomics and proteomics. This review will examine the current diagnostic algorithms in European and American guidelines, evaluate the sensitivity, specificity, and accuracy of current techniques, and explore new diagnostic tools under development.

Keywords:

Endometrial Cancer Diagnosis; Diagnostic Algorithms; Proteomics; Genomics; Pipelle

INTRODUCTION

Endometrial cancer is generally diagnosed at early stages (80% in stage I-II) and is associated with a good prognosis (5-year overall survival of 90%).¹ This is mainly because 90% of patients with endometrial cancer present symptoms at the outset, predominantly with abnormal uterine bleeding or post-menopausal bleeding.² The diagnostic process for endometrial cancer includes imaging techniques such as trans-vaginal ultrasound, along with methods to obtain endometrial tissue for histologic assessment such as endometrial biopsy by aspiration, hysteroscopy, or dilation and curettage. These techniques confirm the diagnosis, determine tumor histology and grade, and establish the molecular profile of the tumor.³ However, diagnostic algorithms for endometrial cancer vary widely between countries, depending on local protocols, resources, and the availability of each technique. These variations range from the endometrial thickness threshold for referring a patient to biopsy to the preferred initial method for histologic assessment.⁴⁻⁹ Moreover, patients frequently undergo multiple tests and medical appointments before a diagnosis is confirmed or

ruled out, although only 5% to 10% of patients with post-menopausal bleeding have endometrial cancer.²

Current techniques for obtaining endometrial tissue have notable drawbacks: endometrial biopsy by aspiration has a significant false-negative rate (10%-20%),^{10,11} and in up to 30% of cases, it fails to provide a definitive diagnosis because of insufficient material or failure of the technique.¹²⁻¹⁴ Outpatient hysteroscopy is painful for up to 65% of patients and often delays diagnosis because of limited immediate availability.^{15,16} Dilation and curettage is an invasive technique that often requires general anesthesia, and is associated with more complications compared with the other 2 procedures.¹⁷⁻²⁰

Given these challenges, various efforts are currently in place for developing new tools to improve the accuracy of endometrial cancer diagnosis using less invasive, one-step-diagnosis methods, such as cervical or urine cytology and liquid biopsies in urine, blood, cervico-vaginal, and endometrial fluid. The aim of this article is to review the differences in the current diagnostic algorithms of the most relevant European and American clinical guidelines. We also intend to

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conduct a review of the sensitivity, specificity, accuracy, and false-positive and false-negative rates of current diagnostic methods. Lastly, we will review all the new diagnostic tools for endometrial cancer that are currently under development or marketed.

RESULTS

Summary of European and American Clinical Guidelines for Diagnosis of Endometrial Cancer

We performed a review of the European (European Society of Gynaecological Oncology [ESGO]), Spanish, Italian, British, German, and American (National Comprehensive Cancer Network and American College of Obstetricians and Gynecologists [ACOG]) guidelines to achieve or rule out the diagnosis of endometrial cancer. All guidelines converge on the need for an initial evaluation (gynecologic history and examination) in case of suspicious symptoms: abnormal uterine bleeding or post-menopausal bleeding. Combined algorithms of all the above-mentioned guidelines are illustrated in the Figure, and differences in clinical pathways in Table 1.

Initial Evaluation

All guidelines state that the first step in the diagnostic pathway of post-menopausal bleeding is to perform a trans-vaginal ultrasound to establish the endometrial thickness and detect abnormalities such as focal lesions, irregularities, or enhanced vascularization of the endometrium. Only the ACOG guidelines state that either trans-vaginal ultrasound or endometrial biopsy by aspiration (also known as Pipelle biopsy) can be performed, irrespectively, as a first procedure (sometimes, Pipelle biopsy is conducted first as a preferred method for obtaining an endometrial tissue sample). However, each country has established a different endometrial thickness threshold to warrant further diagnostic evaluation (Table 1). The ESGO guidelines do not specify an endometrial thickness threshold. Only the British and German guidelines determine a threshold for patients on hormone replacement therapy (5 mm).

First Histologic Assessment

All guidelines converge on the need for a histologic diagnosis in the presence of endometrial thickening or abnormalities. Nevertheless, the preferred initial diagnostic method for obtaining endometrial tissue differs among countries. Spanish, Italian, and US guidelines initially recommend blinded endometrial biopsy by aspiration, followed by histologic assessment. The German and UK guidelines propose different pathways depending on the trans-vaginal ultrasound findings: in the case of endometrial thickening without irregularities, a Pipelle biopsy is recommended. However, in the case of irregularities, endometrial biopsy guided through hysteroscopy (abbreviated as hysteroscopy) followed by histologic assessment is recommended as the initial step (and in Germany, also dilation and curettage under anesthesia).

The presence of an endometrial thickness below the threshold without irregularities does not require further investigation; only the German guidelines recommend performing a 3-month follow-up or directly a Pipelle biopsy. If only clinical follow-up is chosen at 3 months, and the findings are unremarkable, the follow-up process can be concluded. If a Pipelle biopsy is performed and the result is benign, a new 3-month follow-up is recommended. In case of persistent symptoms or high suspicion, even with normal ultrasonographic findings, all guidelines recommend performing a hysteroscopy or dilation and curettage, except the Spanish guidelines, which prefer a Pipelle biopsy.

Second Histologic Assessment

All guidelines recommend continuing the diagnostic process with guided biopsy methods (eg, hysteroscopy) and/or dilation and curettage under anesthesia if symptoms persist despite a negative initial biopsy, or in case of insufficient sample or inconclusive diagnosis with Pipelle biopsy.

