I. 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.

II. Aetna considers endometrial biopsy (sampling) experimental and investigational for the screening of endometrial cancer because of insufficient evidence of its effectiveness in screening for endometrial cancer.

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

IV. Aetna considers endometrial or cervical cytology performed in conjunction with endometrial histology (TruTest™, Gynecor™, Glen Allen, VA) experimental and investigational.
in the diagnostic evaluation of abnormal uterine bleeding in women suspected of having endometrial hyperplasia or endometrial carcinoma because of insufficient evidence of the effectiveness of this method.

V. Aetna considers sentinel lymph node biopsy and mapping experimental and investigational for diagnosis and management of endometrial cancer because its effectiveness for this indication has not been established.

VI. Aetna considers measurement of endometrial thickness as a screening test for endometrial carcinoma in asymptomatic post-menopausal women not using hormone replacement therapy experimental and investigational because its effectiveness for this indication has not been established.

VII. Aetna considers measurement of (i) circulating YKL-40, (ii) serum human epididymis protein 4 (HE4), and (iii) urine microRNAs experimental and investigational for diagnosis of endometrial cancer because their effectiveness for this indication has not been established.

VIII. Aetna considers circulating adiponectin, leptin, and adiponectin-leptin ratio as biomarkers experimental and investigational for the prevention, early diagnosis and disease monitoring of endometrial cancer because their effectiveness for these indications has not been established.

IX. Aetna considers FTO rs9939609 and HSD17B1 rs605059 gene polymorphism testing experimental and investigational for the diagnosis of endometrial cancer because their effectiveness for this indication has not been established.

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 for Ovarian and
Endometrial Cancer Screening and Other Selected Indications (../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 post-menopausal 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
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 1.80. 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.

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 controls).
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 afore-mentioned 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 per each 5 μg/ml increment in circulating APN concentration.
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 (2016) 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.

### 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 "+":*

**ICD-10 codes will become effective as of October 1, 2015:**

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>58100</td>
<td>Endometrial sampling (biopsy) with or without endocervical sampling (biopsy), without cervical dilation, any method (separate procedure)</td>
</tr>
<tr>
<td>+ 58110</td>
<td>Endometrial sampling (biopsy) performed in conjunction with colposcopy (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>58558</td>
<td>Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D &amp; C</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38792</td>
<td>Injection procedure; radioactive tracer for identification of sentinel node</td>
</tr>
<tr>
<td>38900</td>
<td>Intraoperative identification (eg, mapping) of sentinel lymph node(s) includes injection of non-radioactive dye, when performed (list separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>78195</td>
<td>Lymphatics and lymph nodes imaging [sentinel lymph node biopsy]</td>
</tr>
</tbody>
</table>

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>88104 - 88112, 88141 - 88175</td>
<td>Cytopathology</td>
</tr>
<tr>
<td>88305 - 88309</td>
<td>Surgical pathology, gross and microscopic examination</td>
</tr>
</tbody>
</table>

**Other HCPCS codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0123</td>
<td>Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; screening by cytotechnologist under physician supervision</td>
</tr>
<tr>
<td>G0124</td>
<td>requiring interpretation by physician</td>
</tr>
<tr>
<td>G0141 - G0148</td>
<td>Screening, cytopathology</td>
</tr>
</tbody>
</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C54.1 - C54.9</td>
<td>Malignant neoplasm of corpus uteri [except isthmus]</td>
</tr>
<tr>
<td>D06.0 - D07.0</td>
<td>Carcinoma in situ of cervix uteri or other and unspecified parts of uterus</td>
</tr>
<tr>
<td>N85.00 - N85.02</td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>ICD-10 Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<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>
<tr>
<td>Z12.79</td>
<td>Encounter for screening for malignant neoplasm of other genitourinary organs [endometrium]</td>
</tr>
</tbody>
</table>

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

The above policy is based on the following references:


36. Plaxe SC. Endometrial carcinoma: Pretreatment evaluation, staging and surgical treatment. UpToDate


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


45. Bie Y, Zhang Z. Diagnostic value of serum HE4 in


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AETNA BETTER HEALTH® OF PENNSYLVANIA

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

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania
04/2017