Medical Coverage Policy

Effective Date..... 1/15/2020
Next Review Date..... 1/15/2021
Coverage Policy Number 0398

Transvaginal Ultrasound, Non-Obstetrical

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Overview

This Coverage Policy addresses transvaginal ultrasound (TVUS) used in the evaluation of gynecologic disorders, and for cancer screening in asymptomatic women in the general population versus those who are at high risk for cancer.

Coverage Policy

For information on obstetric ultrasonography, refer to the Cigna Coverage Policy Ultrasound in Pregnancy (including 3D, 4D and 5D Ultrasound).

For information on infertility-related ultrasonography, refer to the Cigna Coverage Policy Infertility Services.

Non-obstetrical transvaginal ultrasound is considered medically necessary for the evaluation of suspected pelvic pathology or for screening or surveillance of a woman at increased risk for ovarian or endometrial cancer.

Non-obstetrical transvaginal ultrasound is considered not medically necessary for intrauterine device (IUD) insertion, surveillance, or removal (i.e., without complications).

Non-obstetrical transvaginal ultrasound is considered experimental, investigational or unproven for any other indication including but not limited to screening in the general population for ANY type of cancer.

General Background

Ultrasound imaging, also known as ultrasound scanning or sonography is a method of obtaining images from inside the human body through the use of high-frequency sound waves. The echoes of the sound waves are recorded and displayed as a real-time, visual image. Pelvic ultrasound in females may be performed transabdominally or transvaginally. A transvaginal ultrasound (TVU, TVUS) also known as transvaginal sonography (TVS), involves the insertion of the transducer into the vagina. The images are obtained from different orientations to get the best views of the uterus and ovaries.

Transabdominal and transvaginal scanning are both useful in the evaluation and treatment of a number of pelvic pathologies. One of the more valuable roles of TVUS is evaluating unexplained bleeding in the postmenopausal woman. A thickened or highly echogenic endometrium in a postmenopausal patient can suggest the presence of polyps, abnormal endometrial histology such as adenomatous hyperplasia, or cancer. TVUS can provide information about the location of a pelvic mass relative to the ovary and uterus and provides higher resolution for better delineation of the internal architectural characteristics compared to a transabdominal ultrasound. TVUS also plays a role in evaluating patients with acute pelvic pain. Normal-appearing ovaries with no free intraperitoneal fluid on TVUS essentially eliminates an ovarian primary source for acute pain. The uterus can be evaluated sonographically, and pathologic causes of pelvic pain such as uterine fibroids, with or without degeneration, can be ruled out. TVUS is used in the evaluation of the infertile patient, particularly in the management of controlled ovarian hyperstimulation, which is necessary for modern assisted reproductive technology such as in vitro fertilization (IVF) (Gibbs, et al., 2008).

TVUS has also been investigated as a screening tool for cancer, primarily ovarian and endometrial, in women who are at average risk for malignancy. Screening and diagnostic methods for ovarian cancer include pelvic examination, CA-125 antigen as a tumor marker, TVUS, and, potentially, multimarker panels and bioinformatic analysis of proteomic patterns. TVUS is capable of detecting small ovarian masses and may distinguish some benign masses from some malignant adnexal masses, although it poorly predicts which masses are cancers and which are due to benign diseases of the ovary. As an independent test, TVUS has shown poor performance in the detection of ovarian cancer in average-risk or high-risk women (Fishman, et al., 2005).

The risk for ovarian cancer is increased when there is a hereditary cancer syndrome (e.g., breast-ovarian cancer syndrome, Lynch syndrome [hereditary nonpolyposis colon cancer]). In these hereditary cancer syndromes, ovarian cancer typically occurred in a first- or second-degree relative at under age 50, or relatives in two or more generations had ovarian or related cancers (Carlson, 2019). Endometrial carcinoma risk factors include excess estrogen without adequate opposition by a progestin, tamoxifen therapy, obesity, and nulliparity. Additionally, women with Lynch syndrome are at a markedly increased risk of endometrial cancer (Chen, et al., 2019).

