Performance of the WID-qEC test versus sonography to detect uterine cancers in women with abnormal uterine bleeding (EPI-SURE): a prospective, consecutive observational cohort study in the UK

Iona Evans, Daniel Reisel*, Allison Jones*, Alba Bajrami*, Simrit Nijjar, Sarah Annie Solangon, Rupali Arora, Elisa Redl, Lena Schreiberhuber, Isma Ishaq-Parveen, Julia Rothärmel, Chiara Herzog, Davor Jurkovic, Martin Widschwendter*

Summary

Background To detect uterine cancer, simpler and more specific index tests are needed to triage women with abnormal uterine bleeding to a reference histology test. We aimed to compare the performance of conventional index imaging tests with the novel WID-qEC DNA methylation test in terms of detecting the presence or absence of uterine cancers in women with abnormal uterine bleeding.

Methods EPI-SURE was a prospective, observational study that invited all women aged 45 years and older with abnormal uterine bleeding attending a tertiary gynaecological diagnostic referral centre at University College London Hospital (London, UK) to participate. Women meeting these inclusion criteria who consented to participate were included. Pregnant women and those with previous hysterectomy were excluded. A cervicovaginal sample for the WID-qEC test was obtained before standard assessment using index imaging tests (ie, ultrasound) and, where applicable, reference histology (ie, biopsy, hysteroscopy, or both) was performed. Technicians performing the WID-qEC test were masked to the final clinical outcome. The result of the WID-qEC test is defined as the sum of the percentage of fully methylated reference (ΣPMR) of the *ZSCAN12* and *GYPC* regions. Patients were followed until diagnostic resolution or until June 12, 2023. The primary outcome was to assess the real-world performance of the WID-qEC test in comparison with ultrasound with regard to the area under the receiver-operating-characteristic curve (AUC), sensitivity, specificity, and positive and negative predictive values. EPI-SURE is registered with ISRCTN (16815568).

Findings From June 1, 2022, to Nov 24, 2022, 474 women were deemed eligible to participate. 74 did not accept the invitation to participate, and one woman withdrew after providing consent. 399 women were included in the primary analysis cohort. Based on 603 index imaging tests, 186 (47%) women were recommended for a reference histology test (ie, biopsy, hysteroscopy, or both). 12 women were diagnosed with cancer, 375 were not diagnosed with cancer, and 12 had inconclusive clinical outcomes and were considered study dropouts. 198 reference histology test procedures detected nine cases of cancer and missed two; one further cancer was directly diagnosed at hysterectomy without a previous reference test. The AUC for detection of uterine cancer based on endometrial thickness in mm was 87·2% (95% CI 71·1–100·0) versus 94·3% (84·7–100·0) based on WID-qEC (p=0·48). Endometrial thickness assessment on ultrasound scan was possible in 379 (95%) of the 399 women and a prespecified cut-off of 4·5 mm or more showed a sensitivity of 90·9% (95% CI 62·3–98·4), a specificity of 79·1% (74·5–82·9), a positive predictive value of 11·8% (6·5–20·3), and a negative predictive value of 99·6% (98·0–99·9). The WID-qEC test was possible in 390 (98%) of the 399 patients with a sensitivity of 90·9% (95% CI 62·3–98·4), a specificity of 92·1% (88·9–94·4), a positive predictive value of 25·6% (14·6–41·1), and a negative predictive value of 99·7% (98·3–99·9), when the prespecified threshold of 0·03 ΣPMR or more was applied. When a higher threshold (≥0·3 ΣPMR) was applied the specificity increased to 97·3% (95% CI 95·1–98·5) without a change in sensitivity.

Interpretation The WID-qEC test delivers fast results and shows improved performance compared with a combination of imaging index tests. Triage of women with abnormal uterine bleeding using the WID-qEC test could reduce the number of women requiring histological assessments for identification of potential malignancy and specifically reduce the false positive rate.

Funding The Eve Appeal, Land Tirol, and the European Research Council under the European Union's Horizon 2020 Research and Innovation Programme

Lancet Oncol 2023

Published **Online** November 6, 2023 https://doi.org/10.1016/S1470-2045(23)00466-7

See **Online/Comment** https://doi.org/10.1016/S1470-2045(23)00522-3

*Contributed equally

Department of Women's Cancer (I Evans PhD, D Reisel PhD, A Jones BSc, Prof M Widschwendter MD), **Department of Reproductive Health** (A Bajrami MBBS, S Nijjar MBBS, S A Solangon MBBS, Prof D Jurkovic PhD), **EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London, London, UK; Department of Cellular Pathology, University College London Hospitals NHS Foundation Trust, London, UK** (R Arora MD); **European Translational Oncology Prevention and Screening Institute, University of Innsbruck, Tirol, Austria** (E Redl MSc, L Schreiberhuber MSc, I Ishaq-Parveen, J Rothärmel MSc, C Herzog PhD, Prof M Widschwendter); **Research Institute for Biomedical Aging Research, University of Innsbruck, Innsbruck, Austria** (E Redl, L Schreiberhuber, C Herzog, Prof M Widschwendter); **Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden** (Prof M Widschwendter); **Department of Gynaecology and Obstetrics, Tirol Kliniken, Tirol, Austria** (Prof M Widschwendter)

Correspondence to:
Prof Martin Widschwendter, Department of Women's Cancer, EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London, London WC1E 6AU, UK
martin.widschwendter@uibk.ac.at; m.widschwendter@ucl.ac.uk

Research in context

Evidence before this study

We searched PubMed from database inception up to and including June 12, 2023, for articles published in English on the assessment of abnormal uterine bleeding in a prospective cohort setting (either interventional or observational) comparing conventional diagnostic pathways with novel tools similar to testing for cancer-specific DNA aberrations in cervicovaginal samples. The following search terms were utilised ("abnormal uterine bleeding" OR "postmenopausal bleeding") AND ("sonography" OR "diagnostic pathway" OR "ultrasound") AND "cohort" AND "prospective" AND "DNA", and the resultant literature proved extensive in describing the performance of ultrasound in reducing the number of women who require further tests (ie, hysteroscopies or biopsies). Most studies evaluated retrospective data and only a few described the number of different procedures required to reach a final diagnosis, or the amount of procedures that did not obtain a final diagnosis. Additionally, a plethora of studies (mainly small case-control sets) describe molecular tests (both in plasma and cervicovaginal specimens) aimed to identify women with uterine cancers. No data provide a prospective comparison of conventional diagnostic pathways and novel molecular tests for triage of women with abnormal uterine bleeding for invasive diagnostic procedures.

Added value of this study

To our knowledge EPI-SURE is the first study embedded in a conventional diagnostic pathway that has assessed a novel and easy to apply molecular test in women presenting with abnormal uterine bleeding. A positive DNA methylation test result indicates a higher probability of a uterine cancer diagnosis than does the conventional assessment pathway. Applying the test would lead to a smaller number of women requiring urgent invasive diagnostic procedures to detect cancer, substantially reducing delays in diagnosis. A negative DNA methylation test result indicates a very low probability of cancer; in our study, the only false negative case was a very small 2 mm grade 1 cancer. The DNA methylation test result can help assess the likelihood that abnormal uterine bleeding is due to cancer, providing an objective means to decide which patients require urgent referral to a tertiary cancer referral centre.

Implications of all the available evidence

With reference to the current guidelines, the data from our observational prospective study demonstrate the labour, resources, and skill-intensive and time-consuming endeavours associated with the current assessment of women presenting with abnormal uterine bleeding, and highlights that even these procedures do not have the sensitivity required to detect all cases. Our new DNA methylation test is based on a simple cervicovaginal sample and delivers a quantitative result within 48 h. Those with negative results would be offered conservative and expectant management. Fewer healthy women would be triaged to have invasive hysteroscopy or biopsy procedures, which would reduce the pressures on rapid access gynaecology clinics and the overall costs of managing abnormal uterine bleeding.

