Detecting endometrial cancer

Eleanor R Jones BSc MBChB, a Helena O’Flynn MBChB MPH MRCP, b Kelechi Njoku MBBS MSc MRCP(UK), c Emma J Crosbie BSc MBChB PhD FRCOG* d,e

aClinical Research Fellow in Gynaecological Oncology, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary’s Hospital, Manchester M13 9WL, UK
bNIHR Doctoral Research Fellow and Academic Clinical Lecturer in Primary Care, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary’s Hospital, Manchester M13 9WL, UK
cCancer Research UK Manchester Cancer Research Centre Clinical Research Fellow, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary’s Hospital, Manchester M13 9WL, UK
dProfessor of Gynaecological Oncology, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary’s Hospital, Manchester M13 9WL, UK
eDivision of Gynaecology, St Mary’s Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

*Correspondence: Emma Crosbie. Email: emma.crosbie@manchester.ac.uk

Key content

Endometrial cancer (EC) is the most common gynaecological cancer in the UK.

Ninety percent of women with EC present with postmenopausal bleeding (PMB), but less than 10% of women with PMB have a sinister underlying cause.

National Institute for Health and Care Excellence guidance advises that symptomatic postmenopausal women undergo urgent investigation; however, guidance is unclear for premenopausal women.

Current investigations for PMB, including transvaginal ultrasound scan, endometrial biopsy and/or outpatient hysteroscopy, have advantages and disadvantages.

Novel detection tools are in development, which combine minimally invasive sampling with genomic, proteomic and single cell technologies.

Learning objectives

To understand who is at risk of EC and who should be referred for urgent investigations.

To understand the evidence underpinning the current diagnostic pathway for EC.

To highlight unique and promising perspectives for EC detection and their potential to transform clinical care.

Ethical issues

Current diagnostics for EC are invasive and often painful. There is an urgent need for high-quality randomised controlled trials to inform effective pain relief options.

Premenopausal women with suspected EC do not fit criteria for urgent investigations. How can we identify those at highest risk to ensure they are fast-tracked appropriately?

Novel diagnostic tools hold promise, but they must be robustly validated before being introduced into clinical practice.

Keywords: diagnosis / diagnostic pathway / endometrial cancer / novel diagnostic tests / risk factors

Introduction

Endometrial cancer (EC) is the fourth most common cancer in women in the UK and the most common gynaecological malignancy. In the UK, there are over 9000 new cases each year and the incidence has risen by 57% since the early 1990s. This is attributed to the ageing population, a growing prevalence of obesity and declining rates of hysterectomy for benign disease. Survival rates are dependent on stage at diagnosis, ranging from 95% for stage I cancers to 15% for stage IV, therefore early diagnosis is essential for good outcomes. Early diagnosis may also enable conservative treatment for women of reproductive age or for those for whom surgery carries considerable risks, such as the elderly or morbidly obese.

Risk factors for endometrial cancer

Age and obesity are the strongest risk factors for endometrioid EC, the most common histological subtype (Table 1). Both act through estrogen-triggered endometrial proliferation, which occurs in the absence of progesterone. The probability of acquiring mutations in proto-oncogenes and tumour suppressor genes is increased during
proliferation. Unimpeded by apoptosis, these mutations expand clonally and acquire additional mutations that drive carcinogenesis. Estrogen is produced by adipose tissue through the aromatisation of adrenal androgens. After menopause, a lack of endogenous progesterone leaves the endometrium unprotected from the effects of estrogen. 3 Thus, obesity confers a higher risk of endometrial cancer, 4 with every additional 5 kg/m^2 of body mass index (BMI) associated with a 50% (95% confidence interval [CI] 40–60%) increased risk. 5 Around 85% of EC is diagnosed in women older than 55 years of age. 6 In premenopausal women, anovulatory cycles in polycystic ovary syndrome (PCOS) and obesity are a major risk factor. 7 Lynch syndrome is an autosomal dominant inherited condition of defective DNA mismatch repair, which affects the MSH2, MLH1, MSH6 and PMS2 genes. 8 Women with Lynch syndrome have a 25–60% lifetime risk of EC and present at younger ages than women with sporadic EC. 9,10

Red flag symptoms for endometrial cancer

Postmenopausal bleeding (PMB), defined as vaginal bleeding occurring more than 12 months after the cessation of menstruation at menopause, is the most common red flag symptom for EC. 11 Over 90% of women with EC present with PMB, but over 90% of women with PMB have a benign underlying cause for their symptoms (Box 1). 12,13 PMB can be confused with haematuria, triggering urgent urological investigations. 14 Vaginal discharge or pyometria is less commonly described. Premenopause, women complain of intermenstrual or persistent heavy menstrual bleeding. Late-stage disease presents with abdominal distension, pelvic pressure symptoms or pain. 15 Cytology-based cervical screening detects atypical glandular cells in up to half of women subsequently diagnosed with EC, 16 who might also be identified incidentally on ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) performed for other reasons.

Referral from primary care

The 2015 National Institute for Health and Care Excellence (NICE) suspected cancer guidance (Box 2) recommends that women with PMB or heavy, irregular bleeding who are over 45 years of age should have a full history, pelvic and speculum examinations and urinalysis performed in primary care. 17 Examination is important to exclude a pelvic mass or pathology of the lower genital tract. The probability of EC in women with PMB rises from less than 1% in women under the age of 50 to 24% in women over 80 years old. 18 Women on hormone replacement therapy (HRT) require special consideration. Those with persistent unscheduled bleeding for more than 6 months after starting HRT should be referred for investigation. 17 Those with new onset PMB should only be referred if bleeding continues 6 weeks after stopping HRT.

