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Epidemiology and Investigations for Suspected Endometrial Cancer

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Abstract

Objective: To review the evidence relating to the epidemiology of endometrial cancer and its diagnostic workups.

Options: Women with possible endometrial cancer can undergo an endometrial evaluation by office biopsy, hysteroscopy, or dilatation and curettage. To assist in treatment planning, pelvic ultrasound, CT scan, or MRI may be considered.

Outcomes: The identification of optimal diagnostic tests to evaluate patients with possible endometrial cancer.

Evidence: Published literature was retrieved through searches of PubMed, CINAHL, and The Cochrane Library, using appropriate controlled vocabulary (e.g., endometrial neoplasms) and key words (e.g., endometrium cancer, endometrial carcinoma). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and incorporated in the guideline to December 31, 2011. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, national and international medical specialty societies, and recent conference abstracts.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Benefits, harms, and costs: This document is intended to guide the development of a standardized cost-effective investigation of patients with suspected endometrial cancer.

Validation: The guideline was reviewed for accuracy by experts in pathology, radiation oncology, and medical oncology. Guideline content was also compared with relevant documents from the American Congress of Obstetricians and Gynecologists.

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Key Words: Endometrial cancer, diagnostic workup, endometrial evaluation, ultrasound, magnetic resonance imaging, MRI, postmenopausal bleeding

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[45]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[45]

Recommendations

1. A complete focused history should be taken and a physical examination carried out in patients with suspected endometrial cancer. Attention should be paid to predisposing factors for excess estrogen stimulation of the endometrium such as long history of anovulation, obesity, menstrual irregularity, or long-term use of unopposed estrogen or tamoxifen. Patients with a strong family history of endometrial, ovarian, and colorectal cancers might have inherited Lynch syndrome (hereditary non-polyposis colorectal cancer syndrome) that increases their lifetime risk of developing endometrial cancer. Genetic counselling and testing can be used to individualize risk-management interventions including screening strategies and treatment options. (III-B)
2. Endometrial cancer should be ruled out in perimenopausal and postmenopausal patients with abnormal vaginal bleeding. (II-1A)
3. Depending on access, histologic endometrial evaluation and transvaginal ultrasound are the preferred initial diagnostic investigations for patients with suspected endometrial cancer. (II-1B)
4. Histologic evaluation of the endometrium should be done in all patients in whom endometrial cancer is suspected. (II-1A)
5. Hysteroscopic examination should be considered in patients with persistent uterine bleeding with benign endometrial sampling or insufficient endometrial sampling after ultrasound. (II-2B)
6. Formal review of the histopathology should be considered in patients with high grade tumours or rare histologic types such as serous, clear cell, or mucinous types. (III-B)
7. Additional tumour markers, CT scan, and MRI scan should not be used routinely. (III-D)

ABBREVIATIONS

D&C dilation and curettage

HNPCC hereditary non-polyposis colorectal carcinoma

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INTRODUCTION

Endometrial cancer is the most common gynaecologic cancer in North America. The Canadian Cancer Society estimated that in 2008, about 4200 women in Canada would develop this cancer, and 790 of them would die of the disease.[1] A woman's lifetime risk of developing endometrial cancer is about 2.6%.[2] However, the incidence is rising in developed countries.[3,4] The likelihood of surviving endometrial cancer is significantly affected by age; older patients and diabetic patients have a decreased overall survival, and are more likely to have a higher stage of disease at presentation.[4]

In 1988, FIGO recommended changing the staging system from clinical to surgical-pathologic staging classification because it had been demonstrated that the clinical staging assessment carried a 13% to 22% risk of understaging patients.[5] In 2009, a further revision of the surgical staging classification was adopted by FIGO to reflect the importance of histopathologic prognostic indicators in this disease[6] (Table 2). The major changes included collapsing stage IA and IB of the 1988 system into the new stage IA and removing cervical mucosal involvement and peritoneal cytology results as classification criteria. Parametrial and pelvic peritoneal involvement are taken into account in the

