Endometrial Cancer Screening and Diagnosis

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers endometrial biopsy (sampling) medically necessary for histological tissue examination in the diagnostic evaluation of abnormal uterine bleeding in women suspected of having endometrial hyperplasia or endometrial carcinoma; and for endometrial cancer surveillance in women with Lynch syndrome.

Aetna considers the endometrial brush (Tao brush) an acceptable alternative to an endometrial suction curette (e.g., Pipelle) for medically necessary endometrial sampling.

Aetna considers sentinel lymph node mapping medically necessary for pathologic evaluation and surgical staging in persons with endometrial cancer.

Aetna considers the following experimental and investigational because the effectiveness of these approaches has not been established:

- Circulating adiponectin, leptin, and adiponectin-leptin ratio as biomarkers for the prevention, early diagnosis and disease monitoring of endometrial cancer
- Determination of circular RNAs expression for diagnosis of grade-3 endometrial cancer
- DNA methylation for diagnosis of sporadic endometrial cancer
- Endometrial biopsy (sampling) for the screening of endometrial cancer

www.aetna.com/cpb/medical/data/700_799/0769.html
Endometrial or cervical cytology performed in conjunction with endometrial histology (TruTest(TM), Gynecor(TM), Glen Allen, VA) in the diagnostic evaluation of abnormal uterine bleeding in women suspected of having endometrial hyperplasia or endometrial carcinoma

- FTO rs9939609 and HSD17B1 rs605059 gene polymorphism testing for the diagnosis of endometrial cancer
- Immunohistochemistry for protein phosphatase and tensin homolog (PTEN) for differential diagnosis of benign and pre-malignant endometrial hyperplasia
- Measurement of (i) circulating YKL-40, (ii) serum human epididymis protein 4 (HE4), and (iii) urine microRNAs for diagnosis of endometrial cancer
- Measurement of endometrial thickness as a screening test for endometrial carcinoma in asymptomatic post-menopausal women not using hormone replacement therapy
- Measurement of neutrophil gelatinase-associated lipocalin level for the diagnosis of endometrial cancer
- Measurements of telomeres and telomerase activity for the diagnosis and/or screening of endometrial cancer.

See also
CPB 0433 - Chlamydia Trachomatis - Screening and Diagnosis (../400_499/0433.html),
CPB 0443 - Cervical Cancer Screening and Diagnosis, (../400_499/0443.html) and
CPB 0530 - Transvaginal Ultrasonography (../500_599/0530.html).

Background

The National Cancer Institute (NCI, 2008) has stated that there is insufficient evidence to establish whether a decrease in mortality from endometrial cancer occurs with screening by endometrial sampling. The NCI notes that based on solid evidence, endometrial biopsy (sampling) may result in discomfort, bleeding, infection, and in rare cases uterine perforation. In addition, risks associated with false-positive test results include anxiety and additional diagnostic testing and surgery. Furthermore, endometrial cancers may be missed on endometrial sampling.

Endometrial sampling by means of biopsy for histological examination in the diagnostic evaluation of abnormal uterine bleeding in women suspected of having endometrial hyperplasia or endometrial carcinoma is a minimally invasive alternative for dilatation and curettage (D&C) or hysteroscopy. The Pipelle endometrial sampling device is the most popular method for sampling the endometrial lining (Guido, 2008). Various types of brushes have also been used for endometrial sampling. Although the brush appears to be as effective or better than other blind
methods of endometrial sampling, these devices have been evaluated in only a few studies with small numbers of subjects (Tao, 1995; Tao, 1997; Critchley et al, 2004; Yang et al, 2002; Del Priore et al, 2001; Yang and Wan, 2000; Maksem et al, 2000). In one of the larger comparative trials, 101 women (aged 35 to 86 years) with clinical indications for endometrial biopsy underwent a brush biopsy (Tao Brush, Cook OB-GYN, Bloomington, IN) and a Pipelle biopsy (Cooper Surgical, Shelton, CT) during 1 office visit. Twenty-two had cancer or atypia, the others had benign diagnoses. When correlated with the final diagnosis, sensitivity for the Tao Brush and Pipelle were 95.5 % and 86 %, respectively, and specificity was 100 % for both (Del Priore et al, 2001).

According to the company's website (Gynecor™, Glen Allen, VA), the TruTest™ for total uterine testing is the first test that is able to detect endometrial and cervical cancer, HPV, chlamydia and gonorrhea from the same specimen. Using the Tao Brush, a sampling of the uterine lining is taken and the brush is sent to Gynecor™ for both histology and cytology examination. The testing kit provided by Gynecor has 1 Tao Brush (used for the collection of endometrial tissue) and 2 cytobrushes (one is used to clean mucus and debris from the cervix and the second is used for enhanced cell and tissue collection from the squamo-columnar junction of the uterine cervix). The Tao Brush is an Food and Drug Administration Class II device.

The use of histology for endometrial examination depends on having enough tissue to yield an accurate test result. However, a tissue specimen is sometimes hard to collect, especially in postmenopausal women. Gynecor fixative can be used for both histology and cytology. According to Gynecore's website, "Cytologies are very important because they add about 20 % more information than is obtained with just the histology. Using this method, Gynecor has been able to diagnose ovarian carcinoma in transit, endometrial intraepithelial neoplasia and endometrial intraepithelial carcinoma."

In a feasibility study, Maksem et al (1997) compared the cytologic diagnosis to the histologic diagnosis of endometrium collected from 100 hysterectomy specimens using the Tao Brush and the CytoRich fixative system. Interpretative algorithms that translate histopathologic to cytopathologic diagnoses were used. The authors reported that cytology separated benign endometrium, low-grade (non-atypical) hyperplasia, high-grade (atypical) hyperplasia/FIGO Grade I adenocarcinoma, and higher-grade carcinomas from one another. Endometrial atrophy was diagnosed in 3 patients whose histology showed clinically asymptomatic, benign fibrous endometrial polyps. A low volume of abnormal cell aggregates interpreted as endometrial intraepithelial carcinoma was detected in 1 patient whose initial histology was reported as simple hyperplasia, but whose histology on review after p53 staining revealed intraepithelial surface cancer. In the remaining 96 cases, the cytologic diagnosis consistently represented the histologic diagnosis of the hysterectomy specimen. On a case-by-case basis, any one cytology
slide accurately represented the diagnosis of the other cytology slides. The authors concluded that endometrial brushing with suspension fixation is (i) uniform, (ii) 3-dimensional structures among cell aggregates are preserved, which allows pattern-based histologic diagnostic criteria to be applied to cytologic samples, and (iii) only a limited number of slides need to be examined.

Maksem (1998) also reported on a case of ciliated endometrioid adenocarcinoma of the endometrium, diagnosed by endometrial brush biopsy and confirmed by histology.

In a subsequent paper, Maksem et al (1999) reported on 7 women where liquid-fixed Tao brush cytological samples of the endometrium showing "small amounts of atypical epithelium with cancer-like nuclei" were found after hysterectomy to be associated with a variety of diagnoses, including 3 women with hyperplastic polyps with focal atypical complex hyperplasia, 1 woman with hyperplastic polyps with focal atypical simple hyperplasia, 1 woman with endometrial microcarcinoma, 1 woman with p-53 positive endometrial intraepithelial carcinoma, and 1 with endometrial intraepithelial neoplasia.

Maksem (2000) reported performance characteristics of the ability of the Tao Brush in recognizing histological patterns in cytology preparations of endometrial brushings (n = 113). Correlative tissue examinations comprising Pipelle (Prodimed, Neuilly-en-Thelle, France) biopsy, hysteroscopy and biopsy, D&C, and hysterectomy were available at for 59 cases. In 42 cases, cytology diagnoses could be compared to histology diagnoses. Twenty-five of 63 normal brushings were followed-up; 14 were normal. Eleven Pipelle biopsies of cytologically atrophic endometrium were quantitatively limited and insufficient for diagnosis. Thirty-seven cases were abnormal, and 15 of these showed nuclear anaplasia. Twenty-eight of the abnormal cases were followed up. All correlative tissue examinations confirmed an abnormality. All 15 cases with nuclear anaplasia showed significant histopathology comprising atypical endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN), endometrial intraepithelial carcinoma (EIC), and invasive adenocarcinoma. There were 13 inadequate endometrial brushings. Three cases had insufficient cellular material. The remaining 10 cases were cellular but were mainly cervical/endo-cervical samples. Two of the cellular cases resulted from clinicians failing to replace the protective sheath over the brush bristles before removing the Tao Brush from the endometrial cavity. The remaining 11 cases resulted from inaccessibility of the uterine cavity due to a tight or stenotic cervix. The author concluded that (i) the Tao brush is a reliable uterine sampling device for outpatient assessment of the endometrium of women with patent cervices, (ii) endometrial cytology accurately represents atrophic endometrium, (iii) it is an effective case-finding tool for EIN and EIC, and (iv) women with tight or stenotic cervices are
poor candidates for endometrial brushing, and may experience pain if the procedure is attempted.