EC should be considered in premenopausal women with abnormal bleeding, particularly those with obesity,

| Table 1. Risk and protective factors for endometrial cancer |
|----------------------------------|
| **Risk factors** | **Protective factors** |
| **Increasing age** | Obesity/insulin resistance |
| Obesity/insulin resistance | Healthy diet |
| Obesity | Bariatric surgery-induced weight loss |
| Weight gain in adulthood | High levels of physical activity |
| Increased waist-to-hip ratio | Reproductive |
| Taller than average height | Parity (versus nulliparity) |
| Diabetes mellitus | Later age at last birth |
| (Type 1 and Type 2) | Late menarche |
| Hyper tension | Oral contraceptive use |
| Hypertension | (ever versus never) |
| Reproductive | Progestin therapy |
| Polycystic ovary syndrome | Continuous combined hormone replacement therapy |
| Early menarche | Use of intrauterine devices |
| Late menopause | (any type) |
| Nulliparity | Breastfeeding |
| Unopposed estrogen hormone replacement therapy | Lifestyle/other |
| Genetic | Smoking (ever versus never) |
| Lynch syndrome | Consumption of coffee |
| Cowden syndrome | Increased animal fat intake |
| Family history of endometrial or colorectal cancer | Iatrogenic |
| Lifestyle | Metformin use (ever versus never) |
| Physical inactivity | Bisphosphonate use |
| Dietary factors, e.g. Western diet intake | Iatrogenic |
| Iatrogenic | Tamoxifen therapy |

| Box 1. Causes of postmenopausal bleeding |
|----------------------------------------|
| **Malignant:** |
| Endometrial cancer |
| Cervical cancer |
| Vulval cancer |
| Vaginal cancer |
| Ovarian or fallopian tube cancer |
| Choriocarcinoma |
| Cancer in adjacent organs (e.g. urethra, bladder, bowel) |
| **Pre-malignant:** |
| Endometrial hyperplasia |
| Benign: |
| Endometrial polyps |
| Atrophy of the vaginal mucosa or endometrium |
| Endometritis |
| **Iatrogenic:** |
| Unscheduled bleeding in women using hormone replacement therapy |
| Anticoagulant therapy |
| Post radiation therapy |
| **No cause identified** |
PCOS, a strong family history or other risk factors. A systematic review of premenopausal women with abnormal uterine bleeding found the risk of EC – or its precursor lesion, atypical hyperplasia – was just 1.31%, with intermenstrual bleeding being a better predictor than heavy menstrual bleeding. The risk for premenopausal women increases with BMI and is reportedly five times higher at a BMI of ≥ 30 kg/m². A retrospective review of two-week wait referrals from primary care in England between 2006 and 2010 found that women aged 35–44 years eventually diagnosed with EC were significantly less likely to be referred urgently than women aged 65–74 years (odds ratio 0.09, 95% CI 0.07–0.12, p < 0.001). The lack of clear guidance from NICE on which premenopausal women require urgent review risks diagnostic delay for those at highest risk.

**Diagnostic pathway for endometrial cancer**

The most effective diagnostic strategy for the investigation of PMB remains controversial; there is no evidence-based up-to-date guidance from NICE, the Scottish Intercollegiate Guidelines Network (SIGN), or the Royal College of Obstetricians and Gynaecologists (RCOG). Selective transvaginal sonography (TVS) for ‘high-risk’ women based on age, BMI and other risk factors is the most cost-effective strategy, but risks missing cases. The British Gynaecological Cancer Society (BGCS) recommend TVS as first-line investigation for PMB, followed by endometrial biopsy, with or without hysteroscopy, if the endometrium is thickened (Figure 1).

**One-stop postmenopausal bleeding clinics**

One-stop clinics, in which patients are scanned, reviewed by a clinician and offered endometrial biopsy and/or hysteroscopy in a single visit, reduce delays, improve patient experience and are cost-effective.

---

**Box 2. National Institute for Health and Care Excellence (NICE) Suspected cancer: recognition and referral guidance (NG12) for endometrial cancer**

Two-week wait referral for women aged ≥55 with postmenopausal bleeding (PMB)

Consider a two-week wait referral for women aged <55 with PMB

Consider direct access transvaginal sonography in women aged ≥55 with:

- Unexplained vaginal discharge who:
  - present for the first time or
  - have thrombocytosis or
  - report haematuria, or
- Visible haematuria and:
  - low haemoglobin levels or
  - thrombocytosis or
  - high blood glucose levels

Two-week wait referral for women aged ≥55 with postmenopausal bleeding (PMB)

Consider direct access transvaginal sonography in women aged ≥55 with:

- Unexplained vaginal discharge who:
  - present for the first time or
  - have thrombocytosis or
  - report haematuria, or
- Visible haematuria and:
  - low haemoglobin levels or
  - thrombocytosis or
  - high blood glucose levels

---

Transvaginal sonography for investigation of postmenopausal bleeding

TVS provides a non-invasive assessment of double-layered endometrial thickness, which can be used to triage women for further investigations. A recent systematic review of women with PMB found that women with EC have a mean endometrial thickness of 16.4 mm (95% CI 14.8–18.1 mm), compared with 4.1 mm (95% CI 3.5–4.7 mm) for those investigated but found not to have EC. Interestingly, mean endometrial thickness has increased significantly over time. The mean endometrial thickness of women with PMB found not to have EC was 3.5 mm in studies published before 2000, but 5.7 mm in later studies; this can possibly be attributed to improved resolution of imaging, increased HRT use, or higher obesity rates. This influences the clinical utility of TVS for EC detection, since endometrial thickness cut-offs derived from historical studies might not be transferable to modern day populations.