Table 2. 2009 FIGO staging endometrial carcinoma	
IA	Tumour confined to the uterus, less than 50 % myometrial invasion
IB	Tumour confined to the uterus, more than 50% myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
IIIA	Tumour invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic lymph node involvement and/or pelvic lymph node involvement
IVA	Tumour invasion bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

new system. The 2009 classification also subdivides stage IIIC according to whether pelvic and/or para-aortic nodes are involved. The new staging classification is currently being validated.

ENDOMETRIAL CANCER EPIDEMIOLOGY

Endometrial cancer is commonly grouped into 2 different profiles with distinct risk factors.[2,7] Type 1 endometrial cancer, which is more common (80% of all cases), consists of tumours of endometrioid histology. Type I is believed to be hormone-related and to be significantly associated with both unopposed estrogen therapy and obesity. Type 2 endometrial cancer, which is less common (20% of all cases), consists of less common histological subtypes such as papillary serous, clear cell, mucinous, and carcinosarcoma. This second group is usually not associated with excess estrogen exposure.[3,8]

Endometrial cancers are most frequently diagnosed in the perimenopausal/postmenopausal age group. However, up to 10% to 15% of cancers can occur in premenopausal patients, of whom up to 2% to 5% will be under the age of 40.[9] In these young patients, up to one third will also have either a synchronous ovarian primary or metastasis at the time of diagnosis.[9] The investigation and treatment of these patients should be discussed with a gynaecologic oncologist.

The most common initial presentation for endometrial cancer is abnormal vaginal bleeding. Any perimenopausal and/or postmenopausal bleeding should be promptly investigated with the goal of ruling out endometrial hyperplasia or neoplasia. Most bleeding is caused by a benign pathologic condition rather than cancer; however, the older the patient, the higher the risk of an underlying cancer. According to Feldman, women aged 70 or more with postmenopausal bleeding have an estimated cancer risk of 50%.[10] Histologic evaluation of the endometrium is of paramount importance when a pre-malignant or malignant lesion is suspected.

Screening for endometrial cancer in asymptomatic patients has not been shown to be cost effective.[8] Routine endometrial biopsy is not recommended before starting hormone replacement therapy.[11] Patients with an HNPCC predisposition should, however, be screened with annual endometrial biopsies beginning at age 30 to 35 or 5 to 10 years before the youngest age at which a family member was diagnosed as having cancer, even if they are asymptomatic. Ovarian cancer screening is also recommended.[11,12]

RISK FACTORS FOR THE DEVELOPMENT OF ENDOMETRIAL CANCER

Advancing age is one of the most important risk factors for the development of endometrial carcinoma.[8] This may partially explain why the incidence of endometrial cancer is rising worldwide.[4,8] Most endometrial cancers still appear to be sporadic, except for about 10% that are hereditary.[8]

Among genetically predisposed women, HNPCC syndrome is the most frequently encountered syndrome. Their risk of developing cancer is about 10 times higher than the baseline rate in the general population.[8,11] Patients with a personal history of breast, ovarian, or colon cancer also have an increased risk of developing a subsequent endometrial cancer.[8]

Obesity and physical inactivity are also very important risk factors in the development of endometrial carcinoma.[4,13] Obesity increases the circulating estrogen level from the peripheral aromatisation of androstendione to estrone in adipose tissues.[8] Diabetes is also a risk factor, because hyperadrenocorticism is increased by hyperinsulinemia, which disturbs estrogen metabolism.[8]

Table 3. Epidemiologic risk factors for the development of endometrial cancer

Risk Factor	Relative Risk
Unopposed estrogen replacement	2 to 10
Late menopause > 55 years	2.4
Nulliparity	2
Chronic anovulation	3
Hypertension	1.5
Obesity	10
Diabetes	2.8
HNPCC syndrome	22% to 50% lifetime risk
Tamoxifen use	6 to 8

Tamoxifen is also a causal factor in the pathogenesis of endometrial cancer and can increase the risk as much as 6- to 8-fold.[4] Exposure to excess unopposed estrogen is believed to promote carcinogenesis rather than being a carcinogenic agent itself.[8] Excess endogenous estrogen exposure is common in women who

- Have early menarche
- Have late menopause
- Are nulliparous
- Have polycystic ovary syndrome
- Have a prior history of infertility related to anovulation.