Van den Bosch et al (1998) evaluated the value of cervical cytology in menopausal women at high risk for endometrial disease in 128 consecutive menopausal women presenting with uterine bleeding (n = 116) or in whom endometrial cells were found on a previous cervical cytology smear (n = 12). An endo- and ecto-cervical smear was taken before hysteroscopy with curettage and the results of the cervical cytology were compared with the endometrial histology. Endometrial carcinoma was diagnosed by endometrial sampling in 6 women. In 2 of these cases cervical smears did not contain endometrial cells. The presence of endometrial cells on ecto-cervical cytology showed a sensitivity of 67 % and a specificity of 78 % for endometrial carcinoma versus 80 % and 76 %, respectively, for endo-cervical cytology. The positive predictive value for endometrial malignancy of the presence of endometrial cells on cervical cytology ranged between 13 % and 17 %. The presence of atypical endometrial cells on cervical smear was associated with endometrial malignancy in almost half the cases. The authors concluded that cervical cytology is of limited value in the diagnosis and the management of post-menopausal endometrial disease.

Dijkhuizen et al (2000) performed a meta-analysis to assess the accuracy of endometrial sampling devices in the detection of endometrial carcinoma and atypical hyperplasia. The authors searched the literature for studies published between 1966 and 1999 that compared the results of endometrial sampling with findings at D&C, hysteroscopy, and/or hysterectomy. They found 39 studies that included 7,914 women. For each study, the number of patients in which endometrial sampling failed as well as the sensitivity and specificity for the detection of endometrial carcinoma and atypical hyperplasia was calculated. The detection rate for endometrial carcinoma was higher in post-menopausal women compared with pre-menopausal women. In both post-menopausal and pre-menopausal women, the Pipelle was the best device, with detection rates of 99.6 % and 91 %, respectively. For the detection of atypical hyperplasia, there was only one study that reported explicitly on post-menopausal women, thereby hampering the possibility of subgroup analysis. Again, the Pipelle was the most sensitive technique with a sensitivity of 81 %. The specificity of all devices was greater than 98 %. The authors concluded that endometrial biopsy with the Pipelle is superior to other endometrial techniques in the detection of endometrial carcinoma and atypical hyperplasia. The accuracy of the Pipelle is higher in post-menopausal women compared with pre-menopausal women.

In a case series on the use of the Tao Brush for endometrial biopsy, Wu et al (2003) reported that the sensitivity and specificity in identifying endometrial cancer was 100 % and 96 %; however, diagnosis relied mainly on histologic evaluation of hematoxylin and eosin-stained tissue sections.
and assessment of specimen adequacy was important when interpreting Tao Brush biopsies.

In an unblinded randomized trial, Critchley et al (2004) compared 3 outpatient methods of endometrial evaluation in terms of performance, patient acceptability and cost-effectiveness. Women referred for investigation and management of abnormal bleeding between January 1999 and May 2001 were evaluated using blind biopsy alone, hysteroscopy with biopsy, ultrasound evaluation including transvaginal ultrasound, and, in the low-risk group, the option of no investigation. Within this design, 2 devices for obtaining endometrial biopsy were compared, the Pipelle sampler and the Tao Brush. Minor adverse events (e.g., shock, patient distress) did not occur for ultrasound, but occurred in 16 % and 10 % of women for hysteroscopy and biopsy procedures respectively. Pipelle biopsy provided an acceptable endometrial sample for 79 % of moderate-risk women, but only 43 % of high-risk women. The Tao Brush gave similar performance in moderate-risk women (77 %), but was more successful than the Pipelle sampler in post-menopausal (high-risk) women (72 %).

To determine the performance characteristics of endometrial cytology for the detection of malignancy and atypical hyperplasia using liquid-based cytology specimens collected with the Tao Brush sampler, Kipp et al (2008) obtained brushings of the endometrial cavity from 139 hysterectomy specimens before routine histopathologic evaluation. Cytology specimens were fixed in PreservCyt and processed using ThinPrep technology. Cytology diagnoses were classified as non-diagnostic, negative, atypical, or positive for malignancy. Histopathologic findings were used as the gold standard for determining the performance characteristics of cytology. Histopathologic results from the 139 patients included 81 (58 %) endometrial cancers, 7 (5 %) complex hyperplasias with atypia, 2 (1 %) complex hyperplasias without atypia, and 49 (35 %) patients with benign histology. The number of specimens diagnosed cytologically as positive, atypical, negative, or non-diagnostic was 60 (43 %), 40 (29 %), 37 (27 %), and 2 (1 %), respectively. The overall sensitivity and specificity of cytology for detecting endometrial cancer and atypical hyperplasia were 95 % and 66 % when atypical cytology specimens were considered positive. The authors concluded that direct endometrial sampling by liquid-based endometrial cytology collected with the Tao Brush sampler produces specimens that contain cellular material that may be identified as endometrial cancer or atypical hyperplasia; however, both atypical and positive cytology diagnoses are indicators for triage to more specific methods of diagnosis.

Williams et al (2008) evaluated factors affecting the adequacy of pipelle and Tao Brush endometrial sampling. Women referred to an outpatient clinical for assessment of abnormal vaginal bleeding (n = 200) were assigned to one of two risk groups: "high risk" for post-menopausal women and "moderate risk" for pre-menopausal women aged 40 years or older or with other risk factors. Women in each risk group had both Tao Brush and Pipelle biopsy and
were then randomized to have either hysteroscopy and/or transvaginal ultrasound. Nulliparity was associated with failed insertion for both the Tao Brush and Pipelle (p < 0.001). Among post-menopausal women, inadequate samples were associated with the Pipelle (p < 0.001). Among pre-menopausal women with nulliparity, both the Tao Brush and Pipelle were associated with inadequate samples (p < 0.001). A significantly greater proportion of women preferred the Tao Brush to the Pipelle.

Outpatient endometrial biopsy has a high overall accuracy in diagnosing endometrial cancer when an adequate specimen is obtained. A positive test result is more accurate for ruling in disease than a negative test result is for ruling it out. Therefore, in cases of abnormal uterine bleeding where symptoms persist despite negative biopsy, further evaluation will be warranted (Clark et al, 2002). If the woman is post-menopausal and bleeding has not been persistent; a thin endometrial stripe in this setting is most consistent with atrophy and does not require further invasive studies. A thick endometrial stripe, persistent bleeding, or bleeding in a post- or peri-menopausal woman should be followed by additional endometrial sampling, such as hysteroscopy with curettage. In asymptomatic post-menopausal women, the decision to biopsy is also based upon a variety of factors, including cervical cytology showing endometrial cells or glandular abnormality, and risk factors for endometrial cancer, such as unopposed estrogen and tamoxifen use. In a completely asymptomatic post-menopausal woman with no risk factors and an endometrial stripe less than 5 mm, there is no need for biopsy. However, even one drop of blood in a post-menopausal woman not on hormone therapy constitutes a symptom and is an indication for biopsy.

Current evidence-based guidelines from leading medical professional organizations include no recommendation for endometrial or cervical cytology performed in conjunction with endometrial histology (Gynecor TruTest) in the diagnostic evaluation of abnormal uterine bleeding in women suspected of having endometrial hyperplasia or endometrial carcinoma. There is insufficient evidence to support this approach.

Endometrial surveillance is medically necessary in women with Lynch syndrome. Meyer et al (2009) stated that about 2 to 5% of endometrial cancers may be due to an inherited susceptibility. Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC) syndrome, is an autosomal-dominant inherited cancer susceptibility syndrome. It is caused by a germline mutation in one of the DNA mismatch repair genes, and accounts for the majority of inherited cases. Lynch syndrome is associated with early onset of cancer and the development of multiple cancer types, especially colon and endometrial cancer. The lifetime cumulative risk of endometrial cancer for women with Lynch syndrome is 40 to 60%, which equals or exceeds their risk of colorectal cancer. No current evidence suggests either a survival advantage or disadvantage to endometrial cancer that is associated with Lynch syndrome when
these cases are compared with sporadic cases. A combination of family and personal medical history and tumor testing provides an efficient basis for diagnosing Lynch syndrome in women with endometrial cancer. The authors noted that current gynecologic cancer screening guidelines for women with Lynch syndrome include annual endometrial sampling and transvaginal ultrasonography (TVUS) beginning at age of 30 to 35 years (Lindor et al, 2006).