Intrauterine contraception is highly effective, safe, and generally well tolerated by most women. Intrauterine device (IUD) insertion and removal are usually relatively simple procedures that can be performed in the office setting by trained providers. The technical skills required for device insertion and removal can be obtained through hands-on training in the clinical setting and/or may be provided by the manufacturers of these devices (Bartz and Pocius, 2019). IUDs are considered appropriate for the majority of women, including nulliparous women and adolescents. Insertion can be done at any time during the menstrual cycle, immediately postpartum, within four weeks of placental delivery and post abortion. Complications from IUD placement are relatively rare. The most common complication is IUD expulsion, which occurs in approximately 2–10% of cases. Patients

should be encouraged to feel for their IUD strings on a regular basis at home to ensure correct placement. Method failure and uterine perforation are rare complications of IUD use. Severe pain or loss of resistance during IUD insertion are signs of perforation (Hagood, 2018). Ultrasound guidance is not required for IUD placement, however can be useful in resolving difficult IUD insertions. Specifically, ultrasound guidance has been proposed to guide dilator insertion in women with cervical stenosis or a tortuous cervical canal and to aid in identification of distorted uterine anatomy such as sharp uterine flexion (anteverted or retroverted) or fibroids (Bartz and Pocius, 2019).

U.S. Food and Drug Administration (FDA)
A number of ultrasound devices and probes have received FDA approval. The FDA notes that these devices are considered prescription devices and are to be used only with a physician's order.

Literature Review
Ovarian Cancer: Large clinical trials have evaluated the efficacy of TVUS in screening for ovarian cancer. Jacobs et al. (2016) reported results of a multicenter randomized controlled trial (RCT) (n=202,638) to evaluate the effect of early detection by screening ovarian cancer mortality. Postmenopausal women aged 50–74 years were assigned to multimodal screening (MMS) (n=50,640), annual transvaginal ultrasound screening (USS) (n=50,639), or no screening (n=101,359). Multimodal screening consisted of serum CA-125 interpreted with use of the risk of ovarian cancer algorithm. Exclusion criteria were previous bilateral oophorectomy or ovarian malignancy, increased risk of familial ovarian cancer, and active non-ovarian malignancy. The primary outcome was ovarian cancer death; secondary outcomes included death due to ovarian and primary peritoneal cancer, and complications related to screening and false-positive surgery. At a median follow-up of 11.1 years, ovarian cancer was diagnosed in 1282 (0.6%) women: 338 (0.7%) in the MMS group, 314 (0.6%) in the USS group and 630 (0.6%) in the no screening group. The overall sensitivity for detection of ovarian cancers, diagnosed within a year of a screening, was 84% in the MMS group and 73% in the USS group. Of the primary peritoneal cancers, 81% (13/16) were screen detected with MMS and 30% (3/10) were with USS. A total of 649 (0.32%) women died of ovarian cancer: 347 (0.34%) in the no screening group, 148 (0.29%) in the MMS group and 154 (0.30%) in the USS group. The relative mortality reduction was 15% in the MMS group and 11% in the USS group; these reductions were not found to be statistically significant. Post-hoc analysis suggested a significant reduction in ovarian cancer mortality in the MMS group compared to the no screening group, but not in the USS group. Women in the MMS group had a complication rate of 3.1%, and those in the USS group had a rate of 3.5%. The authors noted that although study results provide encouraging evidence of a mortality reduction, further follow-up is needed to draw firm conclusions on the effectiveness of ovarian cancer screening.

Buhling et al. (2017) performed a systematic review (n=3 RCTs/36,343 subjects). Inclusion criteria were studies that contained at least one population-based intervention screening group with annual TVUS, at least one group of postmenopausal women aged 45 years or older with no personal history or current symptoms associated with ovarian cancer, and at least three years of follow-up. Subjects with a history of bilateral oophorectomy were excluded. A change in mortality, the primary outcome, was not demonstrated by using TVUS for annual screening. It was noted that the heterogeneity in study methods, algorithms and intervention groups, which limited the ability to make comparisons. Evidence of a mortality reduction was found in years seven through 14, but the authors stated "further follow-up is needed before firm conclusions can be reached on the efficacy and cost-effectiveness of ovarian cancer screening".