Introduction

Endometrial cancer is the fourth most common cancer worldwide with 417 000 women diagnosed globally each year,[1,2] and its incidence continues to increase.[3] Previous evidence suggests that a delay in endometrial cancer diagnosis has a negative impact on survival.[4]

No screening exists for endometrial cancer and the most commonly observed symptom is abnormal uterine bleeding.[2] In the USA, approximately 1·4 million cases of abnormal uterine bleeding are reported each year, and 800 000 cases are reported in the UK,[5,6] making this symptom one of the most common reasons for urgent referrals to gynaecological rapid access clinics. However, only 1·2%[7] of premenopausal women (age 45 years and older) and 9%[8] of postmenopausal women presenting with abnormal uterine bleeding are eventually diagnosed with endometrial cancer.

Ultrasonography (performed transvaginally, transabdominally, or transrectally; or based on saline infusion sonography) is used to identify the women with abnormal uterine bleeding who have the highest cancer risk and therefore require a biopsy which is obtained via pipelle or, in the majority of cases, via hysteroscopy and curettage or biopsy.[1,2] Sonographically assessed endometrial thickness in postmenopausal women with a cut-off of at least 3 mm detects endometrial cancer with a sensitivity of 97·9% and a specificity of 35·4%, 4 mm or more detects it with a sensitivity of 94·8% and a specificity of 52·7%, and 5 mm or more detects it with a sensitivity of 90·8% and a specificity of 62·4%;[9–11] although substantially inferior sensitivity and specificity performance has been reported in Black women.[12] Due to the low specificity of ultrasonography, further invasive testing and diagnostic procedures might need to be performed in more than 50% of women with abnormal uterine bleeding. An urgent need exists for a test that detects all uterine cancers (ie, endometrial, endocervical, ectocervical, and uterine metastasis) in patients presenting with abnormal uterine bleeding that is easy to apply, delivers objective results quickly, and improves on sonography performance parameters. A test with a much lower false positive test rate among women presenting with abnormal uterine bleeding would greatly reduce the number of invasive diagnostic procedures required.

Previous evidence suggests that subjective pattern recognition, which uses endometrial morphological features and vascular patterns detected on Doppler ultrasound, can improve the specificity of ultrasound.[13–15]

However, most clinics do not have the dedicated equipment or highly trained staff required to apply subjective pattern recognition. Additionally, to our knowledge, no systematic, prospective, observational study to date has captured all parameters required to evaluate the efficacy of the complete diagnostic pathway to identify malignancy in women with abnormal uterine bleeding.

Overall, the index imaging pathway is highly dependent on a health-care system working at optimal capacity (ie, supported by good infrastructure and high staffing levels). When the robustness of a health-care system is challenged by staffing issues and financial constraints, as is the case in the UK, waiting times for diagnostic pathways are adversely affected.[16] This reinforces the urgent need for a test that is easy to apply, can be analysed within a short period of time, and thereby tangibly decreases the time to and complexity of diagnosis.

Molecular testing of circulating tumour DNA in plasma has limited sensitivity to detect uterine cancers in women with abnormal uterine bleeding (40·0% [95% CI 22·7–59·4]).[17] By contrast, assessment of DNA methylation in samples obtained from the cervicovaginal space by either a tampon[18,19] or a cervical swab[20–23] has shown great promise as a simple tool to identify women with uterine cancer. Recently, the WID-qEC test, which assesses methylation of two genes—*ZSCAN12* and *GYPC*—in cervicovaginal samples (collected by the patient or health-care professionals), was validated in several settings and has shown potential in improving the detection of uterine cancer.[24,25] Identifying those women with abnormal uterine bleeding who should be referred for specialist review has been classified as a top unmet need for uterine cancer research.[26] Hence, we aimed to compare the performance of the WID-qEC test with ultrasonographic risk assessment to identify women requiring urgent specialist review from an unselected population of all women aged 45 years and older who were referred, due to abnormal uterine bleeding, to a rapid access clinic operating within a tertiary gynaecological diagnostic unit over a 6-month period.

Methods

Study design and participants

EPI-SURE was a prospective, observational cohort study of patients who were referred to the Rapid Access Clinic in the Gynaecology Diagnostic and Outpatient Treatment Unit at University College London Hospital (London, UK). All women aged 45 years and older referred for abnormal uterine bleeding were invited to participate in the study. Women meeting these inclusion criteria who consented to participate were included. Pregnant women and those with previous hysterectomy were excluded. Written informed consent was obtained from all participants. At enrolment and before any procedures, a cervicovaginal smear was obtained, stored, and analysed in one batch after recruitment was completed. All women provided baseline data (age, menopausal status, weight, height, and ethnicity by self-reporting) and underwent the standard assessment using index imaging tests (ie, ultrasound imaging or in rare cases MRI) to determine which women required a reference histology test (ie, a biopsy alone or in combination with a hysteroscopy) to reach a final diagnosis. The study was part of the H2020 FORECEE Research Programme, and research ethics was approved by the Health Research Authority, UK (REC 14/LO/1633; IRAS 53431). The results reported herein follow the STROBE guidelines for cohort studies.[27]

Procedures

For sample collection, a standard Cusco speculum was used to access and visualise the cervix before any other interventions. A cervicovaginal sample was obtained by a gynaecologist (registrar or consultant) using a Cervex-Brush (Rovers Medical Devices, Oss, The Netherlands). If a woman was unable to tolerate or declined the use of a speculum, a cervicovaginal sample was obtained using a smaller applicator-style vaginal brush designed for self-sampling (Evalyn Brush, Rovers Medical Devices); all self-samples yielded sufficient DNA to perform the WID-qEC test. The Cervex-Brush or the Evalyn Brush were immersed and rinsed in a ThinPrep vial (Rovers Medical Devices) filled with 20 mL of PreservCyt Solution (Hologic, Marlborough, MA, USA) labelled with a unique Participant ID code.

This was a single centre study, and all experienced operators received training from the same senior gynaecologist to reduce bias. All women underwent a standard assessment by a gynaecologist trained in gynaecological ultrasound using high-level equipment (Voluson E8, GE Healthcare Ultrasound, Milwaukee, WI, USA), furnished with 4–9 MHz transvaginal (also utilised for transrectal and saline infusion sonography) and 3–8 MHz transabdominal probes. All women were evaluated by one or several ultrasound methods. In cases for which a clear sonographic view of the endometrium and uterine cavity was difficult to obtain transvaginally, additional transabdominal and transrectal scans were offered. If further visualisation was required, saline infusion sonography was performed. This procedure involves passing a 3·3 mm soft plastic paediatric nasogastric suction catheter through the cervix into the uterine cavity without grasping the cervix. A volume of 5–10 mL of sterile saline solution is instilled into the uterine cavity and a 3D volume is generated by the automatic sweep of the mechanical transducer. The volumes are stored digitally and analysed using multiplanar visualisation.