Gerritzen et al (2009) evaluated the effectiveness of gynecological surveillance with regard to endometrial and ovarian carcinoma. Included were women from families that fulfilled the revised Amsterdam criteria for HNPCC or who showed a proven mutation in one of the mismatch repair genes. An annual gynecological surveillance was performed (TVUS and cancer antigen 125 (CA-125) assessment). A total of 285 surveillance visits (100 women) were performed. Among these, in 64 visits routine endometrial samplings were carried out: 3 atypical hyperplasias and 1 endometrial carcinoma were diagnosed. This was significantly more than the atypical hyperplasia and 2 endometrial carcinomas that were detected after 28 samples performed because of abnormal surveillance results in 221 visits. There were no interval carcinomas. One invasive ovarian carcinoma stage IIIC was diagnosed at ovarian surveillance. Endometrial surveillance with routine endometrial sampling in women with HNPCC is more efficient in diagnosing endometrial pre-malignancies than TVUS only. Ovarian surveillance is not capable of diagnosing early stage ovarian carcinoma. Prophylactic hysterectomy in HNPCC should be restricted to women in whom abdominal surgery for other reasons is performed and to those with particularly increased risk such as MSH6 mutation carriers and/or women with multiple relatives with endometrial carcinoma.

The American Cancer Society (2011) recommends that all women should be informed about the risks and symptoms of endometrial cancer, and strongly encouraged to report any unexpected bleeding or spotting to their doctors. For women with or at high-risk for hereditary non-polyposis colon cancer (HNPCC, Lynch syndrome), annual screening should be offered for endometrial cancer with endometrial biopsy beginning at age 35.

Robison and colleagues (2011) noted that sentinel lymph node (SLN) dissections have been shown to be sensitive for the evaluation of nodal basins for metastatic disease and are associated with decreased short-term and long-term morbidity when compared with complete lymph node dissection. There has been increasing interest in the use of SLN technology in gynecologic cancers. These investigators evaluated the current evidence-based literature for the use of SLN dissections in gynecologic malignancies. Recent literature continues to support the safety and feasibility of SLN biopsy for early stage vulvar cancer with negative-predictive value approaching 100% and low false-negative rates. Alternatively, for endometrial cancer most studies have reported low false-negative rates, with variable sensitivities and have reported low detection rates of the sentinel node. Studies examining the utility of SLN biopsy in early-stage
cervical cancer remain promising with detection rates, sensitivities, and false-negative rates greater than 90% for stage 1B1 tumors. The authors concluded that SLN dissections have been shown to be effective and safe in certain, select vulvar cancer patients and can be considered an alternative surgical approach for these patients. For endometrial and cervical cancer, SLN dissection continues to have encouraging results and however needs further investigation.

Kang and associates (2011) stated that the validity of the SLN biopsy for the assessment of nodal status in patients with endometrial cancer is unclear. These investigators evaluated the diagnostic performance of this procedure. They searched the PubMed and Embase databases for studies published before June 1, 2011. Eligible studies had a sample size of at least 10 patients, and reported the detection rate and/or sensitivity of the SLN biopsy. These researchers identified 26 eligible studies, which included 1,101 SLN procedures. The overall weighted-mean number of harvested SLNs was 2.6. The detection rate and the sensitivity were 78% (95% confidence interval [CI]: 73% to 84%) and 93% (95% CI: 87% to 100%), respectively. Significant between-study heterogeneity was observed in the analysis of the detection rate (I-squared statistic, 80%). The use of peri-cervical injection was correlated with the increase of the detection rate (p = 0.031). The hysteroscopic injection technique was associated with the decrease of the detection rate (p = 0.045) and the subserosal injection technique was associated with the decrease of the sensitivity (p = 0.049), if they were not combined with other injection techniques. For the detection rate, significant small-study effects were noted (p < 0.001). The authors concluded that although SLN biopsy has shown good diagnostic performance in endometrial cancer, such performance should be interpreted with caution because of significant small study effects. They stated that current evidence is not yet sufficient to establish the true performance of SLN biopsy in endometrial cancer.

An UpToDate review on "Endometrial carcinoma: Pretreatment evaluation, staging and surgical treatment" (Plaxe, 2012) states that "Sentinel lymph node biopsy for endometrial carcinoma is still investigational". Furthermore, the National Comprehensive Cancer Network's clinical practice guideline on "Uterine Neoplasms" (NCCN, 2012) does not mention the use of SLN biopsy as a diagnostic tool.

Robova et al (2013) stated that the prognosis of endometrial cancer (EC) is generally favorable, while lymph node status remains the most important prognostic factor. Sentinel lymph node mapping (SLNM) could help to find women in whom adjuvant therapy could be omitted. These investigators analyzed different techniques of injection and histopathologic elaboration of SLNM in EC. Results of studies on SLNM in ECs seem to be promising, but only a small series have been published so far. The studies were subdivided into 3 groups by the technique of injection: (i) hysteroscopic, (ii) subserosal, and (iii) cervical. Range of detection rate for SLNM varies
from 45 % to 100 %. Hysteroscopic injection is not easy to learn; moreover, exact peri-tumoral
injection in large tumors is often impossible. Subserosal administration of tracer is difficult during
laparoscopic or robotic surgery. Cervical injection is quite a controversial technique because
distribution of SLNs in ECs is different from cervical cancer; moreover, there is no large study
using cervical injection with systematic pelvic and para-aortic lymphadenectomy.

Breijer et al (2012) noted that measurement of endometrial thickness is an important tool in the
assessment of women with post-menopausal bleeding, but the role of endometrial thickness
measurement by ultrasound in asymptomatic women is unclear. These researchers determined:
(i) the normal endometrial thickness measured by ultrasonography, (ii) the prevalence of
serious endometrial pathology, and (iii) the sensitivity and specificity of endometrial
thickness measurement by trans-vaginal ultrasonography (TVUS) for diagnosing pre-
malignant and malignant endometrial disease in asymptomatic post-menopausal women.
A Medline and Embase search (from inception to January 2011) was performed. Articles
reporting on endometrial thickness measurement in the diagnosis of endometrial carcinoma and
atypical hyperplasia in asymptomatic post-menopausal women not using hormone replacement
therapy (HRT) were selected. Endometrial thickness and the prevalence of endometrial
(pre)malignancies were recorded. If possible, 2 × 2 tables were extracted. A total of 32 studies
reporting on 11,100 women were included. The estimated mean endometrial thickness was 2.9
mm (95 % CI: 2.6 to 3.3 mm). The pooled estimated prevalences of endometrial carcinoma and
atypical endometrial hyperplasia were 0.62 % (95 % CI: 0.42 to 0.82 %) and 0.59 % (95 % CI:
0.22 to 0.96 %), respectively. Summary estimates for sensitivity and specificity of TVUS
endometrial thickness measurement in the prediction of endometrial carcinoma were 0.83 (95 %
CI: 0.19 to 1.00) and 0.72 (95 % CI: 0.23 to 0.95) for a 5-mm cut-off and 0.33 (95 % CI: 0.04 to
0.85) and 0.94 (95 % CI: 0.92 to 0.96) for a 6-mm cut-off. The authors concluded that the
findings from this systematic review did not justify the use of endometrial thickness as a
screening test for endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic
post-menopausal women not using HRT.

Godoy and colleagues (2013) evaluated the accuracy of sonographic endometrial thickness and
hysteroscopic characteristics in predicting malignancy in post-menopausal women undergoing
surgical resection of endometrial polyps. A total of 521 post-menopausal women undergoing
hysteroscopic resection of endometrial polyps between January 1998 and December 2008 were
studied. For each value of sonographic endometrial thickness and polyp size on hysteroscopy,
the sensitivity, specificity, positive-predictive value (PPV) and negative-predictive value (NPV)
were calculated in relation to the histologic diagnosis of malignancy. The best values of
sensitivity and specificity for the diagnosis of malignancy were determined by the Receiver
Operating Characteristic (ROC) curve. Histologic diagnosis identified the presence of pre-
malignancy or malignancy in 4.1 % of cases. Sonographic measurement revealed a greater endometrial thickness in cases of malignant polyps when compared to benign and pre-malignant polyps. On surgical hysteroscopy, malignant endometrial polyps were also larger. An endometrial thickness of 13 mm showed a sensitivity of 69.6 %, specificity of 68.5 %, PPV of 9.3 %, and NPV of 98 % in predicting malignancy in endometrial polyps. Polyp measurement by hysteroscopy showed that for polyps 30-mm in size, the sensitivity was 47.8 %, specificity was 66.1 %, PPV was 6.1 %, and NPV was 96.5 % for predicting cancer. The authors concluded that sonographic endometrial thickness showed a higher level of accuracy than hysteroscopic measurement in predicting malignancy in endometrial polyps. Despite this, both techniques showed low accuracy for predicting malignancy in endometrial polyps in post-menopausal women. In suspected cases, histologic evaluation is necessary to exclude malignancy.