Other well-known risk factors are prior pelvic radiation, unopposed estrogen replacement therapy, and estrogen-producing ovarian tumours.[4,8] See Table 3 for epidemiologic risk factors for the development of endometrial cancer.

In view of these risk factors, primary preventive measures should include education for patients and primary care providers about the risk of obesity, the benefits of physical activity, modifiable risk factors, and the importance of early reporting of abnormal bleeding.[8]

RISK MODIFICATION STRATEGIES IN ENDOMETRIAL CANCER

An extensive literature review by Linkov et al. shows that high consumption of isoflavones lowers the risk for endometrial cancer as well as breast carcinoma; however, data are mainly observational.[4] In a study by Xu et al., the risk reduction for endometrial cancer varied from 0.93 to 0.85 or 0.67 depending on soy protein intake. The inverse association was even more true in women with high BMI and waist:hip ratio.[14] Tempfer et al., in a meta-analysis of phytoestrogens, concluded that the incidence of endometrial hyperplasia, endometrial cancer, and breast carcinoma was not increased significantly among users and thus appeared to be safe.[15] A review by Mahady suggested that soy isoflavones are safe as long as the recommended dose of 40 to 80 mg/d is respected.[16] At 30 months, 75% of patients had atrophic or inactive endometrium, indicating that soy isoflavones were acting as anti-estrogens.[16]

Cust et al. in a review demonstrated that physical activity had a definite protective effect in endometrial cancer, with an average risk reduction of about 30%.[17] Patel et al., in the American Cancer Society Cancer Prevention Study II Nutrition Cohort, showed in a prospective cohort that light to moderate physical activity diminished the risk of endometrial cancer and that this was especially true for overweight and obese patients.[18] Physical activity has an effect on circulating estrogen, both directly and indirectly through energy balance, insulin-mediated pathways, and independent pathways.[18] However there are few prospective studies on the subject. Use of unopposed estrogen replacement in patients with an intact uterus should be discouraged.

INVESTIGATIONS IN PATIENTS WITH SUSPECTED ENDOMETRIAL CANCER

A complete focused history and physical examination are important. Detailed menstrual and relevant bleeding history should be documented. Attention should be paid to predisposing factors for excess estrogen stimulation on the endometrium such as long history of anovulation, obesity, menstrual irregularity, and use of hormones and tamoxifen. Evaluation of other concurrent significant medical comorbidities is indicated for optimal investigations and treatment planning.

Role of Pathologic Evaluation in Diagnosis and Treatment Planning of Suspected Endometrial Cancer

The initial workup for patients with significant abnormal vaginal bleeding will often include a pathologic assessment of the endometrial tissue. A wide spectrum of abnormal findings can be encountered. Atypical endometrial hyperplasia is a known precursor of endometrial cancer. Concurrent endometrial cancer can be present in up to 40% of patients operated on for atypical endometrial hyperplasia.[19] A recent retrospective Canadian study showed that 36% of patients with atypical endometrial hyperplasia had concurrent endometrial carcinoma.[20] Sixteen percent of these patients had high-risk pathologic features in which comprehensive surgical staging is routinely recommended.[20]

Formal review of the histopathology should be recommended in patients with high-grade tumours or rare histologic types such as serous, clear cell, or mucinous. Routine pathology review of all endometrioid tumours is controversial and unlikely to be helpful in treatment planning as interobserver variability was shown to be significant when a panel of trained gynaecologic pathologists was surveyed.[20]