Reade et al. 2013 conducted a systematic review and meta-analysis (n=10 RCTs/thousands of subjects) to assess the risks and benefits of screening asymptomatic women for ovarian cancer. Studies were eligible if asymptomatic women were assigned to either screening for ovarian cancer or no intervention, usual care, or education regarding the signs and symptoms of ovarian cancer. All forms of screening were eligible, as were trials including women at high or low risk of ovarian cancer. Screening by TVUS alone occurred in three trials. High risk was defined as having a known BRCA 1/2 mutation or Lynch syndrome, or a strong family history of ovarian cancer. The primary outcomes for this review included all-cause and ovarian cancer specific mortality, and the number of surgeries performed to detect one case of ovarian cancer. Secondary outcomes included rates of false-positive screening tests and complications associated with unnecessary surgery. Moderate quality evidence from two trials suggested no benefit of screening for reducing ovarian cancer-specific mortality (RR=1.08, 95% CI 0.84–1.38). High quality evidence from a single trial suggested no benefit from ovarian cancer screening for reducing all-cause mortality (RR=1.0, 95% CI 0.96 to 1.06). In the eight trials that reported rates of

false positive screening, 10.6% of screened women required additional testing because of abnormal results. A total of nine surgeries were needed to detect one case of ovarian cancer in the pooled estimate across screening arms of the eight trials. Screening for ovarian cancer with TVUS alone resulted in 38 surgeries to detect one case of cancer. Moderate quality evidence suggested that the risk of a severe complication while undergoing surgery where ovarian cancer was not detected was 6%. Acknowledged limitations of this review included the lack of control group information, as a better measure of harm associated with screening would be the total number of surgeries performed for suspected ovarian cancer in both the screening and control groups. Results of this study indicate that screening asymptomatic, low-risk women for ovarian cancer does not reduce mortality and is associated with unnecessary surgical procedures.

Buys et al. (2011) reported results of the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) Trial, a randomized, controlled trial (n=78,216) conducted in the United States to determine the impact of screening on cause-specific mortality for several types of cancer, including ovarian cancer. Women aged 55 to 74 years were randomized to receive either annual screening with CA-125 testing for six years and TVUS for four years or usual medical care. After excluding women with a prior bilateral oophorectomy, 68,557 women remained in the analysis. Women were followed up for a maximum of 13 years, with a median follow-up of 12.4 years. Ovarian, primary peritoneal, and fallopian tube cancer were all considered ovarian cancer cases for this study. Among the 34,253 women in the intervention/screening group, 212 ovarian cancer cases and 118 ovarian cancer deaths were identified. Among the 34,304 women in the usual care group, there were 176 ovarian cancer cases and 100 ovarian cancer deaths. No reduction in ovarian cancer mortality was observed in the intervention group compared with those receiving usual care (mortality rate ratio [RR], 1.18 [95% CI, 0.82–1.71]). The trial concluded that screening women at average risk for ovarian cancer with CA 125 testing and TVUS did not reduce ovarian cancer mortality compared with usual care. In 2017, Pinsky et al. published updated PLCO mortality data for an additional three to six years, which extended the total period of follow-up to 13–19 years from randomization. A total of 187 (intervention) and 176 (usual care) deaths from ovarian cancer were observed, for a risk-ratio of 1.06 (95% CI: 0.87–1.30). Ovarian cancer specific survival was not significantly different across trial arms (p=0.16). The authors concluded that extended follow-up of PLCO indicated no mortality benefit from screening for ovarian cancer with CA-125 and TVUS.

Other studies of average-risk populations have shown TVUS to produce a high number of false-positives (Partridge, et al 2009; Van Nagell, et al., 2007; Lacey, et al., 2006; Buys, et al., 2005). The CA-125 blood test also has a high false-positive rate. Although combining the two tests and stratifying women into risk groups based on family history does increase the positive predictive value somewhat, studies failed to demonstrate a beneficial effect of screening on mortality (Evans, et al., 2009; Van Nagell, et al., 2007; Hermsen, et al., 2007; Woodward, et al., 2007; Lacey, et al., 2006; Bosse, et al., 2006).

There is insufficient evidence in the published peer-reviewed medical literature to lend support to TVUS used as a screening tool for ovarian cancer.