After analyzing these guidelines and identifying the discrepancies in the diagnostic pathways, our team conducted 60-minute online one-to-one double-blinded interviews assisted by a

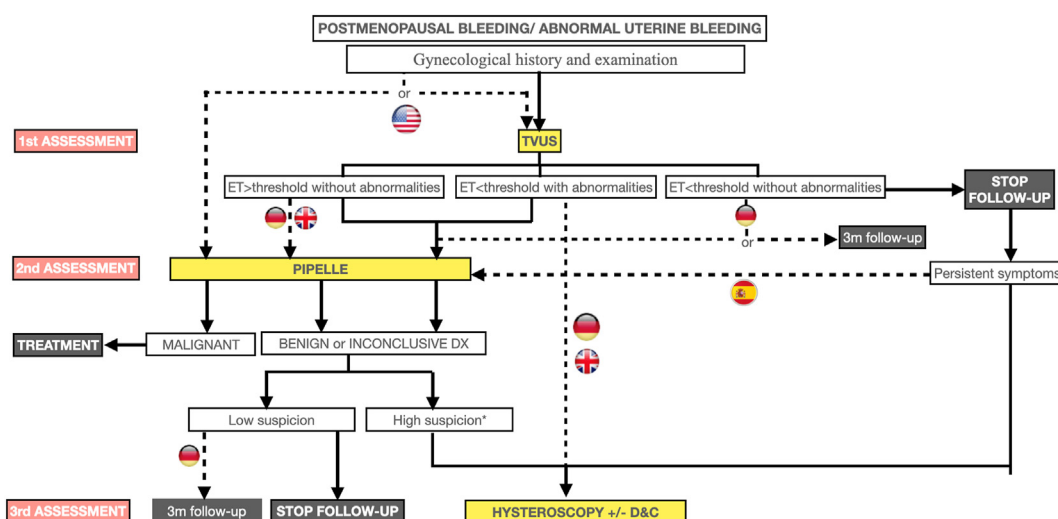


Figure Combination of Spanish, British, German, Italian, and American guidelines for the diagnosis of endometrial cancer. Solid black arrow = general pathway recommended by most clinical guidelines. Dashed arrow = In cases where any clinical guideline differs from this pathway, *Persistent bleeding. ACOG, American College of Obstetricians and Gynecologists; D&C, dilation and curettage; DX, diagnosis; ET, endometrial thickness; NCCN, National Comprehensive Cancer Network; TVUS, trans-vaginal ultrasound; 3m, 3 months.

Table 1 Summary of the Main European and American Guidelines for the Diagnosis of Endometrial Cancer.

Guideline	ET (mm)	First assessment	First histologic assessment
ESGO	NR	NR	Endometrial biopsy or D&C Hysteroscopy for obtaining representative samples/ removing target lesions
Spanish	3	TVUS	Endometrial biopsy
British	4 5 if HRT	TVUS	Endometrial biopsy Hysteroscopy if abnormalities in the endometrium
Italian	5	TVUS	Endometrial biopsy or hysteroscopy
German	3 5 if HRT	TVUS	Endometrial biopsy Hysteroscopy if abnormalities in the endometrium
NCCN	4-5	TVUS	Endometrial biopsy
ACOG	4	TVUS or endometrial biopsy	Endometrial biopsy

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; D&C, dilation and curettage; ESGO, European Society of Gynaecological Oncology; ET, endometrial thickness; HRT, hormonal replacement therapy; NCCN, National Comprehensive Cancer Network; NR, not reported; TVUS, trans-vaginal ultrasonography.

specialized company with 34 key opinion leaders (12 from the United States, 8 from Germany, 8 from the United Kingdom, and 6 from Spain) to gain deeper insights into the landscape of endometrial cancer diagnosis in these countries.

Interestingly, all German specialists confirmed that in Germany, Pipelle biopsy is never performed; instead, 100% of symptomatic patients undergo a trans-vaginal ultrasound followed by a dilation and curettage under anesthesia. Moreover, trans-vaginal ultrasound is not used to exclude patients from further investigation but rather to gather additional information. All German key opinion leaders reported high satisfaction with this approach, considering dilation and curettage the gold standard for endometrial cancer diagnosis.

In the United Kingdom, all the key opinion leaders confirmed that all UK patients with suspected cancer are referred to the Rapid Access Care Pathway for investigation within 14 days. They reported high variability in the relative use of Pipelle biopsy versus hysteroscopy-guided biopsies. In cases of suspicion, an endometrial biopsy using a Pipelle is often conducted, especially in practices without access to a hysteroscope. Practices with hysteroscopy facilities lean toward using them more frequently, while rural or smaller practices rely more on Pipelle biopsies. If Pipelle biopsy results are non-diagnostic, or if patients continue to present with symptoms, they may undergo a hysteroscopy-guided biopsy at some point in their evaluation process.

In the United States, approximately half of the patients undergo ultrasound first, but there is no clear cutoff for endometrial thickness, while the other half proceed directly to endometrial biopsy. Hysteroscopy is widely used, mainly in an inpatient setting, and

most patients who undergo Pipelle biopsy also undergo hysteroscopy if Pipelle biopsy samples are negative or inconclusive.

In Spain, ultrasound is the first-line diagnostic tool. In most centers, ≥ 3 -mm thickness triggers further investigation. In 70% of cases, Pipelle biopsy is the first choice, and in 30% of cases, hysteroscopy is the method of choice. It has been noted that hysteroscopy is used more frequently as the primary diagnostic tool in larger or specialized hospitals. Hysteroscopy is always used after inconclusive Pipelle results or in cases with negative Pipelle results but persistent bleeding.

Advantages and Limitations of Current Available Diagnostic Techniques

Various procedures are used for obtaining endometrial samples, each with its own advantages and limitations. Endometrial biopsy with Pipelle is the most used because it is an outpatient minimally invasive procedure, usually performed without anesthesia. Furthermore, it is associated with very few complications, and can often be conducted at the time of trans-vaginal ultrasound. Outpatient hysteroscopy is typically performed without the need for general anesthesia and is relatively quick, taking approximately 15 to 30 minutes. Hysteroscopy is more invasive than Pipelle biopsy, but it provides a visual aid to guide biopsies, ensuring accurate sampling of suspicious areas. Unlike the Pipelle biopsy, this procedure needs to be scheduled, which may lead to diagnostic delays.