Sonographic risk assessment included measurement of endometrial thickness and judgement based on the previously described subjective pattern recognition[13] as to whether the bleeding was triggered by a malignancy of the endometrium or the endocervical canal, or both. Ultrasound assessments were systematically performed

as previously described.[13] Briefly, the cervix and uterine corpus were identified in the transverse plane. The uterine corpus was then assessed by examining a series of parallel scanning planes from the internal cervical os to the top of the uterine fundus. Endometrial thickness was measured in the longitudinal plane using the double-layer measurement technique.[28] If fluid was present in the endometrial cavity, it was subtracted from the measurement of the endometrial thickness. The cut-off used for clinical decision in this study was 4·5 mm or more, as previously described and applied.[13]

The diagnosis of endometrial polyp was made when a well-defined focal lesion with clear outline and separate from the surrounding endometrium was present within the uterine cavity. In accordance with the standard clinical practice, all polyps detected in symptomatic women were removed hysteroscopically, regardless of the accompanying endometrial thickness.[29]

Subjective pattern recognition classified all women with an abnormal endometrium into one of three groups on the basis of endometrial morphological features on grayscale ultrasound and vascular patterns on colour Doppler: (1) uniformly thickened benign endometrium: the endometrium appears uniform with no focal lesions, an intact midline echo and intact endometrial–myometrial junction and on Doppler ultrasound, it appears avascular or poorly vascularised; (2) benign endometrial polyp: there is a well-defined localised lesion with a regular outline within the endometrial cavity and the surrounding endometrium appears regular with an intact endometrial–myometrial junction and on Doppler ultrasound, there is a single dominant vessel with or without branching, or there is no detectable vascularity; or (3) uterine cancer: the endometrium appears heterogeneous or there is an irregular focal lesion and the endometrial–myometrial junction could be intact or is interrupted, which is suggestive of myometrial invasion; on Doppler ultrasound, there are multiple vessels with focal or multifocal origin. In patients in which the endometrium could not be adequately visualised, the subjective pattern recognition was deemed to be inconclusive.

In the outpatient clinic, endometrial sampling with pipelle biopsy was offered to all women with a suspicion of uterine cancer or with a uniformly thickened endometrium of at least 4·5 mm. Women with endometrial polyps were offered a hysteroscopic polypectomy. All specimens were histologically assessed. Whenever the decision (based on the assessment of the endometrium) was taken to perform a hysterectomy or a biopsy of an organ distant to the uterus, the resulting histological diagnosis was also considered when assigning the final diagnosis.

The WID-qEC test uses quantitative real-time PCR on bisulfite modified DNA to assess DNA methylation and has been performed as previously described[24] with certain modifications—only one *GYPC* marker region was assessed and run in a duplex reaction together with the reference gene *COL2A1*, and *ZSCAN12* was run as a single-plex. The assay was run in duplicate. *GYPC* and *ZSCAN12* percentage of fully methylated reference (PMR) values were calculated. As previously described,[24] the WID-qEC ∑PMR threshold of 0·03 was applied to signify a positive (≥0·03) or negative (<0·03) test.

All performed medical procedures (ie, index tests) and their results were collected from a hospital medical electronic health-care record system before any outcome data became available. Histological outcome data were recorded over a 6-month period after recruitment stopped and the database was locked on June 12, 2023. The DNA samples were shipped to the University of Innsbruck (Zams, Austria) for WID-qEC test analysis.

In the original protocol we specified that all diagnostic outcomes would be available within a 1–4-week period after first presentation. However, due to organisational issues in the health-care system, several of the relevant follow up procedures (eg, hysteroscopy or hysterectomy) were delayed, so we extended the follow up period to June 12, 2023.

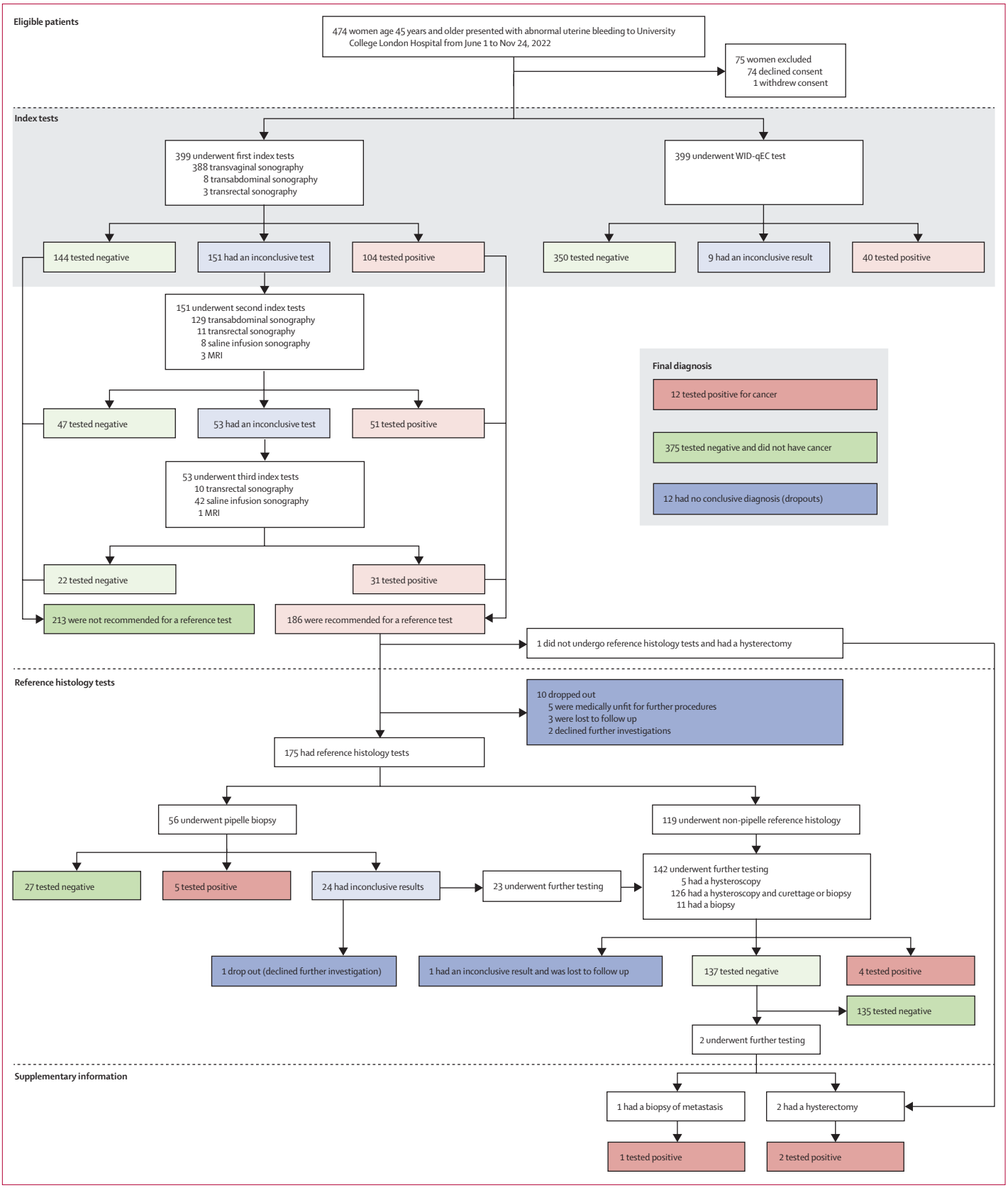
Outcomes

The primary outcome was the direct comparison of the performance of sonography (endometrial thickness) and the WID-qEC test using both prespecified cut-offs (ie, ≥4·5 mm endometrial thickness[13] and ≥0·03 WID-qEC ∑PMR[24]) and the area under the receiver-operating-characteristic curve (AUC) using the numerical values of both parameters to predict the final histological diagnosis (ie, primary or metastatic invasive uterine cancer *vs* no cancer). The secondary outcomes were the total number of index imaging and reference histology tests, the number of conclusive and inconclusive tests, and the performance of subjective pattern recognition. Primary and secondary outcomes were assessed in all participants with available data for the given test modality.