Endometrial Cancer: Fewer large-scale studies have investigated TVUS as a possible screening test for endometrial cancer. Yasa et al. (2016) published the results of a retrospective cohort study (n=276) that assessed the diagnostic accuracy of endometrial thickness measurements via TVUS for the detection of endometrial malignancy. Consecutive asymptomatic postmenopausal women undergoing dilatation and curettage (D&C) and hysteroscopy for an incidental finding of thickened endometrium (≥ 4mm) were included. Different endometrial thickness cutoff values were tested on the basis of a pathologic report with carcinoma conditions (e.g., endometrial hyperplasia with atypia, endometrial carcinoma). The final pathology diagnoses included polyps (n=107) (38.8%), atrophic endometrium (n=42) (15.2%), estrogen exposure (n=39) (14.1%), and normal endometrium (n=19) (6.9%). For carcinoma conditions, nine patients (3.3%) had endometrial hyperplasia with atypia and eight patients (2.9%) had endometrial carcinoma. Endometrial samples were reported as insufficient tissue in 52 (18.8%) patients of the study group. The positive predictive values (PPVs) for carcinoma-related conditions for all given endometrial thickness cutoff values were between 6.1 and 9.6%. The negative predictive values (NPVs) of TVUS were between 94.8 and 100% at all endometrial thickness cutoff values for carcinoma-related conditions. The area under the ROC curve was 0.52 (95% CI 0.44-0.57), which indicated a poor accuracy of endometrial thickness of TVUS for carcinoma conditions. The authors noted that routine use of endometrial thickness measurement with TVUS does not seem to be an effective diagnostic tool for endometrial cancer because it has a low diagnostic performance in asymptomatic postmenopausal women. Acknowledged

study limitations included the retrospective design and the very low incidence of cancer-related conditions in the cohort, which resulted in poor information about very rare occurrences. Further prospective studies are required to evaluate endometrial thickness measurement with TVUS as a screening method for endometrial malignancy.

Jacobs et al. (2011) conducted a nested case-control study of postmenopausal women (n=48,230) who underwent TVUS in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial. The primary outcome measured was endometrial cancer and atypical endometrial hyperplasia. Performance characteristics of endometrial thickness and abnormalities for detection of endometrial cancer within one year of TVUS were calculated. Median follow-up was five-11 years. A total of 136 women with endometrial cancer or atypical endometrial hyperplasia within one year of TVUS were included in the primary analysis. The optimum endometrial thickness cutoff for endometrial cancer or atypical endometrial hyperplasia was 5–15 mm, with sensitivity of 80.5% and specificity of 86.2%. For the analysis of the women with endometrial cancer or atypical endometrial hyperplasia who reported no symptoms of postmenopausal bleeding before diagnosis and had an endometrial thickness measurement available (n=96), a cutoff of 5 mm achieved a sensitivity of 77.1% and specificity of 85.8%. Study results indicate that TVUS screening for endometrial cancer may have good sensitivity in postmenopausal women. However, the role of population screening for endometrial cancer remains uncertain.

In high-risk populations, other studies have indicated that TVUS failed to detect endometrial cancer; the efficacy of TVUS screening for endometrial cancer in high-risk women remains unproven by clinical trials (Renkonen-Sinisalo, et al., 2007; Rijcken, et al., 2003). Due to a low positive predictive value, TVUS has not been proven to be an effective screening procedure for detection of endometrial abnormality in average-risk women.

Intrauterine Device insertion, surveillance, or removal (i.e., without complications): Evidence evaluating TVUS for routine IUD placement, surveillance and removal is primarily in the form of retrospective reviews, prospective case series observational studies and review articles (Goldthwaite et al., 2018; Dias et al., 2015; de Kroon, et al., 2003). TVUS for intrauterine device (IUD) insertion and follow-up is performed by some practitioners. However, clinical evaluation alone has been proven to be adequate for assessing the position of the IUD after insertion and at follow-up. The routine use of TVUS to monitor the position of the IUD is not indicated (de Kroon, et al. 2003). TVUS may be warranted if there is clinical suspicion of mal-positioning or when an IUD string is missing. If it has been determined that if the woman is not pregnant, cervical cytology brushing is typically effective in locating the missing IUD string (Pocius and Bartz, 2019; Curtis et al., 2016). TVUS may be needed to locate the IUD if other methods fail (Prine and Shah, 2018; Prabhakaran and Chuang, 2011).