Dilation and curettage requires anesthesia (local, regional, or general) and the dilation of the cervix to facilitate the insertion of the curette into the uterine cavity and collect the endometrial tissue sample. Unlike hysteroscopy and Pipelle biopsy, this procedure often requires hospital admission because of a higher rate of complications and the use of anesthesia. As with hysteroscopy, it needs to be scheduled, which might lead to diagnostic delays. The advantages and limitations of each technique are summarized in Table 2.

Combination of Trans-Vaginal Ultrasound and Endometrial Sampling

Most diagnostic algorithms recommend performing a trans-vaginal ultrasound first and, according to its results, proceeding with the collection of endometrial tissue for histologic assessment. This approach is primarily due to 2 factors: the changes in endometrial thickness and morphology observed by trans-vaginal ultrasound after endometrial biopsy, and the varying sensitivity and specificity depending on endometrial thickness. The systematic review and meta-analysis of Narice and colleagues²¹ found that Pipelle sampling can make the endometrium approximately 0.4 mm thinner and create echogenic spots.²²

Sensitivity and specificity rates for excluding or diagnosing endometrial cancer can vary with endometrial thickness. Sensitivity is 98%, 95%, and 90% with endometrial thickness cutoff levels of 3, 4, and 5 mm, respectively.^{23,24} When using a 4-mm cutoff, trans-vaginal ultrasonography demonstrates a high negative predictive value, exceeding 99%, which allows to effectively identify women with post-menopausal bleeding who do not need endometrial biopsies, thereby reducing unnecessary sampling.²⁵ A recent systematic review of 44 studies including 17,339 women found that sensitivity was similar for endometrial thickness cutoffs

Table 2 Comparison of Advantages and Disadvantages of the Current Available Diagnostic Techniques.

Diagnostic techniques	Complication rate	Patient tolerance	Cost	Availability	Failure rate	Inadequacy sample	False-negative rate
Pipelle biopsy	+	+	+	+	+++	+++	+++
Outpatient hysteroscopy	++	++	++	++	++	+	+
D&C	+++	+	+++	+++	+	++	++

The green color and “+” indicate the best technique for the specific item being evaluated. Yellow and “++” represent an intermediate option, while orange and “+++” indicate the least favorable technique for the specific item being assessed.

Abbreviation: D&C, dilation and curettage.

of ≥ 3 , ≥ 4 , and ≥ 5 mm (96.2%; 95% CI 92.3 to 89.1), whereas specificity was higher with a cutoff of ≥ 5 mm (51.5%; 95% CI 42.3 to 62.7).²⁶ According to these data, adopting a cutoff ≥ 5 mm would reduce the number of women requiring invasive biopsy by 17%.

Diagnostic Performance

Endometrial Biopsy by Aspiration (Pipelle Biopsy)

The sensitivity of the Pipelle biopsy for diagnosing endometrial cancer varies according to the gold standard method used. When dilation and curettage or hysteroscopy were considered the gold standard, most studies reported 100% sensitivity.^{10,27-32} However, Machado and colleagues³³ found lower sensitivity (84%) and specificity (99%), likely due to combining different gold standards (dilation and curettage and hysterectomy) or combining diagnoses of endometrial cancer with hyperplasia, for which Pipelle biopsy has lower sensitivity. When hysterectomy, the gold standard for uterine disorders, was used, Pipelle biopsy's sensitivity dropped to 64% to 84%.^{11,13,34-38} Specificity was approximately 100%, regardless of the gold standard, and accuracy ranged from 97% to 100%. The false-negative rate also varied according to the gold standard.

Studies using dilation and curettage or hysteroscopy reported a 0% false-negative rate.²⁷⁻³² Gupta and colleagues¹⁰ reported a false-negative rate of 11%, consistent with data reported by the Spanish, British, and American guidelines. When hysterectomy was the gold standard, false-negative rates ranged from 14% to 25%,^{11,34,36} indicating that a negative Pipelle biopsy result can often miss endometrial cancer. In cases of strong suspicion, further testing is recommended. The review of the diagnostic performance of Pipelle biopsy is illustrated in Table 3.^{10,11-14,27-37,39-44}

Hysteroscopy-Guided Endometrial Biopsy

Several studies have reported on the diagnostic performance of outpatient hysteroscopy, with hysterectomy as the preferred gold standard. Sensitivity ranged from 60% to 94%, specificity from

94.4% to 100%, and accuracy was close to 100%. However, a retrospective study by Laban and colleagues³⁷ (including 164 patients and comparing the diagnostic performance of Pipelle biopsy, outpatient hysteroscopy, and dilation and curettage with hysterectomy specimens) found lower accuracy for all 3 techniques compared with other studies. A systematic review and meta-analysis by Clark and colleagues³⁸ in 2002 (hence, not including the articles analyzed in the present review) found a sensitivity of 86.4%, specificity of 99.2%, and 100% accuracy, using either dilation and curettage or hysterectomy as the gold standard. A review of the diagnostic performance of hysteroscopy is included in Table 4.^{15,16,37,38,45-54}

Dilation and Curettage

In most studies, hysterectomy specimens serve as the gold standard for assessing the diagnostic performance of dilation and curettage. A retrospective study reported a sensitivity and negative predictive value of 83.3% and 100%, respectively.⁵⁵ A recent meta-analysis reviewing the diagnostic accuracy of dilation and curettage compared with histopathologic examination of hysterectomy specimens reported 88.2% sensitivity and 98.4% specificity.⁵⁶ The review of the diagnostic performance of dilation and curettage is illustrated in Table 5.^{17-19,27-29,37,43,55,57-59}

Failure to Diagnose

Failure to diagnose refers to the inability of a technique to achieve a diagnosis. This can be due to an inability to access the endometrium (*failure rate*, typically due to cervical stenosis) or an insufficient endometrial sample (*inadequacy sample rate*). Lack of operator experience, inability of the patient to tolerate the pain, presence of an endometrial atrophy, or focal endometrial pathology may reduce the sample adequacy. An inadequate biopsy specimen is a cause of concern due to the increased number of hospital visits (median of 2 visits until the diagnosis [range; 1-4]), as reported by Ewies and colleagues,³⁹ leading to delays in diagnosis and additional cost implications.