Statistical analysis

The study was powered to compare the positive predictive value between ultrasound and the WID-qEC test. A minimum sample size of 200 was determined to be able to detect a significant difference in ultrasound-estimated positive predictive value of 5·8% and WID-qEC-estimated positive predictive value of 22·2% at a power of 75% and alpha level of 5%, using a single sample binomial comparison. The initial study set-up included 300 individuals to improve power to higher than 80% and was expanded to 400 when lower than expected numbers of cancer cases were identified within the first 200 participants. Potential sources of bias were limited

Figure 1: **Study profile**


Eligible patients
474 women age 45 years and older presented with abnormal uterine bleeding to University College London Hospital from June 1 to Nov 24, 2022
75 women excluded
74 declined consent
1 withdrew consent
Index tests
399 underwent first index tests
388 transvaginal sonography
8 transabdominal sonography
3 transrectal sonography
399 underwent WID-qEC test
144 tested negative
151 had an inconclusive test
104 tested positive
350 tested negative
9 had an inconclusive result
40 tested positive
151 underwent second index tests
129 transabdominal sonography
11 transrectal sonography
8 saline infusion sonography
3 MRI
47 tested negative
53 had an inconclusive test
51 tested positive
53 underwent third index tests
10 transrectal sonography
42 saline infusion sonography
1 MRI
22 tested negative
31 tested positive
213 were not recommended for a reference test
186 were recommended for a reference test
Final diagnosis
12 tested positive for cancer
375 tested negative and did not have cancer
12 had no conclusive diagnosis (dropouts)
1 did not undergo reference histology tests and had a hysterectomy
Reference histology tests
10 dropped out
5 were medically unfit for further procedures
3 were lost to follow up
2 declined further investigations
175 had reference histology tests
56 underwent pipelle biopsy
119 underwent non-pipelle reference histology
27 tested negative
5 tested positive
24 had inconclusive results
23 underwent further testing
142 underwent further testing
5 had a hysteroscopy
126 had a hysteroscopy and curettage or biopsy
11 had a biopsy
1 drop out (declined further investigation)
1 had an inconclusive result and was lost to follow up
137 tested negative
4 tested positive
135 tested negative
2 underwent further testing
Supplementary information
1 had a biopsy of metastasis
2 had a hysterectomy
1 tested positive
2 tested positive

by design of a prospective observational cohort, inviting all women aged 45 years and older referred for diagnostic evaluation to the study. Results of medical procedures (index tests) were collected via electronic health-care record systems before outcome availability, and sample handling bias was mitigated by masking research technicians to clinical outcomes. We were unable to prospectively collect or analyse data from those who declined consent. During a prespecified exploratory analysis, data were checked for consistency by visualising endometrial thickness and ∑PMR values in cases and controls and availability of data by case or control status as well as menopausal status. Visual inspection revealed data consistency with case or control status and did not show a dependence of missingness on the assessed covariates. No formal analysis was conducted during data exploration.

For the **register** see https://www.isrctn.com/ISRCTN16815568

	Overall (n=399)	Final diagnosis		
		Cancer (n=12)*	No cancer (n=375)†	Dropouts (n=12)‡
Age at recruitment (years)	56 (53–62)	67 (59–72)	56 (53–62)	59 (53–60)
Body-mass index (kg/m²)	26 (23–31)	29 (25–37)	26 (23–31)	32 (24–36)
Menopausal status				
Premenopausal	31 (8%)	1 (8%)	29 (8%)	1 (8%)
Perimenopausal	49 (12%)	0	49 (13%)	0
Postmenopausal	319 (80%)	11 (92%)	297 (79%)	11 (92%)
Current hormone replacement therapy	135 (34%)	1 (8%)	131 (35%)	3 (25%)
Ethnicity				
White	284 (71%)	10 (83%)	265 (71%)	9 (75%)
Black	55 (14%)	1 (8%)	52 (14%)	2 (17%)
Asian	43 (11%)	0	43 (11%)	0
Mixed	13 (3%)	1 (8%)	12 (3%)	0
Other	4 (1%)	0	3 (<1%)	1 (8%)
Sample collection				
Cervex brush	391 (98%)	10 (83%)	369 (98%)	12 (100%)
Evalyn brush (self-sampling)	8 (2%)	2 (17%)	6 (2%)	0
Endometrial thickness, mm				
<4·5	292 (73%)	1 (8%)	283 (75%)	8 (67%)
≥4·5	87 (22%)	10 (83%)	75 (20%)	2 (17%)
Not measurable	20 (5%)	1 (8%)	17 (5%)	2 (17%)
Subjective pattern recognition				
Not suggestive of cancer	366 (92%)	4 (33%)	352 (94%)	10 (83%)
Suggestive of cancer	10 (3%)	7 (58%)	3 (<1%)	0
Inconclusive	23 (6%)	1 (8%)	20 (5%)	2 (17%)
WID-qEC, ∑PMR				
<0·03	350 (88%)	1 (8%)	338 (90%)	11 (92%)
≥0·03	40 (10%)	10 (83%)	29 (8%)	1 (8%)
Insufficient or inadequate DNA	9 (2%)	1 (8%)	8 (2%)	0

Data are median (IQR) or n (%). *Cancer characteristics: Seven cases of stage I and five cases that were higher than stage I (four stage III and one stage IV); two cases of grade 1, four cases of grade 2, and six cases of grade 3; 11 cases of primary endometrial cancer and one tubal cancer metastasis in endometrium. †Among the 162 patients who had a negative reference histology, 32 had a normal endometrium, ten had a simple hyperplasia, 101 had a polyp without atypia, 12 had benign fibroids, two had endometritis, four had an atypical hyperplasia, and one had cervical intraepithelial neoplasia grade 1. ‡Individuals without a final diagnosis at timing of study cut-off-date: five patients were medically unfit for further procedures, four patients were lost to follow-up, three patients declined further investigations.

Table 1: **Baseline characteristics**

Participant characteristics are presented as median and IQRs for continuous or numerical data, and percentages for categorical data. Based on the analysis type (area under the receiver operating characteristic, computation of diagnostic characteristics including sensitivity, specificity, and positive and negative predictive values), we used either absolute continuous values or dichotomous values based on previously defined cut-offs. Cut-offs were based on values used in clinical practice (endometrial thickness in mm; 3 mm, 4·5 mm, or 5 mm), or previous analyses (WID qEC; ≥0·03 or ≥0·3 ∑PMR; the latter was not prespecified in the original analysis plan). The primary outcome was evaluated by comparison of area under the curves of ultrasound and WID-qEC using DeLong's test (endometrial thickness in mm and WID-qEC ∑PMR values) and computation of sensitivity, specificity, positive, and negative predictive values for each of the tests (dichotomous values). Receiver under the operating characteristic curve plots included only participants for whom data from both tests were available (endometrial thickness on ultrasound in mm and WID-qEC ∑PMR). The area under the curve was additionally assessed in postmenopausal women only to evaluate the test performance in this predominant subgroup of patients. Although we specified in the protocol that in addition to the endometrial thickness we would also assess the texture of the endometrium and presence of focal lesions, we did not stipulate that we would include Doppler ultrasound, the intention being to complete subjective pattern recognition assessment. AUCs and corresponding 95% CIs (DeLong's method) were computed using the pROC package (version 1.18.0). AUCs were compared using the roc.test method in the pROC package, using DeLong's test. Sensitivity, specificity, and positive and negative predictive values were obtained from the epi.tests function (epiR package, version 2.0.62), with 95% CIs computed using the Wilson method. Confidence intervals were compared for assessment of diagnostic measures, with a focus on the positive predictive value.

Participants with missing data were excluded in the analysis of primary outcomes. For comparison of AUCs (primary outcome), only complete cases were used (ie, those that had numerical endometrial thickness data and WID-qEC ∑PMR values). For comparison of sensitivity, specificity, positive predictive value, and negative predictive value, complete cases for the respective diagnostic test were used. No statistical adjustments to control for confounding were made, after exploratory data visualisation and inspection did not reveal substantial bias.