The diagnostic accuracy of TVS for EC detection depends on the endometrial thickness cut-off used. BGCS guidelines currently recommend an endometrial thickness cut-off of ≥ 4 mm. This is based on a systematic review published in 2010, which included 13 studies of 2896 patients with PMB, of whom 259 were diagnosed with EC. A cut-off of ≥ 4 mm had a sensitivity of 94.8% (95% CI 86.1–98.2%) and a specificity of 46.7% (95% CI 38.3–55.2%) for EC detection. A more recent systematic review, based on 44 studies from 25 countries, including 17 339 women with PMB, of whom 1341 were diagnosed with EC, found that an endometrial thickness of ≥5 mm had 96.2% (95% CI 92.3–98.1%) sensitivity and 51.1% (95% CI 42.3–60.7%) specificity for EC detection (Table 2). Based on this systematic review, increasing the cut-off from ≥ 4 mm to ≥ 5 mm in future UK guidance would offer comparable sensitivity and negative predictive value (NPV) to a cut-off of ≥ 4 mm, but improved specificity, reducing the need for invasive diagnostic procedures by up to 17%.

The character of the endometrium can further define risk of malignancy by TVS. A heterogenous endometrium with cystic change is highly suspicious of underlying disease (Figure 2A). A caveat is the benign subepithelial stromal hypertrophy associated with tamoxifen treatment, which causes a grossly abnormal endometrial signal and, consequently, a high false-positive rate. This is particularly challenging because tamoxifen is associated with a three-fold increased risk of EC and therefore triggers a high level of clinical suspicion. Grayscale and colour Doppler sonographic features can be useful to distinguish malignant from nonmalignant endometrial pathology (Figure 2B).

Endometrial thickness is of limited utility as a triage test in premenopausal women, in whom endometrial thickness...
fluctuates naturally during the menstrual cycle. It is also technically challenging to accurately measure endometrial thickness where the uterine cavity is distorted by fibroids and when body habitus compromises test validity (for example, in women with a high BMI).

**Incidental findings in asymptomatic women**

An incidental finding of a thickened endometrium in an asymptomatic postmenopausal woman is a thorny issue because there is no consensus as to what endometrial thickness cut-off requires further investigation. A prospective study of 81 asymptomatic women referred for endometrial sampling following an incidental finding of a thickened endometrium on TVS found EC or atypical endometrial hyperplasia (AEH) in just four women (4.9%), all of whom had an endometrial thickness ≥10 mm. A theoretical cohort study combining published and unpublished data from 10,000 postmenopausal women found an endometrial thickness cut-off of ≥11 mm differentiated between women whose risk of cancer was 6.7% and those whose risk was just 0.002%. In contrast, a systematic review of 32 studies and 11,100 women failed to identify a discriminatory endometrial thickness in asymptomatic postmenopausal women of sufficient clinical utility to rationalise further investigations.

The UK Collaborative Trial for Ovarian Cancer Screening (UKCTOCS) reported asymptomatic endometrial pathology in 125 of 36,861 postmenopausal women within 12 months of TVS and found a cut-off endometrial thickness of ≥5 mm had a sensitivity of 77.1% and specificity of 85.8% for the detection of EC or AEH. A caveat was the lack of a standardised protocol for endometrial investigations at the ≥5 mm cut-off; EC diagnoses were made up to 12 months later, possibly after women developed symptoms, when an up-to-date TVS may have returned a different endometrial thickness. With no clear guidance, an incidental finding of a thickened endometrium is investigated at the discretion of individual clinicians, taking patient preference and risk factors into account.

**Endometrial sampling**

An endometrial biopsy is indicated if a woman presenting with PMB has a thickened endometrium on TVS. While easy and quick to perform in an outpatient setting, endometrial biopsy is an invasive procedure with potential for harm, including failure (11%), inadequate sample (31%), pain,
bleeding, infection and – very rarely – perforation.32 Numerous aspirating, brush and cannulation devices are available that show similar diagnostic accuracy to traditional dilatation and curettage, but enable outpatient sampling.33,34 The Pipelle aspirator (Pipelle de Cornier Mk II, Eurosurgical Ltd., Guildford, UK) is the most commonly used sampling device, with a sensitivity of 90–100% for EC detection when an adequate sample is obtained.32,34–36 It was previously thought that the 30% of women with an inadequate sample could be safely reassured;35 however, given that 4.5% of women were diagnosed with EC after an initial inadequate sample in one study,37 this might not be appropriate and emphasises the importance of restricting endometrial sampling to women with a thickened endometrium in the first place. While most women tolerate endometrial sampling well, pain is a significant barrier for some.34 Failed endometrial sampling is usually associated with pain or cervical stenosis, which are more common in nulliparous women.38 As a blind procedure, endometrial sampling has the potential to miss small, localised cancers.39 Women with benign or inconclusive histology, but persistent symptoms or suspicious ultrasound findings, should be offered hysteroscopy.