Endometrial Biopsy by Aspiration (Pipelle Biopsy)

Three studies reported a 0% failure rate, while most studies reported an inability to access the endometrium in 2% to 8% of cases.^{12,27,30-32,41,55,60} Xie and colleagues³⁰ identified in their multi-variate analysis prior cervical operations and intra-uterine procedures as independent factors for procedure failure. Another study⁴⁰ found post-menopausal bleeding, prior biopsy failure, and provider type (physician vs mid-level provider) as additional risk factors.

Inadequacy sample rates vary significantly: 9 studies reported rates between 15% and 31%, while 9 others reported lower rates of 1% to 7%. Post-menopausal status, endometrial thickness <7 mm, and uterine volume <43 cm³ are described as key factors for inadequate samples,³⁰ while Bakour and colleagues⁶⁰ suggest a cutoff of <5 mm for endometrial thickness. A review by Clark and colleagues³⁸ found failure rates ranging from 0% to 22% and sample inadequacy rates from 0% to 76%, with average rates of 8% for failure and 13% for sample inadequacy. A recent meta-analysis by Van Hanegem and colleagues¹⁴ reported a failure rate of 11% and an inadequacy sample rate of 31% when comparing Pipelle biopsy with dilation and curettage or hysteroscopy in a sample of 1029 women with post-menopausal bleeding (Table 3^{10,11-14,27-37,39-44}).

Endometrial Biopsy With Hysteroscopy-Guided Visual Inspection

Failure of office hysteroscopy, defined as incomplete or canceled procedures, is primarily attributed to technical challenges such as cervical stenosis and excessive uterine bleeding. High levels of patient anxiety and pain also contribute to procedure abandonment. A meta-analysis assessing the feasibility of diagnostic hysteroscopy in women with abnormal uterine bleeding reported a failure rate of 3.4%.⁴⁵ The type and size of hysteroscope can also impact success rates: a study comparing 5-mm and 3.5-mm hysteroscopes found a higher success rate with the mini-hysteroscope (87% vs 44%, respectively).⁴⁶ Failure rates are higher when anesthesia or cervical dilation are not used, with studies reporting rates ranging from 17.8%⁶¹ to 23.6%⁴⁷ under such conditions (Table 4^{15,16,37,38,45-54}).

Dilation and Curettage

Because of the use of anesthesia and cervical dilation, technical failures are rare. However, sample inadequacy is reported in 0% to 10% of cases, as this technique, like the Pipelle biopsy, collects the histologic sample without direct visualization (Table 5^{17-19,27-29,37,43,55,57-59}).

Complications

Endometrial Biopsy by Aspiration (Pipelle Biopsy)

The risks associated with the Pipelle biopsy are minimal, with pain and discomfort being the most common side effects. While there is limited literature focusing on Pipelle-related complications, several studies mention complication rates, although not as a primary outcome. All these studies consistently report a 0% complication rate, indicating an extremely low risk of serious complications^{10,27,30,31} (Table 3^{10,11-14,27-37,39-44}).

Endometrial Biopsy With Hysteroscopy-Guided Visual Inspection

Complication rates for diagnostic hysteroscopy are generally low. Common issues include pain, vasovagal episodes, fluid overload, uterine perforation, infection, and false tract formation. Studies show that 34.8% of patients experience severe pain,¹⁵ and 65.4%

report moderate to severe pain immediately after the procedure.¹⁶

A meta-analysis focusing on the prevalence of pain in hysteroscopy supports the high prevalence of pain in outpatient mini-hysteroscopy.⁶² The risk of vasovagal syncope ranges from 0.21% to 1.85%,^{45,48} with higher rates for rigid hysteroscopes.⁶³

Infections are rare, occurring in 0.06% of cases,⁴⁹ with a meta-analysis demonstrating low overall infection rates regardless of antibiotic use: overall infection was present in 0.52% vs 0.58%, fever in 3.8% vs 1.8%, and the need for post-operative antibiotic therapy in 1.18% vs 1.32%. Serious infections, such as pelvic inflammatory disease, are extremely rare (0.2%).⁵⁰ Clinically significant fluid overload is uncommon in diagnostic hysteroscopies.^{51,64} Uterine perforation occurs in 0.06% to 0.13% of diagnostic hysteroscopies, and in 0.4% during polypectomy.^{45,64} False tract formation, while not usually serious, can prevent the completion of the procedure or cause accidental perforation (Table 4^{15,16,45,48-54}).

Dilation and Curettage

Complications include a 0.4% risk of hemorrhage, 0.3% to 0.5% risk of infection, 0.6% to 1.3% risk of uterine perforation, and a 0.03% to 0.5% risk of an unanticipated major operation. Additionally, there are risks associated with anesthesia administration¹⁷⁻²⁰ (Table 5¹⁷⁻¹⁹).

New Strategies for Diagnosis of Endometrial Cancer

Current diagnostic methods have notable limitations, which often result in diagnostic delays or the need for multiple tests and unnecessary visits for 90% to 95% of patients presenting with post-menopausal bleeding.² For these reasons, several research groups, including our team, are currently focused on developing new strategies for the diagnosis of endometrial cancer. The ideal tool would be minimally invasive, cost-effective, provide a 1-step diagnosis, and be easy to perform, while offering high accuracy and sensitivity and low false-negative rates. Such a tool could be integrated into the routine diagnostic process for endometrial cancer in patients with post-menopausal bleeding.