Secondary outcomes were evaluated by computing and visualising the diagnostic pathway and number of diagnostic tests required. EPI-SURE is registered with ISRCTN (16815568).

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 1, 2022, to Nov 24, 2022, 474 women aged 45 years and older with abnormal uterine bleeding were consecutively referred to the Rapid Access Clinic in the Gynaecology Diagnostic and Outpatient Treatment Unit at University College London Hospital. Of these, 74 (16%) did not accept the invitation to participate, and one woman withdrew after consenting. Therefore, the primary analysis cohort included 399 women who underwent both first index tests and WID-qEC testing (figure 1).

The median participant age was 56 years (IQR 53–62), and median body-mass index was 26 kg/m² (23–31; table 1). Among the 399 women, 31 (8%) were premenopausal, 49 (12%) were perimenopausal, 319 (80%) were postmenopausal, and 135 (34%) were receiving hormone replacement therapy. 284 (71%) participants were White. For most women the cervicovaginal sample was obtained by a Cervex-Brush; however, eight women requested the sample to be taken with an Evalyn Brush. In 20 (5%) women we were unable to assess the sonographic endometrial thickness, in 23 (6%) we were unable to make a judgement based on subjective pattern recognition, and in nine (2%) we were unable to perform the WID-qEC test (table 1).

603 imaging tests (transvaginal, transabdominal, transrectal, and saline infusion sonography, and MRI) were performed (figure 1). Among the 388 women who had a transvaginal ultrasound as their first index imaging test, 146 (38%) provided suboptimal images and required at least one additional index imaging test. Based on these assessments, 213 (53%) of 399 women were determined to be cancer-free based on endometrial thickness of less than 4·5 mm and absence of any findings suggestive of endometrial cancer. In these patients, histological assessment was not recommended. Among the 186 (47%) women referred for histology, 56 (30%) had an endometrial pipelle biopsy with five women testing positive for conclusive cancer, 27 testing negative and conclusive with no cancer, and 24 with inconclusive results who were then recommended for a hysteroscopy, biopsy, or a combination of both, which was performed for all but one participant who declined further investigation. 142 women underwent either a hysteroscopy (n=5), a biopsy (n=11), or a combination of both (n=126), which led to a diagnosis of cancer in four women, or no cancer in 137 women; one woman had an inconclusive result and was lost to follow-up. One woman who underwent an MRI without hysteroscopic assessment was found to have a tubal cancer invading the uterus. Two women with a negative reference histology result were subsequently found to have cancer (figure 1).

Endometrial thickness was measurable in 379 (95%) women of which 369 received a final diagnosis. The AUC for detection of uterine cancer based on endometrial thickness in mm was 87·2% (95% CI 71·1–100·0) overall and 87·3% (70·3–100·0) for postmenopausal women (figure 2). Outcomes of test positive, test negative, and test inconclusive patients are presented in table 2. On the basis of the endometrial thickness cut-off of more than 3 mm (as applied in several European countries) the sensitivity to detect a uterine cancer was 90·9% (95% CI 62·3–98·4) and the specificity was 45·8% (40·7–51·0), with a positive predictive value of 4·9% (2·7–8·8) and a negative predictive value of 99·4% (96·6–99·9; table 3). On the basis of the a-priori defined cut-off of at least 4·5 mm, the sensitivity was 90·9% (95% CI 62·3–98·4) and the specificity was 79·1% (74·5–82·9), with a positive predictive value of 11·8% (6·5–20·3) and a negative predictive value of 99·6% (98·0–99·9). The respective values for a 5 mm endometrial thickness cut-off, which is also commonly applied,[9] were 72·7% (95% CI 43·4–90·3) for sensitivity, 81·0% (76·6–84·7) for specificity, 10·5% (5·4–19·4) for positive predictive value, and 99·0% (97·0– 99·7) for negative predictive value. Test-positivity upon endometrial thickness of at least 4·5 mm or a

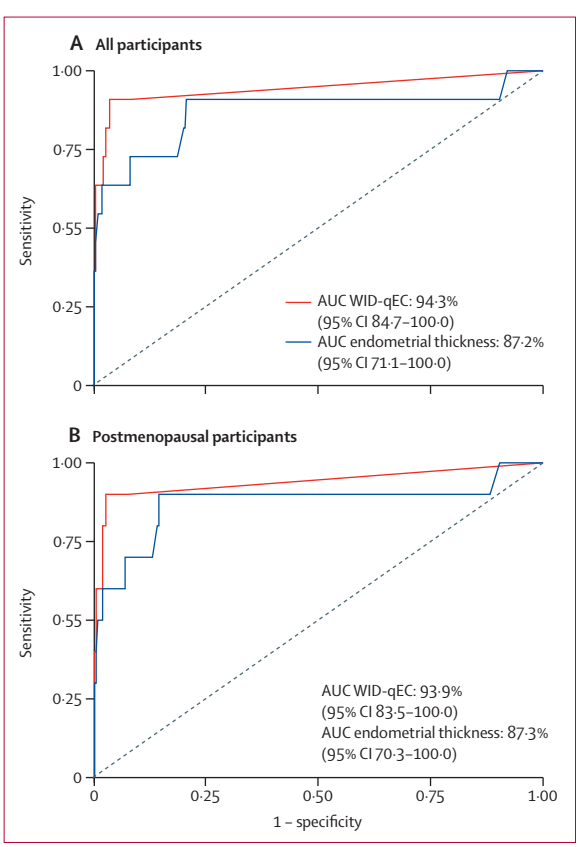


Figure 2: **Area under the receiver operating characteristic curve**
Comparison of sonographically assessed endometrial thickness and WID-qEC ΣPMR in all participants (A) and in postmenopausal participants (B). AUC=area under the receiver operating characteristic curve.

	Cancer (n=12)	No cancer (n=375)	Overall (n=387)
Endometrial thickness >3·0 mm			
Test positive	10 (83%)	194 (52%)	204 (53%)
Test negative	1 (8%)	164 (44%)	165 (43%)
Inconclusive	1 (8%)	17 (5%)	18 (5%)
Endometrial thickness ≥4·5 mm			
Test positive	10 (83%)	75 (20%)	85 (22%)
Test negative	1 (8%)	283 (75%)	284 (73%)
Inconclusive	1 (8%)	17 (5%)	18 (5%)
Endometrial thickness ≥4·5 mm or uterine polyp, or both			
Test positive	10 (83%)	137 (37%)	147 (38%)
Test negative	1 (8%)	221 (59%)	222 (57%)
Inconclusive	1 (8%)	17 (5%)	18 (5%)
Endometrial thickness ≥5·0 mm			
Test positive	8 (67%)	68 (18%)	76 (20%)
Test negative	3 (25%)	290 (77%)	293 (76%)
Inconclusive	1 (8%)	17 (5%)	18 (5%)
Subjective pattern recognition			
Test positive	7 (58%)	3 (<1%)	10 (3%)
Test negative	4 (33%)	352 (94%)	356 (92%)
Inconclusive	1 (8%)	20 (5%)	21 (5%)
Combination of all reference histology tests (pipelle, hysteroscopy and curettage, or biopsy)			
Test positive	9/11 (82%)	0	9/173 (5%)
Test negative	2/11 (18%)	162/162 (100%)	164/173 (95%)
Inconclusive	0	0	0
WID-qEC ≥0·03 ΣPMR			
Test positive	10 (83%)	29 (8%)	39 (10%)
Test negative	1 (8%)	338 (90%)	339 (88%)
Inconclusive	1 (8%)	8 (2%)	9 (2%)
WID-qEC ≥0·3 ΣPMR			
Test positive	10 (83%)	10 (3%)	20 (5%)
Test negative	1 (8%)	357 (95%)	358 (93%)
Inconclusive	1 (8%)	8 (2%)	9 (2%)

Data are n (%) or n/N (%). Only the 387 with a final diagnosis out of the total 399 women are listed. One patient (uterine metastasis of a tubal cancer) had no reference test, but histology was obtained at hysterectomy.