**Hysteroscopy**

Hysteroscopy is direct visualisation of the uterine cavity via a fine bore scope to identify pathology, take directed biopsies and carry out therapeutic procedures, such as polypectomy. Hysteroscopy is indicated for women with a thickened, irregular endometrium, or other concerning features on ultrasound; those with recurrent or prolonged bleeding; or where random endometrial sampling has been nondiagnostic.21 A randomised controlled trial comparing hysteroscopic resection of endometrial polyps with expectant management of PMB found endometrial (pre)malignancy in 6% of women that had been missed by random endometrial sampling.40 This highlights the importance of hysteroscopic assessment in cases where focal pathology is suspected on TVS. A systematic review of 65 studies, including 26 346 women, reported that hysteroscopy has a sensitivity of 86.4% and specificity of 99.2% for EC detection.41 This is the most recent systematic review at the time of writing, although modern technology may offer improved accuracy. Hysteroscopy can be carried out as an outpatient procedure and, when offered as part of a one-stop clinic, this is the most cost-effective and efficient way of investigating unexplained PMB.42 The risks of hysteroscopy include failure (4.2%),

---

**Table 2. The diagnostic accuracy of investigations for endometrial cancer detection**

|                      | Sensitivity (%) | Specificity (%) | Failure of procedure       |
|----------------------|----------------|-----------------|----------------------------|
| Transvaginal sonography23 |                |                 | Very low/not reported      |
| ET ≥3 mm             | 96.2           | 42.1            |                            |
| ET ≥4 mm             | 95.7           | 46.0            |                            |
| ET ≥5 mm             | 96.2           | 51.5            |                            |
| ET ≥6 mm             | 85.2           | 64.0            |                            |
| ET ≥8 mm             | 88.0           | 66.2            |                            |
| ET ≥10 mm            | 78.2           | 83.7            |                            |
| ET ≥15 mm            | 58.9           | 94.2            |                            |
| Endometrial biopsy32  | 90–100         | 98–100          | Failed procedure, 11%      |
|                      |                |                 | Inadequate sample, 31%     |
|                      |                |                 | Total, 42%                 |
| Hysteroscopic opinion41| 86.4           | 99.2            | 3.4% for operative procedures |
|                      |                |                 | 4.2% for ambulatory procedures |

**ET = endometrial thickness.**

---

**Figure 2.** Transvaginal sonography images of endometrial cancer. (a) Transvaginal ultrasound image from a patient with endometrial cancer showing heterogenous endometrium with thickness of 26.5 mm (prior to application of colour Doppler). (b) Transvaginal ultrasound image from same patient showing increased vascularity of the endometrium when colour Doppler is applied. The presence of colour indicates blood flow and the colour represents the direction of the flow.
Detecting endometrial cancer

The aim of screening is to identify occult atypical hyperplasia or EC in asymptomatic women. Detecting cancer at its earliest possible stage is expected to improve cure rates, reduce the morbidity associated with aggressive treatment and offer uterus-sparing management options for younger women wishing to preserve their fertility. There is currently no established EC screening programme in the UK, neither for average-risk nor high-risk populations.

The ideal screening tool is a minimally invasive, inexpensive and easy-to-perform test that is effective at detecting pre-invasive and early invasive disease. In average-risk postmenopausal women, TVS has the advantage of being tried and tested, but the endometrial thickness cut-off chosen is a trade-off between sensitivity and specificity. Ensuring cases are not missed might expose large numbers of women to unnecessary invasive diagnostic tests.

Cervical cytology has not been explicitly tested as a screening tool for endometrial cancer. However, according to a systematic review of 45 studies and 6599 endometrial cancer cases, atypical glandular cells are found in cervical samples of 77% of women with type II, and 44% of those with type I endometrial cancers, respectively. Indeed, a disadvantage of the switch to primary human papillomavirus (HPV) cervical screening is that most samples do not now undergo cytological assessment, thus missing the opportunity to incidentally diagnose EC.

In Japan, endometrial cytology features in an established screening programme for high-risk women. Such high-risk women are defined as those attending routine cervical screening who are nulligravid or postmenopausal and report abnormal bleeding in the past 6 months. Endometrial cytology requires uterine instrumentation and is therefore less acceptable as a screening tool; however, it is associated with much lower rates of inadequate/failed sampling than endometrial biopsy. Screen-detected endometrial cancers are also identified at an earlier stage and boast improved survival outcomes compared with women diagnosed following acute symptomatic presentation.

Screening high-risk groups for endometrial cancer

Current BGCS guidelines recommend that women with Lynch syndrome are offered annual TVS, hysteroscopy and endometrial biopsy after the age of 35 years; however, the evidence supporting this strategy is limited. Sceptics question the benefit of screening when most EC presents at an early stage and has an excellent overall 5-year survival rate. Other high-risk groups include women with class III obesity referred for weight loss management, in whom a high prevalence of occult endometrial abnormalities has been described and breast cancer survivors receiving tamoxifen treatment, although no screening strategy is currently recommended for either group. Risk-stratifying women from the general population based on obesity, insulin resistance, reproductive and genetic biomarkers might identify other high-risk groups that could benefit from screening.

Magnetic resonance imaging

MRI is usually reserved for the preoperative staging of EC. On rare occasions, it might be required for more detailed assessment of a thickened endometrium on TVS where hysteroscopy fails or is contraindicated.

Diagnostic models

Current approaches to the investigation of PMB do not take risk factors into account, yet certain groups of women have a much higher pre-test probability of EC than others. The integration of clinical parameters and ultrasound findings in a diagnostic model could support a more sophisticated risk-based assessment of symptomatic women, which is likely to be more cost-effective. High-risk women could be fast tracked through urgent invasive investigations, while low risk women are safely reassured. To date, six diagnostic models have been developed specifically for women presenting with PMB. Predictors used in these models are age, age of menopause, BMI, parity, recurrent PMB, hypertension, diabetes, HRT and warfarin use, endometrial thickness, detailed ultrasonographic findings and serum HE4 levels. These models are not currently used in clinical practice because none have been externally validated and their clinical efficacy has not yet been established. In their systematic review, Alblass et al. called for the validation of previously published models and their extension with new predictors and biomarkers to build a model for clinical use.