Cytology

Uro-Vaginal Cytology

Endometrial cancer cells may be identified in urine, especially in women with bleeding symptoms, by the microscopic assessment of urine or using single-cell technology.⁶⁵ A prospective study including 216 women with known gynecologic cancer or post-menopausal bleeding analyzed the ability of urinary and vaginal cytology for detecting gynecologic cancer. The combination achieved a sensitivity of 91.7% and a specificity of 88.8%. Vaginal cytology was more sensitive (90.2% vs 72.0%) but less specific (88.7% vs 94.9%) than urine cytology for endometrial cancer detection.⁶⁶ After the promising results of this pilot study, this research group is conducting a multi-center study (the DETECT study) to determine the diagnostic test accuracy of urine and vaginal cytology for endometrial cancer detection in women with post-menopausal bleeding⁶⁷ (Table 6^{66,67}).

Liquid Biopsies

Liquid biopsies have been increasingly investigated as a source for identifying new biomarkers in endometrial cancer. Several techniques, including proteomics, metabolomics, and genomic sequencing, have

Table 3 Diagnostic Performance, Failure to Diagnose, and Complication Rates of Pipelle Biopsy.

Pipelle biopsy												
Study	N	Study type	Sens	Spec	PPV	NPV	Accuracy	Failure rate	Inadequacy rate	Gold standard	Inclusion criteria	Complications
Abdelazim and colleagues, ²⁷ 2013	140	Retrospective	100%	100%	NA	NA	100%	1%	2%	D&C	AUB >40 y + >4 mm ET	0%
Gungorduk and colleagues ²⁸ 2018	466	Prospective	100%	NA	NA	NA	NA	NA	1%	D&C	Patients undergoing hysterectomy	NA
Sanam and Majid, ²⁹ 2015	130	Clinical trial	100%	100%	100%	100%	100%	NA	15%	D&C	AUB >35 y, ET >5 mm in post-menop or >12 mm in pre-menop	NA
Xie and colleagues, ³⁰ 2018	466	Prospective	100%	NA	NA	NA	NA	2%	6%	D&C	Not specified	0%
Gupta and colleagues, ¹⁰ 2022	125	Clinical trial	89.3%	95.7%	86.2%	96.8%	92%	0%	2%	D&C	AUB >40 y + ET >4 mm	0%
Piriyev and colleagues, ³¹ 2020	176	Prospective	100%	100%	NA	NA	100%	NA	3%	Hysteroscopy + D&C	AUB or abnormal endometrium	0%
Utida and Kulak, ³² 2019	45	Prospective	100%	100%	100%	100%	100%	NA	4%	Hysteroscopy	AUB >35 y or PMB	NA
Machado and colleagues, ³³ 2003	131	Retrospective	84.2%	99.1%	94.1%	93.7%	96.9%	NA	16%	D&C or hysterectomy	AUB	NA
Yasmin and colleagues, ³⁴ 2007	100	Prospective	75%	100%	100%	98%	98%	0%	6%	Hysterectomy	AUB and PMB	NA
Reijnen and colleagues, ³⁵ 2017	139	Retrospective	NA	NA	92.6%	85.7%	NA	NA	NA	Hysterectomy	Patients with Pipelle and hysterectomy	NA
Ilavarasi and colleagues, ¹¹ 2019	104	Prospective	75%	100%	100%	97.9%	98%	0%	22%	Hysterectomy	AUB 34-74 y	NA
Sany and colleagues, ³⁶ 2012	191	Retrospective	87%	NA	NA	NA	NA	NA	NA	Hysterectomy	Patients with EC	NA
Laban and colleagues, ³⁷ 2021	164	Retrospective	56.8%	89.5%	97.7%	21%	60.5%	NA	NA	Hysterectomy	Patients with EC	NA
Demirkiran and colleagues, ⁴³ 2012	673	Prospective	NA	NA	NA	NA	NA	0%	3%	Hysterectomy	ET >6 mm	NA
Kazandi and colleague, ¹³ 2012	82	Prospective	NA	NA	NA	NA	NA	NA	7%	Hysterectomy	Patients with indication for Pipelle	NA
Ewies and colleagues, ³⁹ 2014	4576	Retrospective	NA	NA	NA	NA	NA	NA	17.6%	NA	AUB >50 y	NA
Piatek and colleagues, ⁴⁴ 2016	259	Retrospective	NA	NA	NA	NA	NA	NR	17%	NA	Patients with indication for Pipelle	NA
Adambekov and colleagues, ⁴⁰ 2017	201	Retrospective	NA	NA	NA	NA	NA	4%	18%	NA	Patients with indication for Pipelle	NA
Duelholm and colleagues, ⁴² 2020	163	Retrospective	64.6%	95%	99.1%	24.7%	NA	8%	27%	Hysterectomy	PMB	NA

Vroom and colleagues, ¹² 2021	215	Clinical trial	NA	NA	NA	NA	4%	22%	NA	PMB and ET >4 mm	NA
Marcus and colleagues, ⁴¹ 2022	150	Prospective	NA	NA	NA	NA	4%	18%	NA	Patients with indication for Pipelle	NA
Van Hanegem and colleagues, ¹⁴ 2016	1029	Meta-analysis	100% (D&C) 90% (hysteroscopy)	98%-100%	NA	NA	11%	31%	D&C or hysteroscopy	Patients with PMB	NA

Abbreviations: AUB, abnormal uterine bleeding; D&C, dilation and curettage; ET, endometrial thickness; FN, false-negative; NA, not available; NPV, negative predictive value; PMB, post-menopausal bleeding; post-menop, post-menopausal; PPV, positive predictive value; pre-menop, pre-menopausal; Sens, sensitivity; Spec, specificity.

been applied, with multiple studies examining the potential of urine, blood, uterine and cervico-vaginal fluid (Table 6⁶⁶⁻⁷⁸).