Intraoperative frozen section examination has been used to help determine whether to perform comprehensive surgical staging, according to the evaluation of tumour grade and estimated depth of myometrial invasion. However, up to 28% of frozen section diagnoses will be upgraded, and 33% will not match the final pathology.[21] Mao et al. showed an accuracy of 90.3% and sensitivity of 80.6% in diagnosing myometrial invasion on frozen section.[22] However, intraoperative assessment for depth of myometrial invasion obtained by cutting across the unfixed uterus may compromise the pathologist's ability to obtain well-oriented tissue slices for the permanent sections on which some staging parameters will be based. The presence of benign disease such as myoma or adenomyosis can lead to overestimation of myometrial invasion.[22] Because tumour grade and depth of myometrial invasion cannot be accurately diagnosed preoperatively and intraoperatively, one treatment strategy would call for surgical lymph node sampling in all patients with endometrial cancer.

Techniques for Evaluation of the Endometrium and Extent of Disease

Endometrial biopsy

Office endometrial biopsy has largely replaced dilatation and curettage for most patients. The development of different types of instruments has been helpful in this area. The Pipelle device has probably been the most extensively used for endometrial sampling. Office endometrial biopsy offers several advantages over the standard D&C[7,10]:

- Low cost for the health care system.
- Little or no anaesthesia needed.
- Can be done in the same consultation thus limiting loss of work time.
- Less traumatic because biopsy needs no or little cervical dilatation.

Endometrial biopsy compares favourably with the standard D&C, and the correlation is excellent for diagnosing the presence of endometrial cancer.[7,23,24] However, studies have shown that up to 30% of preoperative grade I tumours will be upgraded to a higher grade of disease after examination of the hysterectomy specimen.[21] Upgrading has been reported to occur less frequently after D&C than after Pipelle biopsy.[24] In this study, only 8.7% of tumours diagnosed by D&C were upgraded compared with 17.4% of those diagnosed by Pipelle endometrial biopsy. Similarly, Giede et al. presented Canadian data in which almost one third of patients had the preoperative assessment of their tumours upgraded after the hysterectomy.[20] The discrepancy can be partly explained by there being more tissue available to examine after D&C, allowing a more accurate determination of the percentage of solid pattern, which is important for the assignment of final tumour grade.[24] Outpatient endometrial biopsy presents a fast, easy, and cost-effective method to detect the presence of endometrial cancer, but it might not be accurate in predicting the true tumour grade in the uterus.[8]

Dilation and curettage

Although D&C is used less frequently since the introduction of office endometrial biopsies, it is still the diagnostic method of choice for the evaluation of the endometrium in the following situations:

- Non-diagnostic office biopsy in a high-risk patient when underlying endometrial cancer is suspected
- Benign endometrial biopsy and persistent bleeding
- Insufficient material on the endometrial biopsy with a thickened endometrial lining on ultrasound examination
- Office endometrial biopsy is impossible because of the patient's discomfort and/or anxiety or significant cervical stenosis

Even with a D&C, the entire endometrial cavity is not sampled. In fact, only 60% of the endometrial cavity is investigated.[25,26] The fractional curettage to investigate for cervical involvement is not accurate: the false-positive and false-negative rates are significant at 25% and 10%, respectively.[22]

Hysteroscopy

This method allows direct visualization of the endometrial cavity and endocervical canal with possible directed biopsy of any visualized abnormalities. In patients with persistent uterine bleeding with benign endometrial sampling or insufficient sampling, hysteroscopic examination should be considered. Hysteroscopy is more sensitive for the detection of polyp and other benign endometrial lesions than D&C or endometrial biopsy.[27] However, it is more invasive and costly than office endometrial sampling. The significance of a positive peritoneal cytology after hysteroscopic examination when there are no other associated high-risk pathologic uterine factors, and its effect on survival have not been defined.[28,29]