Cavkaytar et al (2014) evaluated the role of sonographic endometrial thickness and hysteroscopic polyp size in predicting pre-malignant and malignant polyps in post-menopausal women. A total of 328 post-menopausal women with abnormal uterine bleeding and thickened endometrium underwent operative hysteroscopy due to detection of endometrial polyps were included in this retrospective study. Pre-operative endometrial thickness measured by transvaginal ultrasonography and polyp size on hysteroscopy were noted. Hysteroscopic resection with histology was performed for endometrial polyps. Endometrial thickness and polyp size were evaluated on the basis of final diagnosis established by histologic examination. Receiver operator characteristic curves were calculated to assess the sensitivity, specificity, PPV, NPV and diagnostic accuracy of endometrial thickness and polyp size for detecting pre-malignant and malignant polyps. Pre-malignant and malignant polyps were identified in 26 (7.9 %) of cases. Sonographic measurement showed a greater endometrial thickness in cases of pre-malignant and malignant polyps when compared to benign polyps. On surgical hysteroscopy, pre-malignant and malignant polyps were also larger. Endometrial thickness demonstrated a sensitivity of 53.8 %, specificity of 85.8 %, PPV of 24.6 % and NPV of 95.6 % at a cut-off limit of 11.5 mm with diagnostic accuracy of 83.2 %. Polyp size has a diagnostic accuracy of 94.8 % with a sensitivity of 92.3 %, specificity of 95.0 %, PPV of 61.5 % and NPV of 99.3 % at a cut-off point of 19.5 mm. The authors concluded that endometrial thickness measured by transvaginal ultrasonography is not sufficient in predicting pre-malignant and malignant endometrial polyps in post-menopausal women with abnormal uterine bleeding and thickened endometrium. Polyp size on hysteroscopy is a more accurate parameter, because of better sensitivity and specificity. However, while polyp size greater than or equal to 19.5 mm seems to have a great accuracy for predicting pre-malignancy and malignancy, histologic evaluation is still necessary to exclude pre-malignant and malignant polyps.
Ansari and colleagues (2013) stated that sentinel lymph node biopsy is a fairly new approach for staging of gynecological malignancies. In the current study, these researchers comprehensively reviewed the available reports on sentinel node biopsy of EC. They searched Medline, SCOPUS, ISI web of knowledge, Science Direct, Springer, OVID SP, and Google Scholar with the following search terms: "endometrium or endometrial or uterine or uterus and sentinel". The outcomes of interest were detection rate and sensitivity. Overall, a total of 35 studies had enough information for false-negative rate evaluation and 51 studies (including the sub-groups of individual studies) for detection rate evaluation (2,071 patients overall). Pooled detection rate was 77.8 % (95 % CI: 73.5 to 81.5 %) and pooled sensitivity was 89 % (95 % CI: 83 to 93 %). Cervical injection, as well as using both blue dye and radiotracer, results in higher detection rate and sensitivity. New techniques such as fluorescent dye injection and robotic-assisted surgery showed high detection rate and sensitivity. The authors concluded that sentinel node mapping is feasible in EC. Using both blue dye and radiotracer and cervical injection of the mapping material can optimize the sensitivity and detection rate of this technique. Moreover, they stated that larger studies are still needed to evaluate the false negative rate and the factors influencing the sensitivity before considering this method safe.

Furthermore, an UpToDate review on “Endometrial carcinoma: Pretreatment evaluation, staging, and surgical treatment” (Plaxe, 2014) states that “Sentinel lymph node biopsy for endometrial carcinoma is still investigational. A meta-analysis of 26 studies including 1,101 sentinel node procedures found a sensitivity of 93 percent for the detection of lymph node metastases in women with endometrial carcinoma …. There is no consensus about the best surgical approach (open or laparoscopic) for sentinel lymph node biopsy or the utility of preoperative imaging. Further study is required to evaluate whether sentinel lymph node biopsy is clinically useful and, if so, the optimal site for tracer injection and the accuracy of lymphatic mapping in endometrial carcinoma”.

Circulating YKL-40

Cheng and colleagues (2014) stated that in the past 10 years, several studies have suggested a possible link between circulating YKL-40 levels and EC, but have arrived at inconsistent results. These researchers performed a meta-analysis and disclosed a more comprehensive evaluation of the sensitivity, specificity, and diagnostic accuracy of YKL-40 in EC. The authors systematically searched PubMed, Embase, Web of Science, Science Direct, SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure databases for studies that evaluated the diagnostic value of YKL-40 in endometrial cancer. The STATA software 12.0 and Meta-Disc software were used to test the heterogeneity and to evaluate the overall test performance. A total of 7 studies including 234 EC cases and 300 controls were included in the meta-analysis. The summary estimates of YKL-40 for EC diagnosis indicated a moderately high
diagnostic accuracy for circulating YKL-40, with a sensitivity of 0.74, a specificity of 0.87, a positive likelihood ratio (PLR) of 5.74, a negative likelihood ratio (NLR) of 0.30, a diagnostic odds ratio (DOR) of 19.14, and an area under the ROC curve (AUC) of 0.80. The authors concluded that circulating YKL-40 could be promising and meaningful in the diagnosis of EC.

National Comprehensive Cancer Network’s clinical practice guideline on “Uterine neoplasms” (Version 2.2015) does not mention circulating YKL-40 for the diagnosis of EC.

Serum Human Epididymis Protein 4 (HE4)

In a meta-analysis, Bie and Zhang (2014) evaluated the clinical value of serum human epididymis protein 4 (HE4) in the diagnosis of EC. These researchers used MEDLINE, EMBASE, Cochrane Library and CBM databases to search the literature. The meta-analysis was performed by using Meta-Disc 1.4 software. All data showed that the major advantage of HE4 lies in its specificity in EC diagnosis. Its sensitivity in serum was not as high as expected; but this evidence was not enough. The authors concluded that additional studies, particularly to evaluate HE4’s capability in identifying EC at an early stage, are needed.

In a prospective study, Minar et al (2015) evaluated the use of HE4 and CA-125 biomarkers in differential diagnosis of malignant and benign endometrial tumors in a population of Czech women. This study included 115 patients with endometrioid adenocarcinoma and 106 patients with benign endometrial tumors in the control group. They were diagnosed with endometrial biopsy in the period from 7/2010 to 6/2013. The patients with cancer underwent definitive surgical treatment to determine the stage of disease. The median and ranges of serum levels were determined in relation to the histological result (benign versus malignant disease). While analyzing 2 groups of patients with different histology, there was demonstrated a statistically significant difference (p < 0.05), only in HE4, by cut-off 48.5 pmol/L there was achieved sensitivity of 87.8 %, specificity of 56.6 % and NPV of 81.1 %. The authors concluded that diagnostic benefit of HE4 can be considered especially in patients with increased risk of endometrial cancer and in patients with serious internal co-morbidities. They stated that HE4 could help in combination with clinical and ultrasound finding in the differentiation of prognostically various groups of patients and in decision-making in relation to the individualization of the treatment plan. However, they stated that the optimal cut-off for HE4 has not been solved yet, and to do so, it will require more research with larger studies and their comparative analysis.

National Comprehensive Cancer Network’s clinical practice guideline on “Uterine neoplasms” (Version 2.2015) does not mention serum human epididymis protein 4 (HE4) for the diagnosis of EC.
Urine MicroRNAs Expression

Zavesky et al (2015) stated that among gynecological cancers, epithelial ovarian cancers are the most deadly cancers while endometrial cancers are the most common diseases. Efforts to establish relevant novel diagnostic, screening and prognostic markers are aimed to help reduce the high level of mortality, chemo-resistance and recurrence, particularly in ovarian cancer. MicroRNAs, the class of post-transcriptional regulators, have emerged as the promising diagnostic and prognostic markers associated with various diseased states recently. Urine has been shown as the source of microRNAs several years ago; however, there has been lack of information on urine microRNA expression in ovarian and endometrial cancers till now. In this pilot study, these researchers examined the expression of candidate cell-free urine microRNAs in ovarian cancer and endometrial cancer patients using quantitative real-time PCR. They compared the expression between pre- and post-surgery ovarian cancer samples, and between patients with ovarian and endometrial cancers and healthy controls, within 3 types of experiments. These experiments evaluated 3 different isolation methods of urine RNA, representing 2 supernatant and 1 exosome fractions of extracellular microRNA. In ovarian cancer, these investigators found miR-92a significantly up-regulated, and miR-106b significantly down-regulated in comparison with control samples. In endometrial cancer, only miR-106b was found down-regulated significantly compared to control samples. Using exosome RNA, no significant de-regulations in microRNAs expression could be found in either of the cancers investigated. The authors proposed that more research should now focus on confirming the diagnostic potential of urine microRNAs in gynecological cancers using more clinical samples and large-scale expression profiling methods.