Urine

Urine is a non-invasive sample that can be self-collected, making it a promising option for biomarker detection. One study demonstrated high accuracy for endometrial cancer detection (area under the curve [AUC] of 0.96) by combining urine CA125 levels with endometrial thickness measurements obtained via trans-vaginal ultrasound.⁶⁸ DNA methylation markers in urine have also demonstrated high diagnostic performance for endometrial cancer. Wever and colleagues⁶⁹ reported a panel of 3 DNA methylation markers in a case-control study of 320 women. This panel demonstrated excellent diagnostic performance for detecting endometrial cancer (AUC of 0.95, 0.94, and 0.97 in urine, cervico-vaginal self-samples, and cervical scrapes, respectively), even in early-stage disease. Sensitivities ranged from 89% to 93% and specificities from 90% to 92%. The proteomic tests described for the detection of endometrial cancer are scarce. ADKGYNAE is a non-invasive in vitro device kit that analyzes the presence of a protein (MCM5) in urine samples and vaginal swabs. A study including 125 patients aiming to determine the sensitivity of MCM5 for the detection of endometrial cancer reported sub-optimal results, with an AUC of 0.83, a sensitivity of 97.8%, and a specificity of 75.9%.⁷⁰

Blood

Blood samples are commonly used in routine medical practice, but their main drawback is the low concentration of biomarkers, especially in early-stage endometrial cancer. Serum CA125 and WFDC2 are the most extensively assessed protein markers for diagnosing endometrial cancer. Despite being evaluated in numerous studies and meta-analyses, these markers show poor sensitivity and specificity, making them unsuitable for screening and diagnosis of endometrial cancer.^{79,80} Genomic biomarkers such as circulating tumor cells, cell-free DNA, cell-free RNA, circulating tumor DNA (including microRNA and long non-coding RNA), and exosomes have also been investigated.⁸¹⁻⁸⁴ However, their limited presence in circulation and the high costs associated with their detection pose significant challenges.

Cervico-Vaginal Fluid

Cervico-vaginal fluid is another promising source for endometrial cancer biomarkers, with wide patient acceptance due to its non-invasive nature. Genomic biomarkers, particularly DNA methylation, have shown strong diagnostic potential in cervico-vaginal samples.⁶⁹ Bakkum-Gamez and colleagues⁸⁵ conducted a study using a set of 28 tampon-based methylated DNA markers to identify endometrial cancer. This 28-gene methylation panel achieved a specificity of 96% and a sensitivity of 82% (AUC 0.91). Additionally, a post hoc analysis of a smaller panel of 3 genes resulted in an AUC comparable to those of the 28-gene panel. Another study⁷¹ examined CpG island methylation patterns in cervical smear samples from a large cohort of 786 women to detect endometrial cancer, reporting an AUC of 0.81. In a subsequent validation study,⁸⁶ a DNA methylation-based test targeting 500 CpG sites in cervical smears for early endometrial cancer detection was evaluated, achieving 86% sensitivity and 90% specificity. Wang and colleagues⁷² evaluated the detection of endometrial cancer in 382 patients by mutation analysis of 18 genes (the PapSEEK test) using

Table 4 Diagnostic Performance, Failure to Diagnose, and Complication Rates of Outpatient Hysteroscopy.

Hysteroscopy											
Study	N	Study type	Sens	Spec	PPV	NPV	Accuracy	Failure rate/ hysteroscope size	Inadequacy rate	Gold standard	Inclusion criteria
Duelholm and colleagues, ⁴² 2020	211	Clinical trial	97.4%	94.4%	99.5%	77.3%	NA	NA	NA	Hysterectomy	Patients with AH or EC
Laban and colleagues, ³⁷ 2021	125	Retrospective	60.8%	100%	100%	23.1%	64.9%	NA	NA	Hysterectomy	Pre-op or post-op diagnosis of AH or EC
Clark and colleagues, ³⁸ 2002	24,649	Systematic review	86.4%	99.2%	100%	100%	100%	NA	NA	Hysterectomy or D&C	AUB
Sauvan and colleagues, ⁴⁷ 2018	470	Descriptive	NA	NA	NA	NA	NA	23.6%/3.5 mm	NA	NA	PMB or increased ET
Campo and colleagues, ⁴⁶ 2005	240	Clinical trial	NA	NA	NA	NA	NA	13%/3.5 mm 56%/5 mm	NA	NA	NA
Van Dongen and colleagues, ⁴⁵ 2007	4208	Meta-analysis	NA	NA	NA	NA	NA	3.4%/NR	NA	NA	AUB
Complications of hysteroscopy											
Study	N	Study type	Severe pain	Pain after examination	Vasovagal collapse		Infection		Fluid overload	Uterine perforation	Cervical laceration
De Iaco and colleagues, ¹⁵ 2000	1144	Prospective	34.8%	NA	NA		NA		NA	NA	NA
de Carvalho Schettini and colleagues, ¹⁶ 2007	171	Prospective	NA	65.4%	NA		NA		NA	NA	NA
Agostini and colleagues, ⁴⁸ 2004	2079	Prospective	NA	NA	0.21%/flexible 1.85%/rigid		NA		NA	NA	NA
Van Dongen and colleagues, ⁴⁵ 2007	1399	Meta-analysis	NA	NA	0.9%		NA		NA	NA	NA
Florio and colleagues, ⁴⁹ 2019	42,934	Prospective	NA	NA	NA		0.06%		NA	NA	NA
Muzii and colleagues, ⁵⁰ 2020		Meta-analysis	NA	NA	NA		0.52%-0.58%		NA	NA	NA
Aydeniz and colleagues, ⁵¹ 2002	21,676	Prospective	NA	NA	NA		0.01%		0.1%-0.2%	0.12%	NA
Cicinelli and colleagues, ⁵² 2003	2017	Retrospective	NA	NA	2.25% (rigid 3.5 mm)		NA		NA	NA	NA
Bigatti and colleagues, ⁵³ 2018	797	Prospective	NA	NA	NA		NA		NA	NA	0.9%
Jansen and colleagues, ⁵⁴ 2000	13,600	Prospective	NA	NA	NA		NA		0.2%	0.76%	NA

Abbreviations: AH, atypical hyperplasia; AUB, abnormal uterine bleeding; D&C, dilation and curettage; EC, endometrial cancer; ET, endometrial thickness; NA, not available; NPV, negative predictive value; PMB, post-menopausal bleeding; post-op, post-operative; PPV, positive predictive value; pre-op, pre-operative; Sens, sensitivity; Spec, specificity.