Screening for endometrial cancer

The aim of screening is to identify occult atypical hyperplasia or EC in asymptomatic women. Detecting cancer at its earliest possible stage is expected to improve cure rates, reduce the morbidity associated with aggressive treatment and offer uterus-sparing management options for younger women wishing to preserve their fertility.
Developing novel endometrial cancer detection tools

Current investigations for suspected EC are unpleasant, invasive and expensive. No single test is sufficient to both ‘rule in’ and ‘rule out’ disease in women presenting with red flag symptoms, or to identify occult endometrial (pre)cancer in asymptomatic women with risk factors. Technological innovation and an improved understanding of cancer biology have paved the way for novel ways of detecting endometrial cancer early. The goal is to combine patient-friendly tools for biofluid collection with EC biomarker discovery to develop minimally invasive sampling methodologies for screening and diagnosis (Table 3, Figure 3).63

Uterine samples, including endometrial brushings and uterine lavage fluid, are an excellent source of cancer-specific biomarkers, but their collection is invasive and poorly tolerated by some.64,65 The anatomical continuity between the upper and lower genital tracts provides the opportunity

---

### Table 3. Novel endometrial cancer detection tools under development

| Sampling method   | Biomarker                                                                 | Advantages                                                                 | Disadvantages                                                                 |
|-------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Uterine lavage    | Genomic – mutations, methylated DNA64,72                                   | Proximal to tumour, therefore rich in cancer-relevant biomarkers           | Invasive Risk of failed uterine instrumentation Cannot be done in primary care |
|                   | Proteomic – (MMP9 and KPyM)65                                              |                                                                           |                                                                            |
| Uterine brushings | Cytology58                                                                  | Established screening programme in Japan                                    | Invasive Risk of failed uterine instrumentation Cannot be done in primary care |
|                   | Genomic – mutations,66 methylated DNA67                                    | Fewer inadequate samples than etnometrial biopsy Genomic biomarkers have high sensitivities |                                                                            |
| Cervical brush    | Cytology16                                                                  | Non-invasive                                                                | Current thresholds insufficiently sensitive for early (pre)cancer detection |
|                   | Genomic – mutations and copy number alterations (PapSEEK)66                |                                                                           |                                                                            |
| Vaginal tampon    | Genomic – methylated DNA67                                                  | Non-invasive Suitable for self-collection at home                          | Uncomfortable for elderly women                                            |
| Vaginal swab      | Metabolomic23                                                               | Non-invasive Suitable for self-collection at home                          | Proof-of-principle pilot data only                                          |
|                   | Genomic – methylated DNA74 Proteins – CA12525                              |                                                                           |                                                                            |
| Urine             | Genomic – microRNA76 Metabolomic77 Spectroscopic78                         | Non-invasive Suitable for self-collection at home                          | Proof-of-principle pilot data only                                          |
| Blood             | Genomic – circulating tumour cells, ctDNA79 Proteins – CA125, HE480        | Routinely available                                                        | Low concentrations of cancer-specific biomarkers in early cancer             |
|                   | Metabolomic60                                                              |                                                                           |                                                                            |
|                   | Spectroscopic52                                                            |                                                                           |                                                                            |

---

![Figure 3. Sampling methods for novel detection tools. (1) Endometrial lavage and brushings. (2) Cervical brush sample. (3) Vaginal tampon. (4) Vaginal swab. (5) Urine sample. (6) Blood sample.](image-url)
for naturally shed tumour debris to pass through the cervix, enabling collection from the vagina using tampons, brushes and swabs.66,67 These collection tools lend themselves to self-sampling, enabling women to collect their own biofluids at home for postal return to the laboratory. While tampons can be left in the vagina for several hours to collect a representative sample, they are uncomfortable for postmenopausal women to use.68

Urine is the perfect biofluid for non-invasive sampling because it is easy to collect, with the potential for large volumes, repeat samples or collection at pre-specified times of the day. It depends on urinary excretion of systemic cancer biomarkers, or the reliable contamination of urinary flow with uterine-shed tumour debris. Initial studies have yielded promising results.69 Blood biomarkers are also undergoing development. Cancer antigen 125 (CA125) is elevated in advanced stage, poor prognosis EC, but its relatively normal levels in early stage disease precludes its utility as an early detection tool. A panel of protein biomarkers may have more value than a single protein biomarker; indeed, studies combining CA125 with HE4 and other proteins have demonstrated encouraging proof of concept.70 Circulating tumour cells (CTCs), circulating tumour DNA (ctDNA) and microRNA (miRNA) are genomic biomarkers that could facilitate diagnosis, treatment monitoring and the detection of relapse, but their low concentration in early stage cancer limits their applicability at current detection limits.71

Conclusion

Despite its reputation for good prognosis, the rapidly rising incidence and devastating outcomes from advanced disease mean that 40% more women are now dying from EC than they did at the turn of the 21st century.1 Early diagnosis is key to improving outcomes and there is much interest in the development of minimally invasive detection tools for the rapid triage of symptomatic women. Used in combination with validated diagnostic models, these tools could enable fast-tracked invasive diagnostics for those at greatest risk, while avoiding the physical and psychological harms of investigating healthy women. Such a tool may also be useful for screening asymptomatic women who are deemed to be high risk by virtue of age, obesity or hereditary predisposition, where currently no standardised programme exists.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

ERJ and EJC designed and wrote the article. HO’F and KN provided expert material and review. All authors provided critical comment, edited the manuscript, and approved its final version. EJC is this article’s guarantor.

Funding

ERJ is supported by a grant from the JP Moulton Charitable Foundation. KN is supported by a Cancer Research UK Manchester Cancer Research Centre Clinical Research Fellowship (C147/A25254). HO’F is supported by a National Institute of Health Research (NIHR) Doctoral Research Fellowship (DRF-2018-11-ST2-054). EJC is supported by the NIHR Manchester Biomedical Research Centre (IS-BRC-1215-20007).