Professional Societies/Organizations
American Cancer Society (ACS): The ACS cancer screening guidelines (Smith, et al., 2018) stated that currently, no organization recommends screening average risk women for ovarian cancer. Presently, several investigations are underway that may lead to a screening strategy for asymptomatic women, as well as more specific protocols for the evaluation of women who present with symptoms of ovarian cancer.

The 2018 ACS cancer screening guidelines for endometrial cancer were unchanged from the 2011 publication. In 2011, the ACS concluded that there was insufficient evidence to recommend screening for endometrial cancer in women at average risk or who were at an increased risk due to a history of unopposed estrogen therapy, tamoxifen therapy, late menopause, nulliparity, infertility or failure to ovulate, obesity, diabetes, or hypertension. The ACS recommended that women at average and increased risk should be informed about the risks and symptoms (in particular, unexpected bleeding and spotting) of endometrial cancer at the onset of menopause, and should be strongly encouraged to immediately report these symptoms to their physicians. Women at very high risk of endometrial cancer due to 1) known Lynch (HNPCC) genetic mutation carrier status; 2) a substantial likelihood of being a mutation carrier (i.e., a mutation is known to be present in the family); or 3) the absence of genetic testing results in families with a suspected autosomal dominant predisposition to colorectal cancer should consider beginning annual testing for early endometrial cancer detection at age 35 years. The evaluation of endometrial histology with endometrial biopsy is still the standard for determining the status of the endometrium. Women at high risk should be informed that the recommendation for screening is based on expert opinion, and they also should be informed about the potential benefits, risks, and limitations of testing for early endometrial cancer detection (Smith, et al., 2018).

American College of Gastroenterology (ACG): The ACG guideline on genetic testing and management of hereditary gastrointestinal cancer syndromes stated that screening for endometrial and ovarian cancer should be offered to women at risk for or affected with Lynch syndrome by endometrial biopsy and transvaginal ultrasound annually, starting at age 30 to 35 years before undergoing surgery or if surgery is deferred (Syngal et al., 2015).

American College of Obstetricians and Gynecologists (ACOG): ACOG Practice Bulletin on long-acting reversible contraception: implants and intrauterine devices stated "complications related to implant insertion (1.0%) and removal (1.7%) are uncommon". Complications that have been reported included expulsion, method failure, and perforation. The expulsion rate was between 2% and 10% during the first year, perforation was rare, occurring in 1.4 per 1,000 levonorgestrel-releasing intrauterine device (LNG-IUD) insertions and in 1.1 per 1,000 copper IUD insertions (ACOG, 2017). A 2016 ACOG guideline outlining the challenges of long-acting reversible contraceptives noted that the most common reason for a "missing" IUD string is the retraction of the string into the cervical canal or uterine cavity. According to ACOG, if a string is not able to be visualized after sweeping the cervical canal with a cytobrush, then a pelvic ultrasound should be obtained to confirm placement (ACOG, 2016; reaffirmed 2019).

American College of Obstetricians and Gynecologists (ACOG)/Society of Gynecologic Oncology (SGO): The ACOG and SGO published a joint committee opinion on the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer in women at average risk (2017). They stated that TVUS has been evaluated as an early detection method for ovarian cancer under the premise that it may detect changes in ovarian size and morphology before signs or symptoms of cancer develop, and data show it to be ineffective. The guideline further stated that the use of transvaginal ultrasonography and tumor markers (such as CA-125) in average-risk women, alone or in combination, for the early detection of ovarian cancer have not been proved to reduce mortality. There are potential harms that exist from invasive diagnostic testing (e.g., surgery) that could result from false-positive test results. The committee recommended taking a detailed personal and family history for breast, gynecologic, and colon cancer and categorizing women based on their risk (average risk or high risk) of developing epithelial ovarian cancer. The patient and her obstetrician-gynecologist should maintain an appropriate level of suspicion when potentially relevant signs and symptoms of ovarian cancer are present.

The ACOG and SGO joint practice bulletin on hereditary breast and ovarian cancer syndrome (2017; reaffirmed 2019) stated "available screening procedures (measurement of serum CA-125 and transvaginal ultrasonography) have not been proved to decrease the mortality rate or increase the survival rate associated with ovarian cancer in high-risk populations." However, transvaginal ultrasonography or measurement of serum CA-125 level may be reasonable for short-term surveillance in women at high risk of ovarian cancer (e.g., BRCA mutations, personal or family history of ovarian cancer) who have not had risk-reducing bilateral salpingo-oophorectomy, starting at age 30–35 years.