Table 5 Diagnostic Performance, Failure to Diagnose, and Complication Rates of Dilatation and Curettage.

D&C												
Study	N	Study type	Sens	Spec	PPV	NPV	Accuracy	Calculated FN rate	Failure rate	Inadequacy rate	Gold standard	Inclusion criteria
Laban and colleagues, ³⁷ 2021	125	Retrospective	61.9%	95.5%	99%	26.3%	64.9%	66.1%	NA	NA	Hysterectomy	Patients with EC
Sanam and Majid, ²⁹ 2015	130	Clinical trial	NA	NA	NA	NA	NA	NA	NA	10%	D&C	AUB >35 y, ET >5 mm in post-menop and >12 mm in pre-menop
Demirkiran and colleagues, ⁴³ 2012 (88)	673	Prospective	NA	NA	NA	NA	70%	NA	NA	2%	Hysterectomy	ET >6 mm
Liberis and colleagues, ⁵⁷ 2021	203	Retrospective	95% (G1), 75% (G2), 76% (G3)	86.8% (G1), 93.5% (G2), 98% (G3)	94.3% (G1), 75% (G2), 81.3% (G3)	88.5% (G1), 93.5% (G2), 97.5% (G3)	92.6% (G1), 89.7% (G2), 96% (G3)	NA	NA	NA	Hysterectomy	Patients with EC
Kanis and colleagues, ⁵⁸ 2016	818	Retrospective	85%	33%	NA	NA	NA	NA	NA	NA	Hysterectomy	Patients with EC
Moradan and colleagues, ⁵⁵ 2017	163	Retrospective	83.3%	NA	NA	100%	NA	NA	NA	NA	Hysterectomy	AUB
Abdelazim and colleagues, ²⁷ 2013	140	Retrospective	NA	NA	NA	NA	NA	NA	NA	0%	D&C	AUB >40 y + >4 mm ET
Abdelazim and colleagues, ⁵⁹ 2015	220	Retrospective	NA	NA	NA	NA	NA	NA	NA	0%	D&C	AUB
Gungorduk and colleagues, ²⁸ 2015	245	Retrospective	NA	NA	NA	NA	NA	NA	NA	7.7%	D&C	Patients undergoing hysterectomy
Complications of D&C												
Study	N	Study type	Hemorrhage		Infection	Acute inflammation	Uterine perforation	Unanticipated major operation				
Deckardt and colleagues, ¹⁷ 2002	1286	Comparative study	NA		NA	NA	1.4%	NA				
Grimes, ¹⁸ 1982	13,598	Comparative study	0.4%		0.3%-0.5%	NA	0.6%-1.3%	0.03%-0.5%				
Mackenzie and Bibby, ¹⁹ 1978	1029	Clinical study	0.4%		NA	0.3%	0.9%	0.1%				
Abbreviations: AUB, abnormal uterine bleeding; D&C, dilation and curettage; EC, endometrial cancer; ET, endometrial thickness; FN, false-negative; G1-3, Grade 1 to grade 3. NA, not available; NPV, negative predictive value; post-menop, post-menopausal; PPV, positive predictive value; pre-menop, pre-menopausal; Sens, sensitivity; Spec, specificity.												

Table 6 Summary of New Tools for the Diagnosis of Endometrial Cancer.

New tools	Urine	Cervico-vaginal	Uterine
Cytology	O'Flynn and colleagues, ⁶⁶ 2021; <i>N</i> = 216 Combination of urine and cervico-vaginal samples, S: 91.7%, SP: 88.8% Urine, S: 72%, SP: 94.9% Cervico-vaginal, S: 90.2%, SP: 88.7% DETECT study (Jones and colleagues, ⁶⁷ 2021) Prospective study assessing the role of urine, vaginal, and cervical cytology in the diagnosis of EC		
Genomics	Wever and colleagues, ⁶⁹ 2023; <i>N</i> = 320 Panel of 3 DNA methylation markers Urine: <i>CDH13</i> + <i>GHSR</i> + <i>SST</i> . AUC 0.95; S and SP 90% Cervico-vaginal: Self-samples: <i>CDO1</i> + <i>GHSR</i> + <i>ZIC1</i> . AUC 0.94; S 89%, SP 92% Clinician-taken: <i>CDO1</i> + <i>GHSR</i> + <i>ZIC1</i> . AUC 0.97. S 93%, SP 90%	PapSEEK; Wang and colleagues, ⁷² 2018; panel of 18 genes; <i>N</i> = 382 Cervico-vaginal: S: 81%, SP: 98.6% including 78% early-stage Uterine: S: 93%, SP: 100% Bakkum-Gamez and colleagues, ⁸⁵ 2023: 28 methylated-DNA markers; <i>N</i> = 100 S: 82%, SP: 96%, AUC 0.91 Barrett and colleagues, ⁷¹ 2022; CpG island methylation patterns; <i>N</i> = 786 AUC 0.81 Barrett and colleagues, ⁸⁶ 2023; WID-EC test; DNA methylation-based test (500 CpG sites) <i>N</i> = 1086; S: 86%, SP: 90%, AUC 0.92 Herzog and colleagues, ⁷³ 2022; WID-qEC test; <i>N</i> = 726 DNA methylation in gene regions of GYPC and ZSCAN12 Cervical smear: S: 97.2%, SP: 75.8% Self-collected: S: 90.1%, SP: 86.7% Vaginal swab: S: 100%, SP 89.1%	GynEC-Dx (Pérez-Sánchez 2013 ⁷⁷ ; <i>N</i> = 514 5-gene qRT-PCR assay combined with histology S 91%, SP 97%, NPV 99%
Proteomics	Njoku and colleagues, ⁶⁸ 2022; <i>N</i> = 153 CA125 and ET by TVUS AUC: 0.96	He and colleagues, ⁷⁵ 2011; CA125 levels; <i>N</i> = 242 Higher levels of CA125 in cervical sample in patients with EC compared with controls Calis and colleagues, ⁷⁴ 2016; CA125 levels S: 78%, SP: 57% Njoku and colleagues, ⁷⁶ 2024; 5-biomarker panel (HPT, LG3BP, FGA, LY6D, IGHM) <i>N</i> = 118; AUC: 0.95, S: 91%, SP: 86% In stage I EC, AUC: 0.92 Stockley and colleagues, ⁷⁰ 2020; <i>N</i> = 125; MCM5 protein Urine: AUC: 0.83, S: 87.3%, SP: 75.9% Cervico-vaginal: no differences	Martinez-Garcia and colleagues, ⁷⁸ 2017; 2-protein panel (MMP9, KPYM); <i>N</i> = 116 S: 94%, SP: 87%