Table 2: **Outcome of test positive, test negative, and test inconclusive patients**

sonographic visible polyp, or both, resulted in a specificity of 61·7% (95% CI 56·6–66·6) with a positive predictive value of 6·8% (3·7–12·1; table 3).

Subjective pattern recognition gave a conclusive result in 366 women who had a final diagnosis (table 2). Sensitivity and specificity to detect a uterine cancer were 63·6% (95% CI 35·4–84·8) and 99·2 (97·5–99·7), respectively, with a positive predictive value of 70·0% (39·7–89·2) and a negative predictive value of 98·9% (97·1–99·6; table 3).

Of the 173 women with at least one conclusive reference histology test result (hysteroscopy only is also included), the outcome was test negative (ie, no cancer) for 164 women. Among these women assumed cancer-free after biopsy, one woman had a hysterectomy due to an atypical hyperplasia and was found to have an invasive endometrial cancer. One participant with normal endocervical and necrotic tissue obtained at hysteroscopy and biopsy later had a biopsy of a liver metastasis which unequivocally indicated a primary endometrial cancer (figure 1). Therefore, the sensitivity of the biopsy to detect endometrial cancer was 82% (nine of 11; table 2).

Sufficient DNA to conduct the WID-qEC test was isolated from cervical samples from 390 (98%) of the 399 women. Eight women provided insufficient DNA. Due to the fact that gross anatomical alterations of the cervix completely block or at least severely limit the drainage from the endometrial cavity, one volunteer who presented with a large endocervical polyp (35×30×10 mm; subsequently found to be benign on histology) that protruded into the vagina was excluded from the WID-qEC analysis.

The AUC for uterine cancer was 94·3% (95% CI 84·7–100·0) overall and 93·9% (83·5–100) for postmenopausal women (figure 2). Although the comparison of the AUC to endometrial thickness in mm was not significant (p=0·48), the shape of the WID-qEC curve indicates that a high sensitivity is already reached at a high specificity. On the basis of the previously defined cut-off of 0·03 ΣPMR or more,[24] the sensitivity to detect a uterine cancer was 90·9% (95% CI 62·3–98·4)

	Endometrial thickness (n=369)				Pattern recognition (n=366)	WID-qEC (n=378)	
	>3 mm	≥4·5 mm	≥5 mm	≥4·5 mm or polyp, or both	Suggestive of cancer	≥0·03 ΣPMR	≥0·3 ΣPMR
Population prevalence (number of cancer cases out of total individuals with available test)	11 (3%)	11 (3%)	11 (3%)	11 (3%)	11 (3%)	11 (3%)	11 (3%)
Sensitivity (95% CI)	90·9% (62·3–98·4)	90·9% (62·3–98·4)	72·7% (43·4–90·3)	90·9% (62·3–98·4)	63·6% (35·4–84·8)	90·9% (62·3–98·4)	90·9% (62·3–98·4)
Specificity (95% CI)	45·8% (40·7–51·0)	79·1% (74·5–82·9)	81·0% (76·6–84·7)	61·7% (56·6–66·6)	99·2% (97·5–99·7)	92·1% (88·9–94·4)	97·3% (95·1–98·5)
Positive predictive value (95% CI)	4·9% (2·7–8·8)	11·8% (6·5–20·3)	10·5% (5·4–19·4)	6·8% (3·7–12·1)	70·0% (39·7–89·2)	25·6% (14·6–41·1)	50·0% (29·9–70·1)
Negative predictive value (95% CI)	99·4% (96·6–99·9)	99·6% (98·0–99·9)	99·0% (97·0–99·7)	99·5% (97·5–99·9)	98·9% (97·1–99·6)	99·7% (98·3–99·9)	99·7% (98·4–100·0)

ΣPMR=sum of the percentage of fully methylated reference.

Table 3: **Performance characteristics of sonographic assessments and the WID-qEC test in women with a final diagnosis**

and the specificity was 92·1 (88·9–94·4), with a positive predictive value of 25·6% (95% CI 14·6–41·1) and a negative predictive value of 99·7 (98·3–99·9; table 3). Nevertheless, of the 40 patients with a positive WID-qEC, 28 (70%) had a histological assessment. Among patients with a false positive WID-qEC test result were two women with an atypical hyperplasia, one of whom had a granulosa cell tumour. Among 12 women without histology, 11 had sonographic features which did not justify histological assessment (normal or atrophic endometrium). Additionally, hysteroscopy was not possible in one patient due to morbid obesity. This patient eventually had a hysterectomy revealing a grade 1 stage Ia endometrioid endometrial cancer, 8 months after collection of the cervicovaginal sample which was WID-qEC positive; she was not included in the performance analyses as the histology was obtained after database lock.

Applying a cut-off of 0·3 ∑PMR, which was considered a high specificity cut-off, would have substantially increased the specificity (97·3% [95% CI 95·1–98·5]) and the positive predictive value (50% [29·9–70·1]) without affecting the sensitivity (table 3). The single WID-qEC-false negative case was a 2 mm grade 1 invasive endometrial cancer on a background of atypical hyperplasia.

Applying our data and a 3 mm endometrial thickness cut-off, as recommended in several countries,[10,11] to a population of 100 women presenting with abnormal bleeding would generate 52·6 false positive results requiring further investigation with hysteroscopy and biopsy. By contrast, when applying the WID-qEC test with a ∑PMR cut-off of 0·3, the number of false positive results could be reduced by 95% to 2·6 without affecting the number of true positive test results (figure 3). As prevalence is an important factor for positive predictive value and negative predictive value, these parameters might vary depending on the prevalence of endometrial cancer in the population tested.