National Comprehensive Cancer Network® (NCCN®): The NCCN Clinical Practice Guidelines in Oncology™ (NCCN Guidelines™) for Genetic/Familial High-Risk Assessment: Breast and Ovarian stated that although TVUS combined with serum CA-125 for ovarian cancer screening is of uncertain benefit, it may be considered for at-risk patients who have not elected ovarian cancer risk reducing surgery starting at age 30–35 years, at the clinician's discretion. The NCCN states that one or more of the following criteria are suggestive of hereditary breast/ovarian cancer (HBOC) syndrome that warrants further professional evaluation (NCCN, 2019a):

- individual from a family with a known BRCA1/BRCA2 mutation
- personal history of breast cancer (including invasive and ductal carcinoma in situ breast) plus one or more of the following:
  - diagnosed at age ≤ 45 years
  - diagnosed at age 46–50 years with one or more close blood relative* with ANY of the following:
    - an additional breast cancer primary (including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) at any age
    - breast cancer at any age
    - high grade prostate cancer (Gleason score of ≥7 or greater)
    - unknown or limited family history
  - diagnosed at age ≤ 60 or younger with a triple negative breast cancer
  - diagnosed at any age with at least one or more close blood relative*with ANY of the following:

        - breast cancer at age 50 or younger
        - ovarian cancer
        - male breast cancer
        - metastatic prostate cancer
        - pancreatic cancer
        - two or more additional diagnoses (including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) of breast cancer at any age in patient and/or close blood relatives
    - Ashkenazi Jewish Ancestry
- personal history of ANY of the following:
    - ovarian (includes fallopian tube and primary peritoneal cancers) cancer
    - male breast cancer
    - pancreatic cancer
    - metastatic prostate cancer (radiographic evidence of biopsy-proven disease)
- personal history of high-grade prostate cancer (Gleason score ≥ 7) at any age with ANY of the following:
    - one or more close blood relatives* with ovarian cancer, pancreatic cancer or metastatic prostate cancer
    - breast cancer (diagnosed at 50 or younger)
    - two or more close blood relatives with breast or prostate cancer (any grade)
    - Ashkenazi Jewish Ancestry
- BRCA1/BRACA2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type without germline pathogenic/likely pathogenic variant analysis
- an individual with BRCA related cancer, regardless of history, may benefit from genetic testing for targeted treatment
- individual does not meet the other criteria and but has one of the following (significant limitations of interpreting test results for an unaffected individual should be discussed):
    - first- or second-degree blood relative that meets ANY of the above criteria
    - third-degree blood relative, if related through two male relatives (parenteral grandfather's mother or sister)

*A close blood relative/close family member includes first-, second-, and third-degree relatives on the same side of the family.

The NCCN noted that when investigating family histories, the maternal and paternal sides should be considered independently. Close relatives are considered to include first-, second-, and third-degree relatives. A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children. A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings. A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual's great-grandparents and first-cousins. The early onset of breast or epithelial ovarian/fallopian tube/primary peritoneal cancers at any age also increases suspicion of HBOC. Other malignancies reported in some families with hereditary breast and ovarian cancer includes prostate, pancreatic, and melanoma.

National Cancer Institute (NCI): The NCI stated that there is "solid evidence to indicate that screening women aged 55 to 74 years at average risk of developing ovarian cancer with the serum marker CA-125 annually for six years and TVUS for four years does not result in a decrease in ovarian cancer mortality, after a median follow-up of 14.7 years". According to the NCI, solid evidence indicated that screening for ovarian cancer results in false-positives with higher rates of oophorectomy (NCI, 2019c).

The NCI also stated that there is inadequate evidence that ultrasonography screening (e.g., endovaginal ultrasound or transvaginal ultrasound) reduces mortality from endometrial cancer. Most cases of endometrial cancer (85%) are diagnosed at low stage because of symptoms and therefore survival rates are high. "Based on solid evidence, screening asymptomatic women will result in unnecessary additional biopsies because of false-positive test results. Risks associated with false-positive tests include anxiety and complications from biopsies" (NCI, 2019a).