National Comprehensive Cancer Network’s clinical practice guideline on “Uterine neoplasms” (Version 2.2015) does not mention microRNAs expression for the diagnosis of EC.

Giglio et al (2019) noted that endometrial cancer is the most common gynecologic malignancy in developed countries. Estrogen-dependent tumors (type I, endometrioid) account for 80% of cases and non-estrogen-dependent (type II, non-endometrioid) account for the rest. Endometrial cancer type I is generally thought to develop via precursor lesions along with the increasing accumulation of molecular genetic alterations. Endometrial hyperplasia with atypia / endometrial intraepithelial neoplasia is the least common type of hyperplasia but it is the type most likely to progress to type I cancer, whereas endometrial hyperplasia without atypia rarely progresses to carcinoma. MicroRNAs are a class of small, non-coding, single-stranded RNAs that negatively regulate gene expression mainly binding to 3’-untranslated region of target mRNAs. In the current study, these researchers identified a microRNAs signature (miR-205, miR-146a, miR-1260b) able to discriminate between atypical and typical endometrial hyperplasia in 2 independent cohorts of patients. The identification of molecular markers that can distinguish
between these 2 distinct pathological conditions is considered to be highly useful for the clinical management of patients because hyperplasia with an atypical change is associated with a higher risk of developing cancer. These investigators showed that the combination of miR-205, -146a, and -1260b has the best predictive power in discriminating these 2 conditions (greater than 90%). With the aim to find a biological role for these 3 microRNAs, these researchers focused their attention on a common putative target involved in endometrial carcinogenesis: the onco-suppressor gene SMAD4. They showed that miRs-146a, -205, and-1260b directly target SMAD4 and their enforced expression induced proliferation and migration of endometrioid cancer derived cell lines, Hec1a cells. The authors concluded that these data suggested that microRNAs-mediated impairment of the TGF-β pathway, due to inhibition of its effector molecule SMAD4, is a relevant molecular alteration in endometrial carcinoma development. These researchers stated that these findings showed a potential diagnostic role of this microRNAs signature for the accurate diagnosis of endometrial hyperplasia with atypia / endometrial intraepithelial neoplasia and improve the understanding of their pivotal role in SMAD4 regulation.

Circulating Adiponectin, Leptin, and Adiponectin-Leptin Ratio

In a systematic review and meta-analysis, Zeng and co-workers (2015) evaluated the association between serum adiponectin (APN) concentrations and the risk of endometrial cancer. PubMed, Embase, the Chinese Biomedical Literature Database and the Science Citation Index (ISI Web of Science) were searched for studies that examined the association between blood APN concentrations and the risk of endometrial cancer. Data from studies that met the inclusion criteria were systematically reviewed, and pooled analyses were performed according to the guidelines of Meta-Analysis of Observational Studies in Epidemiology and PRIMSA. A total of 8 case-control studies (including 1,257 endometrial cancer patients and 2,008 controls) and 4 nested case-control studies (including 659 endometrial cancer patients and 1,398 controls) were included. These researchers found that serum APN level was inversely correlated with the risk of endometrial cancer development after pooling the case-control studies (OR = 0.50, 95 % CI: 0.39 to 0.60; p < 0.001). However, meta-analysis of nested case-control studies did not support a broad linkage between serum APN level and endometrial cancer, although a correlation may exist in the subgroup of post-menopausal women (OR = 0.81, 95 %CI: 0.65 to 1.00; p = 0.060), especially in post-menopausal women without current hormone replacement therapy (OR = 0.62, 95 % CI: 0.44 to 0.86; p = 0.004). The authors concluded that meta-analysis of currently available clinical evidence supported the association between high serum APN concentration and reduced risk of endometrial cancer development, particularly in the group of post-menopausal women without current hormone replacement therapy. However, they stated that additional studies with prospective design are needed to validate this linkage.
Gong and associates (2015) performed a meta-analysis of epidemiologic studies to investigate the associations between circulating APN, leptin (LT) and APN-LT (A/L) ratio and endometrial cancer risk. Relevant manuscripts were identified by searching PubMed and ISI Web of Science databases as well as by manual searching the references cited in retrieved manuscripts. Random-effects models were used to estimate summary OR (SOR) and 95 % CIs for the aforementioned associations. A total of 14 manuscripts with 13 studies (5 nested case-control and 8 case-control studies) cumulatively involving a total of 1,963 endometrial cancer cases and 3,503 non-cases were included in the analyses. Overall, comparing persons with circulating concentrations of APN, LT and A/L ratio in the top tertile with persons with concentrations of these biomarkers in the bottom tertile yielded SORs of 0.47 (95 % CI: 0.34 to 0.65; I(2) = 63.7 %; n = 13), 2.19 (95 % CI: 1.44 to 3.31; I(2) = 64.2 %; n = 7), and 0.45 (95 % CI: 0.24 to 0.86; I(2) = 90.1 %; n = 5), respectively. Notably, there was an 18 % reduction in risk for each 5 μg/ml increment in circulating APN concentrations (SOR = 0.82; 95 % CI: 0.74 to 0.90; I(2) = 49 %; n=8). Stratifying by study characteristics and whether these studies considered or adjusted for potential confounders, the findings were robust in the analyses of circulating APN and LT. No evidence of publication bias was detected. The authors concluded that the findings from this meta-analysis suggested that increased circulating APN and A/L ratio or decreased LT concentrations were associated with reduced risk of endometrial cancer. They stated that further prospective designed studies are needed to confirm these findings.

Li and colleagues (2016) noted that previous epidemiological studies have presented conflicting results regarding associations between circulating APN levels and the risk of endometrial cancer. In a meta-analysis, these researchers examined the association between these factors. Multiple electronic sources, including PubMed, SpringerLink and Google Scholar databases were searched to identify relevant studies for the present meta-analysis. All of the selected studies examined the correlation between circulating APN levels and endometrial cancer. The standardized mean difference (SMD) and 95 % CIs were estimated and pooled using meta-analysis methods. A total of 18 case-control studies met the inclusion criteria; 5,692 participants and 2,337 cases of endometrial cancer were included in this meta-analysis. The SMD of the pooled analysis (95 % CI) were -1.96 (-2.60 to -1.31), p = 0.000. When the cancer grades were compared, the APN values were not significantly different between the grades of endometrial cancer [G1 versus G3, 1.02 (-0.68 to 2.72), p > 0.05; G1 versus G2, 0.34 (-0.86 to 1.54), p > 0.05]. However, there was a significant association between high APN levels and post-menopausal endometrial cancer cases with an SMD (95 % CI) of -2.27 (-4.36 to -0.18) and p < 0.05, however, no association was observed in pre-menopausal endometrial cancer cases with an SMD (95 % CI) of -1.52 (-3.49 to 0.45) and p > 0.05. The low circulating APN level increased the risk of endometrial cancer, whereas the high APN level decreased this risk in post-
menopausal women. The authors concluded that circulating APN as simple biomarkers may be a promising tool for the prevention, early diagnosis and disease monitoring of endometrial cancer.

FTO rs9939609 Gene Polymorphism Testing

Huang and colleagues (2017) noted that obesity is a risk factor of cancer. Several genes have been found to play an important role in the etiology of obesity and tumourigenesis. Recent studies suggested that rs9939609 polymorphism might be significantly associated with cancer risk, while the results of some other studies were controversial. In a meta-analysis, these investigators examined the association between FTO gene polymorphism (rs9939609) and cancer risk. Databases with time limitation from January 1984 to April 2015 were searched. The pooled OR with 95 % CI was calculated to assess the associations, and subgroup meta-analyses were performed according to the type of cancer and ethnicity of the study populations. Overall, the significant association between rs9939609 polymorphism and cancer risk was found in homozygote model and recessive model. As to subgroup classified by cancer type, there was significant association in endometrial cancer and pancreatic cancer, while no statistical significance was detected in other kind of cancers. Besides, in the subgroup analysis of ethnicity, these results indicated that rs9939609 polymorphism was significantly associated with cancer risk in Asians. The rs9939609 polymorphism may be involved the susceptibility of endometrial cancer and pancreatic cancer, especially in Asian populations. The authors concluded that rs9939609 may be a potential biomarker in early diagnosis or gene therapy target of endometrial cancer and pancreatic cancer.