References

1 Cancer Research UK. Uterine cancer statistics [https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Zero].
2 Mackintosh ML, Crosbie EJ. Obesity-driven endometrial cancer: is weight loss the answer? BJOG 2013;120:791–4.
3 Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11:1531–43.
4 Kitson S, Crosbie E. Endometrial cancer and obesity. The Obstetrician & Gynaecologist 2019;21:237–45.
5 Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, et al. Risk factors for endometrial cancer: an umbrella review of the literature. Int J Cancer 2018;45:1719–30.
6 Zhou Y, Mendonca SC, Abel GA, Hamilton W, Walter FM, Johnson S, et al. Variation in ‘fast-track’ referrals for suspected cancer by patient characteristic and cancer diagnosis: evidence from 670 000 patients with cancers of 35 different sites. Br J Cancer 2018;118:24–31.
7 Wise MR, Jordan V, Lagas A, Showell M, Wong N, Lensen S, et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: a systematic review. Am J Obstet Gynecol 2016;214:689.e1–17.
8 Ryan NAJ, McFahon RFT, Ramchander NC, Seif MW, Evans DG, Crosbie EJ. Lynch syndrome for the gynaecologist. The Obstetrician & Gynaecologist 2021;23:9–20.
9 Ryan NAJ, Morris J, Green K, Laloo F, Woodward ER, Hill J, et al. Association of mismatch repair mutation with age at cancer onset in Lynch syndrome: implications for stratified surveillance strategies. JAMA Oncol 2017;3:1702–6.
10 Dominguez-Valentin M, Sampson JR, Sepalla TT, Ten Brooke SW, Plazzer JP, Nakken S, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 2020;22:15–25.
11 Funston G, O’Flynn H, Ryan NAJ, Hamilton W, Crosbie EJ. Recognizing gynecological cancer in primary care: risk factors, red flags, and referrals. Adv Ther 2018;35:577–89.
12 Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkm-Gamez JN, Wentzensen N. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. JAMA Intern Med 2018;178:1210–22.
13 Clarke MA, Long BJ, Sherman ME, Lemens MA, Podratz KC, Hopkins MR, et al. A prospective clinical cohort study of women at increased risk for endometrial cancer. Gynecol Oncol 2020;156:169–77.
14 Walker S, Hyde C, Hamilton W. Risk of uterine cancer in symptomatic women in primary care: case-control study using electronic records. Br J Gen Pract 2013;63:643–8.
15 Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet 2016;387:1094–108.
16 Frias-Gomez J, Benavente Y, Ponce J, Brunet J, Ibañez R, Peremiquel-Trillas P, et al. Sensitivity of cervico-vaginal cytology in endometrial carcinoma: a systematic review and meta-analysis. Cancer Cytopathol 2020;128:792–802.
17 National Institute for Health and Care Excellence (NICE). Suspected cancer: recognition and referral. London: NICE; 2015 [https://www.nice.org.uk/guidance/ng12/resources/suspected-cancer-recognition-and-referral-pdf-1837268071621].