Abbreviations: AUC, area under the curve; EC, endometrial cancer; qRT-PCR, quantitative reverse transcription polymerase chain reaction; S, sensitivity; SP, specificity.

cervical smear DNA, reporting a sensitivity of 81% and a specificity of 98.6%, including 78% of early-stage cases. The WID-qEC test, which evaluates DNA methylation in symptomatic women, identified 90.9% of endometrial cancer cases and outperformed ultrasound in early detection. The test also demonstrated consistent performance regardless of the collection device, sample collector (clinician or patient), or the sampling site.^{73,87}

Five studies^{70,88–93} evaluated the ability of the microbiome in cervical smears in detecting endometrial cancer, and all observed significant differences in the microbiome between patients diagnosed with endometrial cancer and healthy controls. Barczyński and colleagues⁸⁸ observed a predominance of *Mobiluncus curtisii* and *Dialister pneumosintes* among patients diagnosed with endometrial cancer compared with healthy controls. Similarly, the presence of *Atopobium vaginae* combined with *Porphyromonas* species and high pH was suggestive of endometrial cancer in the case–control study by Walther-Antônio and colleagues.⁹²

Regarding proteomics, 5 studies^{70,74–76,93} have analyzed its utility in the diagnosis of endometrial cancer from cervical fluid. He and colleagues⁷⁵ and Calis and colleagues⁷⁴ have demonstrated higher levels of CA125 in cervico-vaginal fluid in patients with endometrial cancer. Interestingly, a recent study found an AUC of 0.95, with sensitivity and specificity of 91% and 86%, respectively, for detecting endometrial cancer in women with post-menopausal bleeding using a 5-biomarker panel derived from cervico-vaginal fluid–derived proteins.⁷⁶ Further studies are still required to determine how proteomics could contribute to the early detection of endometrial cancer.

Uterine Fluid

Uterine fluid, which is in direct contact with endometrial tumors, is an appealing source of biomarkers and can be easily obtained through aspiration. Two genomic tests, PapSEEK and GynEC-Dx[®], have shown promising results in detecting endometrial cancer. PapSEEK, a polymerase chain reaction (PCR) test, identified genetic alterations in 93% of endometrial cancer cases, including 90% of early-stage patients, with close to a 0% false-positive rate.⁷² GynEC-Dx[®], which uses a 5-gene quantitative reverse transcription PCR assay, showed a sensitivity of 91%, specificity of 97%, and negative predictive value of 99% when combined with histologic analysis in a multi-center study including women with abnormal uterine bleeding.⁷⁷

Proteomic testing in uterine fluid has been assessed in several studies. A case–control study involving 38 women,⁷⁸ later validated in an independent cohort of 116 women using mass spectrometry, identified a 2-protein panel with 94% sensitivity and 87% specificity for endometrial cancer detection.⁷⁸ The findings of these studies, among further developments in our laboratory, were crucial for the development of an in vitro diagnostic immunoassay, initially named WomEC, designed to aid in diagnosing endometrial cancer in women with post-menopausal bleeding referred to endometrial biopsy. This test aims for a 97% negative predictive value and is intended as a tool to rule out endometrial cancer. This in vitro diagnostic immunoassay analyzes a protein biomarker panel in the fluid fraction of Pipelle biopsies and provides a semi-quantitative result (Positive/Negative) based on a numeric threshold. In addition, as this test detects soluble proteins in uterine fluid rather than relying on the cellular material, the inadequacy rate, which affects 30% of Pipelle biopsies because of insufficient

cellular material,¹⁴ is significantly reduced. Finally, protein measurement can be conducted using antibody-based immunoassay methods, such as ELISA (enzyme-linked immunosorbent assay), a low-cost and easily implementable technology for routine clinical laboratory testing. Currently, an investigational multi-center clinical study is being performed in Spain to explore the diagnostic performance of this new in vitro diagnostic immunoassay device (Clinical Trials: NCT06192017).

Closing Summary

Current techniques for diagnosing endometrial cancer have important limitations such as high false-negative rates, inability to provide a diagnosis in up to 30% of cases, and need for invasive procedures that are often associated with pain and delay in the diagnosis.

This highlights the need for the development of new tools that are minimally invasive, cost-effective, easy to perform, and capable of providing a 1-step diagnosis with high accuracy and sensitivity and low false-negative rates. Emerging strategies, such as genomics and proteomics through vaginal, urinary, or endometrial samples, are currently under development with the goal of improving sensitivity, efficacy, and patient comfort for patients affected by post-menopausal metrorrhagia.

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