HSD17B1 rs605059 Gene Polymorphism Testing

In a systemic review and meta-analysis, Mu and associates (2015) evaluated the HSD17B1 gene polymorphisms in the risks of endometrial cancer, endometriosis and uterine leiomyoma. A comprehensive electronic search was conducted in PubMed, Medline (Ovid), Embase, Weipu, Wanfang and CNKI. The pooled ORs were performed using the Revman 5.2 software. A total of 8 case-control studies were included: 3 were about endometrial cancer, 4 were about endometriosis and 1 was about uterine leiomyoma. The result showed no significant association between HSD17B1 rs605059 gene polymorphisms and risks of endometrial cancer (AA versus AG+GG: OR = 1.11, 95 % CI: 0.94 to 1.32; AA+AG versus GG: OR = 1.79, 95 % CI: 0.42 to 7.52; AG versus AA+GG: OR = 0.87, 95 % CI: 0.76 to 1.00; AA versus GG: OR = 1.43, 95 % CI: 0.62 to 3.30; A versus G: OR = 1.00, 95 % CI: 0.91 to 1.11) or endometriosis (AA versus AG+GG: OR = 0.99, 95 % CI: 0.75 to 1.32; AA+AG versus GG: OR = 1.73, 95 % CI: 0.92 to 3.25; AG versus AA+GG: OR = 1.24, 95 % CI: 1.00 to 1.53; AA versus GG: OR = 1.54, 95 % CI: 0.79 to 2.97; A versus G: OR = 1.23, 95 % CI: 0.90 to 1.68). No association was found in a
subgroup analysis based on Asian ethnicity for endometriosis. The authors concluded that the findings of this meta-analysis suggested that HSD17B1 rs605059 polymorphisms were not associated with the risks of endometrial cancer and endometriosis. They stated that further studies are needed to validate the conclusion and clarify the relationship between HSD17B1 rs605059 polymorphisms and the risk of uterine leiomyoma.

Neutrophil Gelatinase-Associated Lipocalin for Diagnosis of Endometrial Cancer

Roli and colleagues (2017) noted that some studies have reported differentially altered neutrophil gelatinase-associated lipocalin (NGAL) levels in several malignancies. These researchers evaluated NGAL measured in plasma or urine as both prognostic and diagnostic marker for different types of human tumors. They performed systematic electronic searches in Medline, Embase and CRDTAS. Studies were included if they evaluated NGAL as a prognostic or diagnostic marker for human cancers. The selection of the studies, screening of the full texts and data extraction were conducted independently by 2 authors. They used the random-effects model for the meta-analyses. A methodological assessment was completed. These investigators included 35 studies dedicated to colorectal, pancreas, breast, thyroid, gastric, kidney, endometrial, brain, liver, lung, esophageal, oral and ovarian cancers. Meta-analyses showed that, in patients with colorectal and breast cancer, positive NGAL expression was associated with a decrease of disease-free survival (hazard ratio [HR] = 2.27, 95 % CI: 1.54 to 3.36; HR = 1.78, 95 % CI: 1.33 to 2.38, respectively). NGAL was a negative prognostic marker of overall survival (OS) in colorectal (HR = 2.37, 95 % CI: 1.68 to 3.34) and endometrial (HR = 4.38, 95 % CI: 1.9 to 10.12) cancers. Discriminative power of NGAL between cancer patients and control was moderate in colorectal cancer (area under the curve [AUC] = 0.6; pooled sensitivity 0.56; pooled specificity 0.72), acceptable in pancreatic cancer (AUC = 0.8; pooled sensitivity 0.6; pooled specificity 0.8) and good in thyroid cancer (AUC = 0.9; pooled sensitivity 0.85; pooled specificity 0.96). The authors concluded that NGAL determination in plasma and urine could be useful in the prognosis of colorectal and breast cancer, but its prognostic accuracy remains uncertain for other human tumors.

Telomeres and Telomerase Activity for Diagnosis and/or Screening of Endometrial Cancer

Valentijn and associates (2015) noted that critical shortening of telomeres may result in permanent cell cycle arrest while the enzyme telomerase maintains telomere length (TL) and replicative capacity of cells. Telomerase expression and activity change in the human endometrium with the ovarian hormone cycle, however the effect of this on endometrial TL and cell growth is not known. In a prospective, observational study, which included endometrial and blood samples collected from 196 women, these researchers studied how regulation of
telomerase activity (TA) in human endometrial epithelial cells (EEC) by ovarian hormones impact on TL and cell proliferation? These investigators studied endometrial samples from 5 different groups of women. Endometrial and matched blood TL and circulating steroid hormones were studied in samples collected from 85 women (Group 1). Fresh epithelial and stromal cell isolation and culture in-vitro for TL and TA was done on endometrial biopsies collected from a further 74 healthy women not on hormonal therapy (Group 2) and from 5 women on medroxyprogesterone acetate (MPA) for contraception (Group 3). The epithelial TL and telomerase protein expression was examined in active, peritoneal, ectopic endometriotic and matched uterine (eutopic) endometrial samples collected from 10 women with endometriosis (Group 4); the in-vivo effect of mifepristone on telomerase protein expression by immunohistochemistry (IHC) was examined in endometrium from 22 healthy women in mid-secretory phase before (n = 8), and after administering 200-mg mifepristone (n = 14) (Group 5); TA was measured by telomere repeat amplification protocol (TRAP) assay; TL by qPCR, and Q-FISH; cell proliferation was assessed by immunoblotting of histone H3 and 3D-culture to assess the ability of EECs to form spheroids; telomerase reverse transcriptase protein levels and Ki-67 (proliferative index) were assessed with IHC. Endometrial TLs correlated negatively with serum progesterone levels (n = 58, r = -0.54) and were significantly longer than corresponding blood TLs (4,893 ± 929 bp versus 3,955 ± 557 bp, p = 0.002) suggesting a tissue-specific regulation. High TA and short TLs were observed in proliferating EECs in-vivo and in-vitro. During the progesterone dominant mid-secretory phase endometrial TL were significantly shorter compared with the proliferative phase (p = 0.0002). Progestagen treatment suppressed EEC TA in-vivo and reduced endometrial TA in explant (p = 0.01) and in-vitro cultures (p = 0.02) compared with untreated cells. Mifepristone (progesterone receptor antagonist) increased telomerase protein levels in vivo (P < 0.05). In 2D culture, imetelstat inhibited EEC TA (P = 0.03), proliferation (P = 0.009) and in 3-D culture disrupted endometrial glandular architecture (p = 0.03). The authors concluded that the observed effects of telomerase inhibition in-vitro on epithelial cell proliferation, suggested that telomerase might be an attractive target in developing new therapies for proliferative disorders of the endometrium, such as endometriosis. This study had 2 major drawbacks: (i) The in-vitro telomerase inhibition data were tested in a mono-cellular system for a short-term period; further confirmation of the results in an in-vivo model is needed, and (ii) The women in Group 2 included a high proportion of women although with a regular menstrual cycle, with an increased body mass index (BMI) greater than 25, thus this may affect extrapolation of data to other groups.

Hapangama and colleagues (2017) stated that eukaryotic chromosomal ends are linear and are protected by nucleoprotein complexes known as telomeres. The complex structural anatomy and the diverse functions of telomeres as well as the unique reverse transcriptase enzyme, telomerase that maintains telomeres are under intensive scientific scrutiny. Both are involved in
many human diseases including cancer, but also in ageing and chronic disease such as diabetes. Their intricate involvement in many cellular processes and pathways is being dynamically deciphered in many organs including the endometrium. These investigators summarized the current knowledge on the topic of telomeres and telomerase and their potential role in providing plausible explanations for endometrial aberrations related to common gynecological pathologies. They outlined the recent major findings in telomere and telomerase functions in the context of endometrial biology; and highlighted the contemporary discoveries in hormonal regulation, normal endometrial regeneration, stem cells and common gynecological diseases such as endometriosis, infertility, recurrent reproductive failure and endometrial cancer (EC). These researchers performed systematic PubMed (Medline) and Ovid searches using the key words: telomerase, telomeres, telomere length, human telomerase reverse transcriptase, telomeric RNA component, with endometrium, hormonal regulation, endometrial stem/progenitor cells, endometrial regeneration, endometriosis, recurrent miscarriage, infertility, endometrial hyperplasia, EC and uterine cancer. Publications used in this review dated from 1995 to June 31, 2016. The human endometrium is a unique somatic organ, which displays dynamic TA related to the menstrual cycle. Telomerase is implicated in almost all endometrial pathologies and appeared to be crucial to endometrial stem cells. In particular, it is vital for normal endometrial regeneration, providing a distinct route to formulate possible curative, non-hormonal therapies to treat chronic endometrial conditions. Furthermore, the current understanding of telomere maintenance in EC is incomplete. Data derived from other malignancies on the role of telomerase in carcinogenesis cannot be extrapolated to EC because unlike in other cancers, TA is already present in proliferating healthy endometrial cells. The authors concluded that since telomerase is pivotal to endometrial regeneration, further studies elucidating the role of telomeres, telomerase, their associated proteins and their regulation in normal endometrial regeneration as well as their role in endometrial pathologies are essential.