110 © 2021 The Authors. The Obstetrician & Gynaecologist published by John Wiley & Sons Ltd on behalf of Royal College of Obstetricians and Gynaecologists.
18 Gredmark T, Kvint S, Havel G, Mattsson LA. Histopathological findings in women with postmenopausal bleeding. BJOG 1995;102:133–6.
19 Parent ME, Mehta R, Moody P, Hackett G, Prentice A, Sharp SJ, et al. Premenopausal abnormal uterine bleeding and risk of endometrial cancer. BJOG 2017;124:404–11.
20 Cooper NA, Barton PM, Breijer M, Caffrey O, Opmeer BC, Timmermans A, et al. Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis. Health Technol Assess 2014;18:1–21, v–vi.
21 Sundar S, Balega J, Crosbie E, Drake A, Edmondson R, Fotopoulou C, et al. BGCS uterine cancer guidelines: recommendations for practice. Eur J Obstet Gynecol Reprod Biol 2017;213:71–97.
22 Friedemann Smith C, Tompson A, Holtman GA, Bankhead C, Gleeson F, Lasserson D, et al. General practitioner referrals to one-stop clinics for symptoms that could be indicative of cancer: a systematic review of use and clinical outcomes. Fam Pract 2019;36:255–61.
23 Long B, Clarke MA, Morillo ADM, Wentzensen N, Bakkum-Gamez JN. Ultrasound detection of endometrial cancer in women with postmenopausal bleeding: systematic review and meta-analysis. Gynecol Oncol 2020;157:624–33.
24 Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol 2010;116:160–7.
25 Epstein E, Fischerova D, Valentin L, Testa AC, Franchi D, Sladkevicius P, et al. Ultrasound characteristics of endometrial cancer as defined by International Endometrial Tumor Analysis (IETA) consensus nomenclature: prospective multicenter study. Ultrasound Obstet Gynecol 2018;51:818–28.
26 Gerber B, Krause A, Muller H, Reimer T, Kulz T, Makovitzky J, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J Clin Oncol 2000;18:3464–70.
27 Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
28 Ghobara A, Emovon E, Sundar S, Ewies A. Thickened endometrium in asymptomatic postmenopausal women – determining an optimum threshold for prediction of atypical hyperplasia and cancer. J Obstet Gynaecol 2018;38:1146–9.
29 Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound Obstet Gynecol 2004;24:558–65.
30 Breijer MC, Peeters JA, Opmeer BC, Clark TJ, Verheijen RH, Mol BW, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2012;40:621–9.
31 Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol 2011;12:38–48.
32 van Hanegem N, Breijer MC, Slockers SA, Zafarmand MH, Geomini P, van Hanegem M, et al. Tamoxifen for prevention of breast cancer: a prospective long-term study using transvaginal ultrasound. Ultrasound Obstet Gynecol 2004;24:558–65.
33 Mossa B, Ebano V, Marziani R. Reliability of outpatient endometrial brush cytology vs biopsy in postmenopausal symptomatic women. Eur J Gynaecol Oncol 2010;31:621–6.
34 Narice BF, Delaney B, Dickson JM. Endometrial sampling in low-risk patients with abnormal uterine bleeding: a systematic review and meta-synthesis. BMC Fam Pract 2018;19:135.
35 Clarritt TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG 2002;109:313–21.
36 Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer 2000;89:1765–72.
37 van Doom HC, Opmeer BC, Burger CW, Duk MJ, Kooi GS, Mol BWJ, et al. Inadequate office endometrial sampling requires further evaluation in women with postmenopausal bleeding and abnormal ultrasound results. Int J Gynaecol Obstet 2007;99:100–4.
38 Williams AR, Brechin S, Porter AJ, Warner P, Critchley HO. Factors affecting adequacy of Pipelle and Tao Brush endometrial sampling. BJOG 2008;115:1028–36.
39 Bagaria M, Shields E, Bakkum-Gamez JN. Novel approaches to early detection of endometrial cancer. Curr Opin Obstet Gynecol 2017;29:40–6.
40 van Hanegem N, Breijer MC, Slockers SA, Zafarmand MH, Geomini P, van Hanegem M, et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. BJOG 2017;124:231–40.
41 Clark TJ, Vort D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA 2002;288:1610–21.
42 Sulaiman S, Chong KW, Gaudoin M. One-stop postmenopausal bleeding clinics reduce patient waiting times and theatre costs. Scott Med J 2004;49:152–4.
43 Jansen FW, Vredevoogd CB, van Ulen K, Hermans J, Trimbos JB, Trimbos-Kemper TC. Complications of hysteroscopy: a prospective, multicenter study. Obstet Gynecol 2000;96:266–70.
44 Paulo AAS, Solheiro MHR, Paulo COS, Afreixo VM. What proportion of women refers moderate to severe pain during office hysteroscopy with a mini-hysteroscope? A systematic review and meta-analysis. Arch Gynecol Obstet 2016;293:37–46.
45 Royal College of Obstetricians and Gynaecologists (RCOG), British Society of Gynaecological Endoscopists. Best practice in outpatient hysteroscopy. Green-top guideline no. 59. London: RCOG; 2011.
46 Ahmad G, Saluja S, O’Hlynn H, Sorrentino A, Leach D, Watson A. Pain relief for outpatient hysteroscopy. Cochrane Database Syst Rev 2017;(10): CD007710.
47 Smith PP, Kolhe S, O’Connor S, Clark TJ. Vaginoscopy against standard treatment: a randomised controlled trial. BJOG 2019;126:891–9.
48 Cooper NA, Smith P, Khan KS, Clark TJ. Vaginoscopic approach to outpatient hysteroscopy: a systematic review of the effect on pain. BJOG 2010;117:532–9.
49 Bennett A, Lepage C, Thavorn K, Fergusson D, Murnaghan O, Coyle D, et al. Effectiveness of outpatient versus operating room hysteroscopy for the diagnosis and treatment of uterine conditions: a systematic review and meta-analysis. J Obstet Gynaecol Can 2019;41:930–41.
50 Madkour NM. An ultrasound risk-scoring model for prediction of endometrial cancer in post-menopausal women (using IETA terminology). Middle East Fertil Soc J 2017;22:201–5.
51 Giannella L, Mfuta K, Setti T, Cerami LB, Bergamini E, Boselli F. A risk-scoring model for the prediction of endometrial cancer among symptomatic postmenopausal women with endometrial thickness >= 4 mm. BioMed Res Int 2014;2014:130569.
52 Opolskiene G, Sladkevicius P, Valentin L. Prediction of endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness >= 4.5 mm. Ultrasound Obstet Gynecol 2011;37:232–40.
53 Burbos N, Musonda P, Giareni I, Shiner AM, Giamouzannis P, Morris EP, et al. Predicting the risk of endometrial cancer in postmenopausal women presenting with vaginal bleeding: the Norwich DEcFb rate risk assessment tool. Br J Cancer 2010;102:1201–6.
54 Burbos N, Musonda P, Duncan TJ, Crocker SG, Morris EP, Nieto JJ. Estimating the risk of endometrial cancer in symptomatic postmenopausal women: a novel clinical prediction model based on patients’ characteristics. Int J Gynecol Cancer 2011;21:500–6.
55 Wong AS, Cheung CW, Fung LW, Lau TT, Mol BW, Sahota DS. Development and validation of prediction models for endometrial cancer in postmenopausal women. Eur J Obstet Gynecol Reprod Biol 2018;223:220–4.
56 Alblas M, Veit KB, Pashayan N, Widschwendter M, Stereberg EW, Vergouw Y. Prediction models for endometrial cancer for the general population or symptomatic women: a systematic review. Crit Rev Oncol Hematol 2018;126:92–9.
57 Gentry-Maharaj A, Karpinskyj C. Current and future approaches to screening for endometrial cancer. Best Pract Res Clin Obstet Gynaecol 2020;65:79–97.
Detecting endometrial cancer

58 Fambri M, Sorbi F, Sisti G, Cioni R, Turrini I, Taddei G, et al. Endometrial carcinoma in high-risk populations: is it time to consider a screening policy? Cytopathology 2014;25:71–7.