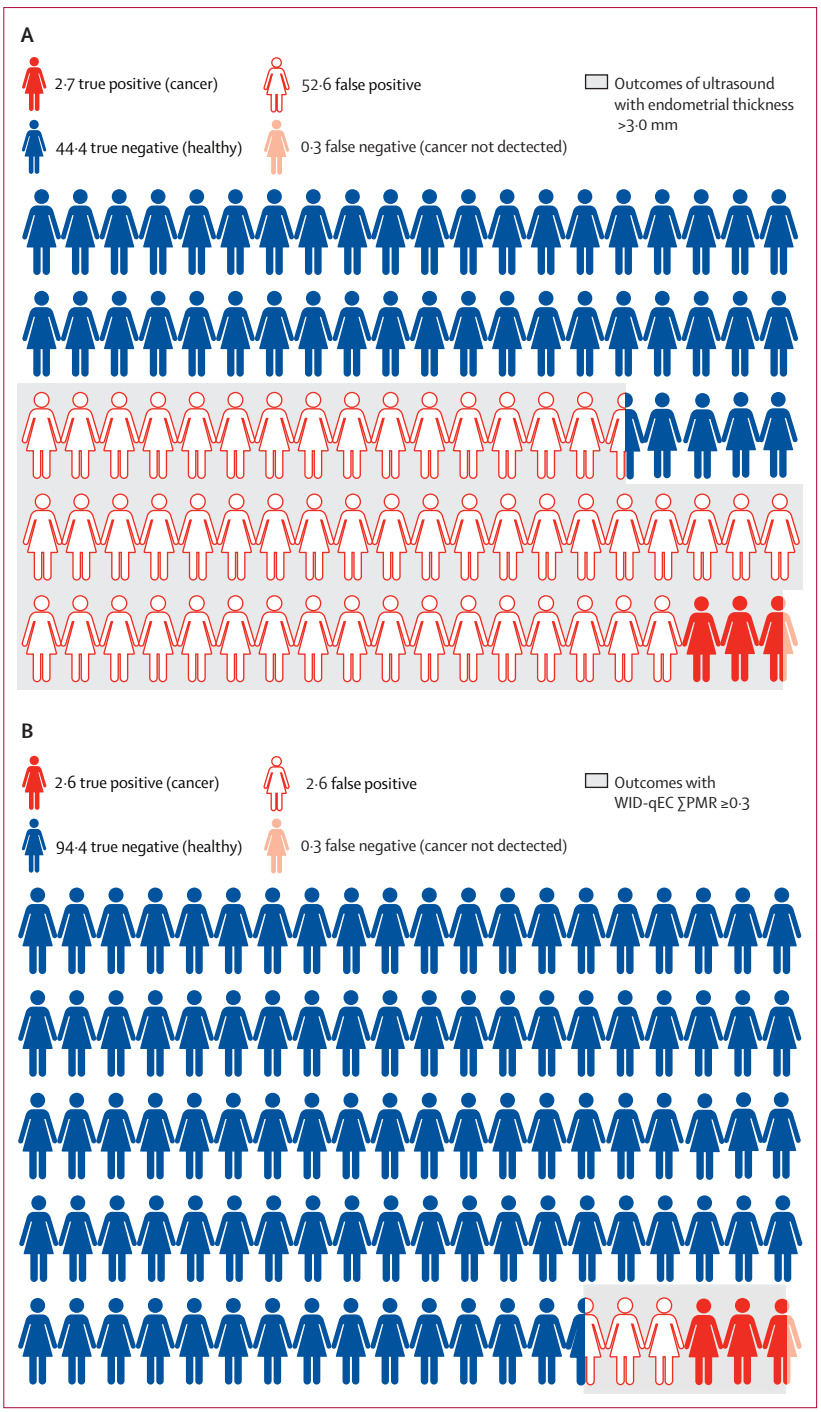


Figure 3: **Modelled outcomes for assessment of 100 women presenting with abnormal uterine bleeding**
Potential outcomes for an ultrasound endometrial thickness cut-off of more than 3 mm (A) and WID-qEC with ∑PMR cut-off of 0·3 or more (B).

Discussion

In this prospective, observational cohort study, we compared the performance of molecular testing and sonography to detect uterine cancers in women presenting with abnormal uterine bleeding. The conventional assessment of 399 women with abnormal uterine bleeding required a total of 801 diagnostic procedures (603 imaging procedures, 56 pipelle biopsies, and 142 non-pipelle biopsies and hysteroscopies) to identify ten cases of uterine cancer; two cancers were only diagnosed after further assessments (one at hysterectomy and one at biopsy of a liver metastasis). For both the index imaging and the WID-qEC, test results were inconclusive for one patient who was eventually diagnosed with a cancer; the endometrial cavity could not be visualised by ultrasound and the sample was inadequate for the DNA test. Both methods missed one cancer; ultrasound did not detect the tubal metastasis in the endometrium and the WID-qEC test missed a 2 mm grade 1 endometrial cancer.

Ultrasound-assessed endometrial thickness as an index test in our cohort had a similar sensitivity but showed a substantially higher specificity than reported in previously

published data. The specificity in our cohort was 79·1% for a cut-off of 4·5 mm or more compared with previous studies which showed specificities of 35·4% for a cut-off of more than 3 mm, 52·7% for a cut-off of 4 mm or more, and 62·5% for a cut-off of 5 mm or more.[9,10] Combining data from women with an endometrial thickness of 4·5 mm or more with those with the presence of a polyp did not affect sensitivity but resulted in a drop of specificity to 61·7%. The comparably high specificity of ultrasound might be explained by the multimodal approach in our study. Transvaginal sonography provided suboptimal images in 37·6% of patients in our cohort (ie, women who underwent transvaginal sonography required at least one additional index imaging test), which is similar to the results of a previous study[30] reporting a 38% rate of suboptimal endometrial assessment on transvaginal sonography in their patients. It has been previously shown that suboptimal imaging of the uterine cavity leads to overestimation of endometrial thickness, resulting in a higher proportion of false positive findings.[15] By using transrectal and transabdominal routes to examine the endometrium, and saline infusion sonography in selected cases, we eventually obtained optimal images of the endometrium in 95% of our patients, which translated into the increased index imaging test specificity.

Despite the excellent performance of sonography in our study, the WID-qEC test outperformed all current strategies for assessing women with abnormal uterine bleeding. For the WID-qEC, only one sample (obtained either by a health-care professional or by the study participant) was required and only nine samples were inconclusive, whereas the initial sonographic assessment (ie, first index imaging test) led to 151 inconclusive results and hence 16·7 times more inconclusive results compared to the WID-qEC test.

Comparing tests providing a numerical value (ie, endometrial thickness or ∑PMR), the WID-qEC test delivered a higher AUC than endometrial thickness, but the difference was not significant. Direct comparison of sensitivities might be challenging due to the low number of cancer cases. However, when using predefined cut-offs or parameters the sensitivity of endometrial thickness and WID-qEC were comparably high (90·9%) whereas the sensitivity of the subjective pattern recognition was low (63·6%) and did not offer a level of improvement that would warrant the wider use of it to triage women with abnormal uterine bleeding. Hysteroscopy and biopsy—deemed to be the gold standard—missed two cancer cases, both of which were WID-qEC test positive.

Although the strength of our study is the prospective cohort design embedded in a real-life setting, a limitation is the fact that we did not act on positive WID-qEC test results. The fact that the study is predominantly based on White women is a limitation and ongoing studies are assessing the performance of the WID-qEC test in Black women in whom the performance of ultrasound is poor.[12]

Women undergoing outpatient hysteroscopy suffer from high levels of preoperative anxiety,[31] comparable to levels experienced before major surgery under general anaesthesia and, for a proportion of women, the procedure is painful and traumatising,[32] meaning that efforts to reduce the number of these interventions required will be welcomed by clinical and patient communities.[26] Inclusion of the WID-qEC test in the clinical diagnostic pathway for endometrial cancer offers five key advantages: (1) the test can be carried out in a primary care setting without the need for expensive equipment or highly skilled staff as evidenced by our previous data in cervicovaginal samples self-collected by study participants;[24] (2) the assay is suitable for high-throughput analysis; (3) it delivers an objective result within less than 48 h; (4) the decision to conduct a hysteroscopy or biopsy will be reached after fewer investigations; and (5) overall, fewer hysteroscopy and biopsy procedures will be required.

Data show that in some countries (eg, Northern Ireland) approximately 80% of patients presenting with signs of gynaecological cancer must wait for more than 62 days before initiation of treatment.[33] Most of this delay is triggered by delays in obtaining an appointment at a gynaecological diagnostic centre. Hence, our recommendation is that women with a very high likelihood of cancer as the underlying cause of abnormal uterine bleeding (ie, WID-qEC ∑PMR >0·3) are referred for a hysteroscopy and an endometrial biopsy in a tertiary cancer referral centre. Women with a WID-qEC ∑PMR of higher than 0·03 and lower than 0·3 could be referred as a lower priority to general gynaecological clinics to investigate and treat possible causes of their abnormal uterine bleeding.

The present study limited enrolment to patients aged 45 years and older and thereby the proportion of premenopausal women was low. Performance of the WID-qEC test in menstruating women is therefore unclear; however, based on previous data,[24,25] sensitivity of the test is likely to be similar in premenopausal and postmenopausal women.

Overall, these data indicate that the WID-qEC test outperforms currently established strategies on important diagnostic test parameters (ie, specificity and number of women required to be triaged for a reference histology test) for detection of uterine cancer in women who present with abnormal uterine bleeding. Implementation of the WID-qEC test in the clinical diagnosis of women presenting with abnormal uterine bleeding could substantially reduce the complexity of the diagnostic pathway by decreasing the number of required tests and help to target those most in need of rapid histological assessment.