Sentinel Lymph Node (SLN) Mapping

Bodurtha and associates (2017) noted that in the staging of endometrial cancer, controversy remains regarding the role of sentinel lymph node (SLN) mapping compared with other nodal assessment strategies. These researchers conducted a systematic review to evaluate the diagnostic accuracy and clinical impact of SLN mapping in the management of endometrial cancer. They searched Medline, Embase, and the Cochrane Central Registry of Controlled trials for studies published in English before March 25, 2016. Studies were included if they contained 10 or more women with endometrial cancer and reported on the detection rate, sensitivity, and/or impact on treatment or survival of SLN mapping. Two authors independently reviewed abstracts and full-text articles for inclusion and assessed study quality. The detection rate, sensitivity, and factors associated with successful mapping (study size, BMI, tumor histology and grade, injection site, dye type) were synthesized through random-effects meta-analyses and meta-
regression. These investigators identified 55 eligible studies, which included 4,915 women. The overall detection rate of SLN mapping was 81% (95% CI: 77 to 84) with a 50% (95% CI: 44 to 56) bilateral pelvic node detection rate and 17% (95% CI: 11 to 23) para-aortic detection rate. There was no difference in detection rates by patient BMI or tumor histology and grade. Use of indocyanine green (ICG) increased the bilateral detection rate compared with blue dye. Additionally, cervical injection increased the bilateral SLN detection rate but decreased the para-aortic detection rate compared with alternative injection techniques. Intra-operative SLN frozen section increased the overall and bilateral detection rates. The sensitivity of SLN mapping to detect metastases was 96% (95% CI: 91 to 98); ultra-staging did not improve sensitivity. Compared with women staged with complete lymphadenectomy, women staged with SLN mapping were more likely to receive adjuvant treatment. The authors concluded that SNL mapping was feasible and accurately predicted nodal status in women with endometrial cancer. They stated that the current data favored the use of cervical injection techniques with ICG. They stated that SNL mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.

Rossi and co-workers (2017) measured the sensitivity and NPV of SLN mapping compared with the gold standard of complete lymphadenectomy in detecting metastatic disease for endometrial cancer. In the FIRES multi-center, prospective, cohort study patients with clinical stage 1 endometrial cancer of all histologies and grades undergoing robotic staging were eligible for study inclusion. Patients received a standardized cervical injection of ICG and SLN mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. A total of 18 surgeons from 10 centers (tertiary academic and community non-academic) in the USA participated in the trial. Negative SLNs (by hematoxylin and eosin staining on sections) were ultra-staged with immunohistochemistry for cytokeratin. The primary end-point, sensitivity of the SLN-based detection of metastatic disease, was defined as the proportion of patients with node-positive disease with successful SLN mapping who had metastatic disease correctly identified in the SLN. Patients who had mapping of at least 1 SLN were included in the primary analysis (per protocol). All patients who received study intervention (injection of dye), regardless of mapping result, were included as part of the assessment of mapping and in the safety analysis in an intention-to-treat manner. Between August 1, 2012, and October 20, 2015, a total of 385 patients were enrolled; SLN mapping with complete pelvic lymphadenectomy was done in 340 patients and para-aortic lymphadenectomy was done in 196 (58%) of these patients. A total of 293 (86%) patients had successful mapping of at least 1 SLN; 41 (12%) patients had positive nodes, 36 of whom had at least 1 mapped SLN. Nodal metastases were identified in the SLNs of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97.2% (95% CI: 85.0 to 100), and a NPV of 99.6% (97.9 to 100). The most common grade 3 to 4 adverse events (AEs) or serious AEs (SAEs) were post-operative neurological disorders (4 patients) and post-operative respiratory distress or failure (4 patients). A total of 22 patients had
SAEs, with 1 related to the study intervention: a ureteral injury incurred during SLN dissection. The authors concluded that SNLs identified with ICG had a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer. Sentinel lymph node biopsy will not identify metastases in 3% of patients with node-positive disease, but has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.

How and colleagues (2018) stated that appropriate extent of lymphadenectomy in clinically, early stage endometrial cancer remains controversial but SLN mapping has emerged as an alternative staging strategy, until the advent of molecular prognostic markers. These researchers performed a systematic review of the literature to determine pooled estimates for SLN detection rate and diagnostic accuracy, while exploring impact of the SLN on adjuvant therapy and oncologic outcomes. They performed a systematic search utilizing Medline, Embase, and Web of Science electronic databases for all studies published in the English language until October 31, 2017. Studies were included for review and potential aggregate analyses if they contained at least 30 endometrial cancer patients with undergoing SLN mapping and reported on detection rates (overall, bilateral or para-aortic) or diagnostic accuracy (sensitivity and NPV). Pooled estimates were calculated via meta-analyses utilizing a random-effects model. Studies reporting on the impact of SLN on adjuvant therapy, as well as studies comparing SLN mapping to completion lymphadenectomy were qualitatively reviewed and analyzed as well. These investigators identified 48 eligible studies, which included 5,348 patients for review and inclusion in the meta-analysis for SLN detection or diagnostic accuracy. The pooled SLN detection rates were 87% (95% CI: 84 to 89%, 44 studies) for overall detection, 61% (95% CI: 56 to 66%, 36 studies) for bilateral detection, and 6% (95% CI: 3 to 9%, 31 studies) for para-aortic detection. Use of ICG improved overall (94%, 95% CI: 92 to 96%, 19 studies) SLN detection rates compared to blue tracer (74% versus 59%, respectively). There was no difference in para-aortic SLN detection rate between each tracer. The pooled estimates for diagnostic accuracy for 34 studies were 94% (95% CI: 91 to 96%) for sensitivity and 100% (95% CI: 99 to 100%) for NPV. Diagnostic accuracy of SLN mapping was not negatively affected in patients with high-grade endometrial histology.

Patients with SLN mapping are more likely to receive adjuvant therapy and did not have inferior survival or recurrence outcomes compared to those undergoing completion lymphadenectomy. The authors concluded that SLN mapping is a feasible and accurate alternative to stage patients with endometrial cancer. Utilizing ICG resulted in the highest SLN detection rates. Moreover, they stated that future studies should prospectively examine the impact of SLN mapping on progression-free survival (PFS) and OS.
Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Uterine neoplasms” (Version 1.2018) notes that SNL mapping may be considered for pathologic evaluation and surgical staging.

DNA Methylation for Diagnosis of Sporadic Endometrial Cancer

Fan and colleagues (2017) stated that although increasing numbers of methylated genes have been identified as biomarkers for endometrial cancer, the results have been inconsistent. These investigators performed a systematic review and meta-analysis to evaluate the diagnostic accuracy of methylated genes as markers for sporadic endometrial cancer. A total of 22 studies including 1,930 participants (sporadic endometrial cancer patients and normal individuals) met the eligibility criteria. The pooled sensitivity and specificity were 0.93 (95 % confidence interval: 0.91 to 0.94) and 0.48 (95 % CI: 0.46 to 0.50), respectively. The area under the summary receiver operating characteristic curve was 0.8834. The presence of DNA methylation was significantly associated with lymph node metastasis of endometrial cancer (pooled OR: 0.28, 95 % CI: 0.15 to 0.52, p < 0.001). These investigators searched the relevant literature systematically using the PubMed and Web of Science databases up to April 2017. Diagnostic accuracy variables were pooled and analyzed using Meta-DiSc software. Sensitivity analysis and publication bias were evaluated using Review Manager. The authors conclude that the findings of this meta-analysis suggested that the detection of DNA methylation is associated with lymph node metastasis, with high sensitivity but relatively low specificity for the diagnosis of sporadic endometrial cancer. Moreover, they stated that further meta-analyses need to be conducted to address the use of accurate methylated targets and suitable detection techniques, while more prospective studies utilizing consistent and standardized methodologies are urgently needed to resolve these problems.