59 Yang X, Ma K, Chen R, Zhao J, Wu C, Zhang N, et al. Liquid-based endometrial cytology associated with curettage in the investigation of endometrial carcinoma in a population of 1987 women. Arch Gynecol Obstet 2017;296:99–105.

60 Crosbie EJ, Ryan NAi, Arends MJ, Bosse T, Burn J, Cornes JM, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med 2019;21:2390–400.

61 Mackintosh ML, Derbyshire AE, McVey DJ, Bolton J, Nickkho-Amiry M, Higgins CI, et al. The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk. Int J Cancer 2019;144:641–50.

62 Kitson SJ, Evans DG, Crosbie EJ. Identifying high-risk women for endometrial cancer prevention strategies: proposal of an endometrial cancer risk prediction model. Cancer Prev Res 2017;10:1–13.

63 Badrick E, Cresswell K, Ellis P, Renehan AG, Crosbie EJ. Top ten research priorities for detecting cancer early. Lancet Public Health 2019;4:e551.

64 Nair N, Camacho-Vanegas G, Rykunov D, Dashkoff M, Camacho SC, Schumacher CA, et al. Genomic analysis of uterine lavage fluid detects early endometrial cancers and reveals a prevalent landscape of driver mutations in women without histopathologic evidence of cancer: a prospective cross-sectional study. PLoS Med 2016;13:e1002206.

65 Martinez-Garcia E, Lesur A, Devis L, Cabrera S, Matias-Guiu X, Hirschfeld M, et al. Targeted proteomics identifies proteomic signatures in liquid biopsies of the endometrium to diagnose endometrial cancer and assist in the prediction of the optimal surgical treatment. Clin Cancer Res 2017;23:6458–67.

66 Wang Y, Li L, Douville C, Cohen JD, Yen TT, Kinde I, et al. Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of cervical and endometrial cancers. Sci Transl Med 2018;10:eaap8793.

67 Bakkum-Gamez JN, Wentzensen N, Maurer MJ, Hawthorne KM, Voss JS, Kroneman TN, et al. Detection of endometrial cancer via molecular analysis of DNA collected with vaginal tampons. Gynecol Oncol 2015;137:14–22.

68 Woolderink JM, De Bock GH, van Hemel BM, Geuken E, Hollema H, Werner N, et al. Feasibility of endometrial sampling by vaginal tampons in women with Lynch syndrome. BMC Women Health 2020;20:54.

69 Njoku K, Chiasserini D, Jones ER, Barr C, O’Flynn H, Whetton AD, et al. Urinary biomarkers and their potential for non-invasive detection of endometrial cancer. Front Oncol 2020;10:559016.

70 Njoku K, Chiasserini D, Whetton AD, Crosbie EJ. Proteomic biomarkers for the detection of endometrial cancer. Cancers (Basel) 2019;11:1572.

71 Muinelo-Romay L, Casas-Arozamena C, Abal M. Liquid biopsy in endometrial cancer: new opportunities for personalized oncology. Int J Mol Sci 2018;19:2311.

72 Maritschnegg E, Wang Y, Pecha N, Horvat R, Van Nieuwenhuysen E, Vergote I, et al. Lavage of the uterine cavity for molecular detection of mullerian duct carcinomas: a proof-of-concept study. J Clin Oncol 2015;33:4293–300.

73 Cheng SC, Chen K, Chiu CY, Lu KY, Lu HY, Chiang MH, et al. Metabolomic biomarkers in cervicovaginal fluid for detecting endometrial cancer through nuclear magnetic resonance spectroscopy. Metabolomics 2019;15:146.

74 Doufekas K, Zheng SC, Ghazali S, Wong M, Mohamed Y, Jones A, et al. DNA methylation signatures in vaginal fluid samples for detection of cervical and endometrial cancer. Int J Gynecol Cancer 2016.

75 Calis P, Yuce K, Basaran D, Salman C. Assessment of cervicovaginal Cancer Antigen 125 Levels: a preliminary study for endometrial cancer screening. Gynecol Obstet Invest 2016;81:518–22.

76 Zavesky L, Jandakova E, Turyna R, Langmeierova L, Weinberger V, Zaveska Drabkova L, et al. Evaluation of cell-free urine microRNAs expression for the use in diagnosis of ovarian and endometrial cancers. A pilot study. Pathol Oncol Res 2015;21:1027–35.

77 Njoku K, Sutton C, Whetton AD, Crosbie EJ. Metabolomic Biomarkers for Detection, Prognosis and Identifying Recurrence in Endometrial Cancer. metabolites 2020;10:314.

78 Parasekavi M, Morais CLM, Lima KMG, Ashton KM, Stringfellow HF, Martin-Hirsch PL, et al. Potential of mid-infrared spectroscopy as a non-invasive diagnostic test in urine for endometrial or ovarian cancer. Analyst 2018;143:1156–63.

79 Kiss I, Kolostova K, Matkowski R, Jedryka M, Czekanski A, Pavlasek J, et al. Correlation between disease stage and the presence of viable circulating tumor cells in endometrial cancer. Anticancer Res 2018;38:2983–7.

80 Li LM, Zhu YK, Zhong Y, Su T, Fan XM, Xi Q, et al. Human epididymis protein 4 in endometrial cancer: a meta-analysis. Clin Chim Acta 2018;482:215–23.

81 Troisi R, Sarno L, Landolfi A, Scala G, Martinelli P, Venturrella R, et al. Metabolomic signature of endometrial cancer. J Proteome Res 2018;17:804–12.

82 Parasekavi M, Morais C, Ashton KM, Stringfellow HF, McVey RJ, Ryan NAi, et al. Detecting endometrial cancer by blood spectroscopy: a diagnostic cross-sectional study. Cancers (Basel) 2020;12:1256.