Contributors

IE, DR, AJ, and AB contributed equally to this manuscript.
MW designed the study and drafted the first version of the manuscript.
IE, DR, AJ, ER, LS, II-P, JR, CH, and MW were responsible for data

collection. DR, AB, RA, SN, SAS, and DJ were responsible for clinical data acquisition. CH and MW were responsible for data analysis and generation of figures. MW, IE, DR, AJ, DJ, and CH were responsible for data interpretation. IE, DR, AJ, DJ, and MW verified the data. All authors participated in reviewing of the manuscript, approved the final draft for submission, have access to the reported data, and accept responsibility for the decision to submit for publication.

Declaration of interests

CH and MW are shareholders of Sola Diagnostics GmbH, which holds an exclusive licence to the intellectual property that protects the commercialisation of the WID-qEC test. DJ is an unpaid advisory board member of the International Society for Ultrasound in Obstetrics and Gynecology. MW received funding from the Land Tirol, The Eve Appeal, and the European Research Council. All other authors declare no competing interests.

Data sharing

Anonymised individual-level patient data can be provided to researchers upon written request 24 months after publication of the Article. A detailed proposal for how the data will be used should be sent to the corresponding author and is required to allow assessment of the application.

Acknowledgments

This study was funded by The Eve Appeal, Land Tirol, and the European Research Council under the European Union's Horizon 2020 Research and Innovation Programme (grant agreement No 742432; BRCA-ERC; ISRCTN registry number 16815568). We thank all patients who participated, staff, and investigators. We thank Sara Sleigh (PhD) for her assistance during the study and her critical assessment of the manuscript.

References

1 Lu KH, Broaddus RR. Endometrial cancer. *N Engl J Med* 2020; **383:** 2053–64.
2 Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. *Lancet* 2022; **399:** 1412–28.
3 Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* 2023; **73:** 17–48.
4 Sud A, Torr B, Jones ME, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. *Lancet Oncol* 2020; **21:** 1035–44.
5 Matteson KA, Raker CA, Clark MA, Frick KD. Abnormal uterine bleeding, health status, and usual source of medical care: analyses using the Medical Expenditures Panel Survey. *J Womens Health (Larchmt)* 2013; **22:** 959–65.
6 Whitaker L, Critchley HO. Abnormal uterine bleeding. *Best Pract Res Clin Obstet Gynaecol* 2016; **34:** 54–65.
7 Clarke MA, Long BJ, Sherman ME, et al. Risk assessment of endometrial cancer and endometrial intraepithelial neoplasia in women with abnormal bleeding and implications for clinical management algorithms. *Am J Obstet Gynecol* 2020; **223:** 549.e–e13.
8 Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-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.
9 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.
10 Timmermans A, Opmeer BC, Khan KS, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. *Obstet Gynecol* 2010; **116:** 160–67.
11 Emons G, Steiner E, Vordermark D, et al. Endometrial cancer. Guideline of the DGGG, DKG and DKH (S3-Level, AWMF Registry Number 032/034-OL, September 2022). Part 1 with recommendations on the epidemiology, screening, diagnosis and hereditary factors of endometrial cancer, geriatric assessment and supply structures. *Geburtshilfe Frauenheilkd* 2023; **83:** 919–62.
12 Doll KM, Romano SS, Marsh EE, Robinson WR. Estimated performance of transvaginal ultrasonography for evaluation of postmenopausal bleeding in a simulated cohort of black and white women in the US. *JAMA Oncol* 2021; **7:** 1158–65.
13 Wong M, Thanatsis N, Amin T, Bean E, Madhvani K, Jurkovic D. Ultrasound diagnosis of endometrial cancer by subjective pattern recognition in women with postmenopausal bleeding: prospective inter-rater agreement and reliability study. *Ultrasound Obstet Gynecol* 2021; **57:** 471–77.
14 Wong M, Amin T, Thanatsis N, Naftalin J, Jurkovic D. A prospective comparison of the diagnostic accuracies of ultrasound and magnetic resonance imaging in preoperative staging of endometrial cancer. *J Gynecol Oncol* 2022; **33:** e22.
15 Wong M, Amin T, Thanatsis N, Foo X, Jurkovic D. Efficacy of transrectal ultrasound in assessing endometrium of postmenopausal women with axial uterus. *Ultrasound Obstet Gynecol* 2022; **60:** 414–19.
16 Price P, Sullivan R, Ahmed A, Wishart GC. UK cancer care: a watershed moment and the need for urgent intervention. *Lancet Oncol* 2023; **24:** 133–38.
17 Nicholson BD, Oke J, Virdee PS, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *Lancet Oncol* 2023; **24:** 733–43.
18 Fiegl H, Gattringer C, Widschwendter A, et al. Methylated DNA collected by tampons—a new tool to detect endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 2004; **13:** 882–88.
19 Bakkum-Gamez JN, Sherman ME, Slettedahl SW, et al. Detection of endometrial cancer using tampon-based collection and methylated DNA markers. *Gynecol Oncol* 2023; **174:** 11–20.
20 Jones A, Teschendorff AE, Li Q, et al. Role of DNA methylation and epigenetic silencing of HAND2 in endometrial cancer development. *PLoS Med* 2013; **10:** e1001551.
21 Wentzensen N, Bakkum-Gamez JN, Killian JK, et al. Discovery and validation of methylation markers for endometrial cancer. *Int J Cancer* 2014; **135:** 1860–68.
22 Huang RL, Su PH, Liao YP, et al. Integrated epigenomics analysis reveals a dna methylation panel for endometrial cancer detection using cervical scrapings. *Clin Cancer Res* 2017; **23:** 263–72.
23 Wen KC, Huang RL, Chen LY, et al. Endometrial cancer detection using a cervical dna methylation assay (mpap) in women with abnormal uterine bleeding: a multicenter hospital-based validation study. *Cancers (Basel)* 2022; **14:** 4343.
24 Herzog C, Marín F, Jones A, et al. A simple cervicovaginal epigenetic test for screening and rapid triage of women with suspected endometrial cancer: validation in several cohort and case/control sets. *J Clin Oncol* 2022; **40:** 3828–38.
25 Schreiberhuber L, Herzog C, Vavourakis CD, et al. The WID-qEC test: performance in a hospital-based cohort and feasibility to detect endometrial and cervical cancers. *Int J Cancer* 2023; **152:** 1269–74.
26 Wan YL, Beverley-Stevenson R, Carlisle D, et al. Working together to shape the endometrial cancer research agenda: the top ten unanswered research questions. *Gynecol Oncol* 2016; **143:** 287–93.
27 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370:** 1453–57.
28 Leone FP, Timmerman D, Bourne T, et al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group. *Ultrasound Obstet Gynecol* 2010; **35:** 103–12.
29 Wong M, Crnobrnja B, Liberale V, Dharmarajah K, Widschwendter M, Jurkovic D. The natural history of endometrial polyps. *Hum Reprod* 2017; **32:** 340–45.
30 Goldstein SR, Khafaga A. Ability to successfully image endometrium on transvaginal ultrasound in asymptomatic postmenopausal women. *Ultrasound Obstet Gynecol* 2021; **58:** 625–29.
31 Gambadauro P, Navaratnarajah R, Carli V. Anxiety at outpatient hysteroscopy. *Gynecol Surg* 2015; **12:** 189–96.
32 O'Flynn H, Murphy LL, Ahmad G, Watson AJ. Pain relief in outpatient hysteroscopy: a survey of current UK clinical practice. *Eur J Obstet Gynecol Reprod Biol* 2011; **154:** 9–15.
33 Venkatesan P. Gynaecological cancer waiting times in Northern Ireland. *Lancet Oncol* 2023; **24:** 962.