The authors stated that this study had several drawbacks. First, selection bias might have occurred due to enrichment of studies reporting positive results, and the relatively small sample sizes in some of the selected literature may also have led to bias. Furthermore, the included studies were mostly from East Asia, and the conclusions may therefore not be universally applicable. The use of different methylation-specific polymerase chain reaction primers and/or equipment, and the lack of a well-accepted methylated gene in sporadic endometrial cancer might also have been potential sources of bias.

Circular RNAs Expression for Grade-3 Endometrial Cancer

Ye and colleagues (2019) noted that circular RNAs (circRNAs), a class of newly discovered endogenous non-coding RNAs, have shown large capabilities in gene regulation. Patients with the grade-3 endometrial cancer (EC) have a generally poor prognosis, and the specific role of
circRNAs in the grade-3 EC remains unclear. These investigators examined the roles of circRNAs in the grade-3 EC. They screened the expression profiles of circRNAs taken from 2 women with the grade-3 EC and adjacent non-cancerous endometrial tissue using circRNAs sequencing. Bioinformatic analyses were applied to study these differentially expressed circRNAs. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) of 6 dysregulated circRNAs was performed to validate the sequencing results. Bioinformatic analyses, including the negative correlation network analyses of circRNAs-microRNAs (miRNAs)-messenger RNAs (mRNAs) and the Cytoscape, were used to delineate the interaction of circRNAs/miRNAs of the entire network. Data of circRNA sequencing showed a significant change in 75,928 unique circRNAs (p < 0.05). The up-regulated hsa_circ_0039569 and hsa_circ_0001610 and down-regulated hsa_circ_0000437, hsa_circ_0001776, and hsa_circ_0009043 were validated by qRT-PCR analysis. Using bioinformatical methods, these researchers found that hsa_circ_0039569 had the MRE of hsa-miR-542-3p and hsa-let-7c-5p. Hsa-miR-542-3p and hsa-let-7c-5p were down-regulated in the grade-3 EC validated by qRT-PCR analysis. In the clinicopathological parameters, the expression level of hsa_circ_0039569 was significantly correlated with tumor differentiation (p = 0.001). The authors concluded that this was the 1st study, which demonstrated that there were a lot of differences between the tissue of the grade-3 EC and adjacent non-cancerous endometrial in circRNA expression and may offer novel molecular candidates for diagnosis and clinical treatment of the grade-3 EC.

Immunohistochemistry for Protein Phosphatase and Tensin Homolog (PTEN) for Differential Diagnosis of Benign and Pre-Malignant Endometrial Hyperplasia

Raffone and associates (2019) noted that endometrial hyperplasia (EH) may be either a benign proliferation or a pre-malignant lesion. In order to differentiate these 2 conditions, 2 possible histologic classifications could be used: the World Health Organization (WHO) classification and the EIN classification. The 2017 European Society of Gynecological Oncology guidelines recommend the use of immunohistochemistry for tumor suppressor protein phosphatase and tensin homolog (PTEN) to improve the differential diagnosis. Nonetheless, its diagnostic accuracy has never been defined. These researchers examined the diagnostic accuracy of PTEN immunohistochemistry in the differential diagnosis between benign and pre-malignant EH. Electronic databases were searched from their inception to May 2018 for studies assessing immunohistochemical expression of PTEN in EH specimens. PTEN status ("loss" or "presence") was the index test; histological diagnosis ("pre-cancer" or "benign") was the reference standard. Sensitivity, specificity, PLR, NLR, DOR, and area under the curve (AUC) on summary receiver operating characteristic (SROC) curves were calculated (95 % CI), with a subgroup analysis based on the histologic classification adopted (WHO versus EIN). A total of 27 observational studies with 1,736 cases of EH were included. Pooled estimates showed low diagnostic accuracy: sensitivity 54 % (95 % CI: 50 % to 59 %), specificity 66 % (63 % to 69 %), PLR 1.55
When the WHO subgroup was compared with the EIN subgroup, higher accuracy (AUC 0.694 versus 0.621), and higher heterogeneity in all analyses, were observed. The authors concluded that immunohistochemistry for PTEN showed low diagnostic usefulness in the differential diagnosis between benign and pre-malignant EH. These researchers stated that in the absence of further evidence, the recommendation regarding its use should be reconsidered; they stated that further studies are needed to clarify the prognostic value of PTEN immunohistochemistry in EH, with specific regard to the progression to cancer.

Travaglino and colleagues (2019) stated that guidelines recommend PTEN immunohistochemistry for differentiating between benign EH (BEH) and atypical EH (AEH) / EIN. However, it is unclear when PTEN expression should be defined as "lost" and thus suggestive of AEH / EIN. In a systematic review and meta-analysis, these investigators determined the optimal immunohistochemical criteria to define PTEN loss in EH. Electronic databases were searched for studies assessing immunohistochemical expression of PTEN in both BEH and AEH / EIN specimens. PTEN status ("loss" or "presence") was the index test; histological diagnosis ("AEH / EIN" or "BEH") was the reference standard. Accuracy was quantified based on the AUC on SROC curves, for several different thresholds of PTEN expression. A total of 18 studies with 1,362 hyperplasia were included; 6 different criteria to define PTEN loss were assessed. Low diagnostic accuracy was found for complete loss of expression (AUC = 0.71), presence of any null gland (AUC = 0.63), positive cells less than 10% (AUC = 0.64), positive cells less than 50% (AUC = 0.71) and moderate-to-null intensity (AUC = 0.64). Barely moderate diagnostic accuracy was only found for the subjective criterion "weak-to-null intensity" (AUC = 0.78). The authors concluded that the clinical usefulness of PTEN immunohistochemistry in this field should be further examined.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+.

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<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<td>Injection procedure; radioactive tracer for identification of sentinel node</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>38900</td>
<td>Intraoperative identification (eg, mapping) of sentinel lymph node(s) includes</td>
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<td>injection of non-radioactive dye, when performed (list separately in addition to</td>
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<td>Endometrial sampling (biopsy) with or without endocervical sampling (biopsy),</td>
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<tr>
<td></td>
<td>separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>58558</td>
<td>Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy,</td>
</tr>
<tr>
<td></td>
<td>with or without D &amp; C</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

- Neutrophil gelatinase-associated lipocalin (NGAL), Telomeres and telomerase activity, DNA methylation, Circular RNAs expression for diagnosis of grade-3 endometrial cancer. No specific code:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>78195</td>
<td>Lymphatics and lymph nodes imaging [sentinel lymph node biopsy]</td>
</tr>
<tr>
<td>81321</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma</td>
</tr>
<tr>
<td></td>
<td>tumor syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81322</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma</td>
</tr>
<tr>
<td></td>
<td>tumor syndrome) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81323</td>
<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma</td>
</tr>
<tr>
<td></td>
<td>tumor syndrome) gene analysis; duplication/deletion variant</td>
</tr>
<tr>
<td>86305</td>
<td>Human epididymis protein 4 (HE4)</td>
</tr>
</tbody>
</table>

Other CPT codes related to the CPB:

- 88104 - 88112, 88141 - 88175: Cytopathology

- 88305 - 88309: Surgical pathology, gross and microscopic examination

Other HCPCS codes related to the CPB:

- G0123: Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; screening by cytotechnologist under physician supervision

- G0124: requiring interpretation by physician

- G0141 - G0148: Screening, cytopathology

ICD-10 codes covered if selection criteria are met:

- C54.1 - C54.9: Malignant neoplasm of corpus uteri [except isthmus]
- D06.0 - D07.0: Carcinoma in situ of cervix uteri or other and unspecified parts of uterus
- N85.00 - N85.02: Endometrial hyperplasia
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N92.1</td>
<td>Excessive and frequent menstruation with irregular cycle</td>
</tr>
<tr>
<td>N92.4</td>
<td>Excessive bleeding in the premenopausal period</td>
</tr>
<tr>
<td>N92.5, N93.8</td>
<td>Other abnormal bleeding from female genital tract</td>
</tr>
<tr>
<td>N93.9</td>
<td>Abnormal uterine and vaginal bleeding, unspecified</td>
</tr>
<tr>
<td>Z15.04</td>
<td>Genetic susceptibility to malignant neoplasm of endometrium [due to Lynch syndrome]</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z12.79</td>
<td>Encounter for screening for malignant neoplasm of other genitourinary organs [endometrium]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


36. Plaxe SC. Endometrial carcinoma: Pretreatment evaluation, staging and surgical treatment. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed July 2012.


39. Breijer MC, Peeters JA, Opmeer BC, et al. Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal...


43. Plaxe SC. Endometrial carcinoma: Pretreatment evaluation, staging, and surgical treatment. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed July 2014.


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Amendment to
Aetna Clinical Policy Bulletin Number: 0769
Endometrial Cancer Screening and Diagnosis

There are no amendments for Medicaid.