TRANSVAGINAL ULTRASOUND

Double wall endometrial thickness in the sagittal plane is commonly used to evaluate the endometrium. Endometrial thickness of ≤ 5 mm is associated with a low endometrial cancer risk.[30–32] In two large studies involving 930 and 1138 postmenopausal women who were symptomatic but not taking hormone therapy, using less than 4 mm thickness as normal, the sensitivity was 98% with a range of specificity between 36% to 68% for the detection of endometrial cancer.[23,25,30] Furthermore, an endometrial thickness of less than 5 mm in a symptomatic postmenopausal woman would indicate only a 1% chance of underlying endometrial cancer. Unfortunately, there is no consensus on what normal endometrial thickness is in premenopausal patients or in patients taking hormone therapy.[11] Patients with persistent symptoms need further diagnostic testing of the endometrium. In patients taking tamoxifen, ultrasound may be unreliable. Most studies have found that the endometrium is thicker in the tamoxifen group than in the control group.[11] In a study of 103 asymptomatic patients in which one half were on tamoxifen, Lahti et al. noted that 84% of tamoxifen patients had an endometrium measuring more than 5 mm, but no endometrial cancer was diagnosed on further investigation.[33] Considerably more endometrial polyps were noted in the tamoxifen group.[11] Sub-endometrial vacuoles are frequently observed in patients taking tamoxifen, giving rise to an apparent thickened endometrial stripe.

Management of the asymptomatic postmenopausal patient for whom a thickened endometrium is encountered during an ultrasound, is dealt with in an SOGC guideline.[34]

Infusion sonohysterography

This technique allows better visualization of the irregularities of the endometrial cavity and any anomalies by instilling liquid media into the uterus before ultrasound examination. No specimen is taken for analysis. The procedure can be more uncomfortable than simple transvaginal ultrasound but is usually well tolerated.[35] There is the theoretical risk of spillage of malignant cells into the peritoneal cavity, the significance of which is not clearly understood.[29]

Papanicolaou smear

Papanicolaou smear is not recommended as a primary diagnostic test for endometrial cancer. However, up to 25% of patients with atypical endometrial cells on the Pap smear have a concurrent endometrial carcinoma and should undergo further diagnostic measures.[7] The presence of atypical/neoplastic endometrial cells on the Pap smear in menopausal or perimenopausal patients warrants an endometrial investigation.[7] A positive Pap smear may have a prognostic significance, as reported by Münstedt et al. In their study, patients with positive cytology had a risk of nodal metastasis up to 91% compared with 2% in patients with negative cytology.[8]

Preoperative Evaluation and Staging

Since 1988, FIGO has recommended assigning endometrial cancer stages on the basis of surgical-pathologic factors rather than clinical factors. The exact extent of surgical staging was not clearly defined and remains a subject of major debate. Once a histologic diagnosis of endometrial carcinoma has been made, surgical treatment is often recommended. Since a vast proportion of patients may have existing comorbidities that may distinguish them from a healthier, younger gynaecologic population, an evaluation to ensure surgical fitness, potential for metastatic disease, and perioperative risk should be undertaken At a minimum, preoperative investigations should include the following[3,11]:

- Complete blood count
- Clotting profile
- Serum electrolytes
- Renal panel
- Liver function tests
- Urinalysis
- Chest X-ray
- Electrocardiogram

Imaging studies such as a CT scan are not routinely recommended in the evaluation of most endometrial cancer patients since they rarely alter treatment recommendations, are not cost effective, and could potentially delay definitive surgical treatment.[3] However, they could be useful in the further preoperative workup of papillary serous tumours or more aggressive histologic types such as uterine sarcoma.[36] Contrast-enhanced MRI can also be helpful in assessment if locoregional extension in the pelvis is clinically suspected.[3] Contrast-enhanced MRI has been shown to be more accurate in assessing the extent of myometrial and cervical invasion than ultrasonography, CT, or non-enhanced MRI.[37] Its accuracy is about 91%.[38] MRI could identify patients who are at highest risk for metastatic disease and who would need more radical surgeries and surgical nodal evaluations.[36,39]

Extensive gastrointestinal investigations are not needed unless there are clinical signs and symptoms suggestive of

bowel involvement.[11] Liver, brain, or bone scans should be ordered only in accordance with clinical suspicion of extensive disease involvement.

The need for preoperative review of all endometrial biopsies in tertiary care centres has been debated in the literature. Santoso et al. reported a 2% major discrepancy rate that can alter treatment recommendation. The cost for diagnosing a case of discrepancy was estimated at US$7200.[40] Cost effectiveness must not be the only consideration in determining whether all pathology should be reviewed preoperatively by gynaecologic pathologists. At present, no study has examined the effect of treatment delays resulting from mandatory slide review, which can take up to several weeks in most Canadian centres.

Elevated CA-125 level has been associated with a higher chance of extrauterine involvement and a shorter survival.[4,41] CA-125 elevation can correlate with tumour size and stage at presentation. Hsieh et al. concluded that a CA-125 level > 40 U/mL should prompt a full nodal dissection in patients with endometrial cancer (sensitivity 77.8%, specificity 81.1%).[8,42] Other tumour markers have been studied in combination with CA-125, but no recommendations can be made thus far.[43,44] The role of CA-125 in identifying patients at high risk needs further study but could be a marker for triaging patients especially in the postmenopausal age group.

CONCLUSION

Perimenopausal and/or postmenopausal bleeding should be thoroughly investigated because of the significant underlying risk of endometrial adenocarcinoma. Initial investigation with transvaginal ultrasound appears to be adequate to determine needs for further investigations. Endometrial hyperplasia and adenocarcinoma are pathologic diagnoses that can be made only through endometrial tissue sampling. Office endometrial biopsy appears to be an adequate diagnostic modality in the majority of patients.

Once a diagnosis of endometrial carcinoma has been made, patients should be evaluated for fitness to undergo surgical treatment. Routine CT scans, MRI, and tumour markers are not necessary in all patients, but in specific clinical situations such as high-grade tumours, or clinical suspicion of extrauterine spread, they may help to triage patients to tertiary centres for consideration of aggressive surgical debulking or extended surgical staging.

Recommendations

1. A complete focused history should be taken and a physical examination carried out in patients with suspected endometrial cancer. Attention should be paid to predisposing factors for excess estrogen stimulation of the endometrium such as long history of anovulation, obesity, menstrual irregularity, or long-term use of unopposed estrogen or tamoxifen. Patients with a strong family history of endometrial, ovarian, and colorectal cancers might have inherited Lynch syndrome (hereditary non-polyposis colorectal cancer syndrome) that increases their lifetime risk of developing endometrial cancer. Genetic counselling and testing can be used to individualize risk-management interventions including screening strategies and treatment options. (III-B)
2. Endometrial cancer should be ruled out in perimenopausal and postmenopausal patients with abnormal vaginal bleeding. (II-1A)
3. Depending on access, histologic endometrial evaluation and transvaginal ultrasound are the preferred initial diagnostic investigations for patients with suspected endometrial cancer. (II-1B)
4. Histologic evaluation of the endometrium should be done in all patients in whom endometrial cancer is suspected. (II-1A)
5. Hysteroscopic examination should be considered in patients with persistent uterine bleeding with benign endometrial sampling or insufficient endometrial sampling after ultrasound. (II-2B)
6. Formal review of the histopathology should be considered in patients with high grade tumours or rare histologic types such as serous, clear cell, or mucinous types. (III-B)
7. Additional tumour markers, CT scan, and MRI scan should not be used routinely. (IIID)

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