According to the NCI executive summary on the genetics of colorectal cancer, endometrial cancer is the most common extracolonic cancer observed in Lynch syndrome families, affecting at least one female in about 50% of Lynch syndrome families. Given the increased risk of endometrial cancer, endometrial screening for women with Lynch syndrome has been suggested. Proposed modalities for screening include transvaginal ultrasound (TVUS) and/or endometrial biopsy. TVUS continues to be widely recommended without data to support its use. Lynch syndrome patients/families are also at higher risk of ovarian cancer. However, no studies on the effectiveness of ovarian screening are currently available for women in Lynch syndrome families. TVUS used for endometrial cancer screening has been extended to include ovarian cancer screening in clinical practice for those women who do not undergo risk-reducing surgery for gynecological cancer prevention (NCI, 2019b).

U.S. Preventive Services Task Force (USPSTF): The 2018 USPSTF recommendation statement on screening for ovarian cancer stated they do not recommend ovarian cancer screening for asymptomatic women who are without known genetic mutations that increase the risk for ovarian cancer. They do not recommend routine screening using any method. Transvaginal ultrasonography and serum CA-125 testing are both highly accessible and most commonly used to evaluate women with signs and symptoms of ovarian cancer, and both have been evaluated in screening studies. The USPSTF evaluated the evidence and concluded that screening for ovarian cancer does not reduce ovarian cancer mortality. Screening can lead to important harms, including false-positive screening test results and subsequent surgery in women who do not have cancer. The harms of screening for ovarian cancer outweigh the benefits. The report further stated that women with BRCA1 and BRCA2 genetic mutations are at increased risk for ovarian cancer. Women with an increased-risk family history should be considered for genetic counseling to further evaluate their potential risks.

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative (2013): The Choosing Wisely® Initiative echoes ACOG's position of not recommending screening for ovarian cancer in asymptomatic women at average risk. The foundation states that in population studies, there is only fair evidence that screening of asymptomatic women with serum CA-125 level and/or transvaginal ultrasound can detect ovarian cancer at an earlier stage than it can be detected in the absence of screening. Because of the low prevalence of ovarian cancer and the invasive nature of the interventions required after a positive screening test, the potential harms of screening outweigh the potential benefits.

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determination (LCD):No LCD's found

Use Outside of the US

The Cancer Council Queensland has optimal care pathways for both endometrial cancer and ovarian cancer. For the early detection of endometrial cancer, the council stated that there is no standard or routine population screening. As far as ovarian cancer screening, they stated that there is no effective population screening program to detect ovarian cancer in asymptomatic women (Cancer Council Queensland, 2016).

The European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) participated in a consensus conference on the diagnosis, treatment and follow-up for endometrial cancer. They recommended that there is no evidence for endometrial cancer screening in the general population. However, surveillance of the endometrium should be offered to all Lynch syndrome mutation carriers. The recommended surveillance methods are gynaecological examination, transvaginal ultrasound and aspiration biopsy starting from the age of 35 years (annually until hysterectomy) (Colombo, et al., 2016).

The Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of women with epithelial ovarian cancer stated that screening for ovarian cancer in the general population should not be performed outside of the research setting (SIGN, 2013; Revised 2018).

The Society of Obstetricians and Gynaecologists of Canada (SOGC) published clinical practice guidelines on the use of contraceptive methods to prevent pregnancy. They stated that routine ultrasound imaging after IUD insertion is not required. Following insertion, women should be follow-up in four to 12 weeks. If there is suspicion of perforation, and health care providers should obtain ultrasound imaging. If a woman using an IUD is unable to

palpate the IUD strings or during a difficult IUD removal, a speculum examination should be performed and the cervical canal may be explored (with a cotton swab, cytobrush, forceps, or similar instrument) to see if the strings can be found. If the strings cannot be found, ultrasound is the preferred method to identify the location of the IUD (Black et al., 2016).

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
76830	Ultrasound, transvaginal

ICD-10-CM Diagnosis Codes	Description
B37.3	Candidiasis of vulva and vagina
D64.9	Anemia, unspecified
M81.0	Age-related osteoporosis without current pathological fracture
M81.6	Localized osteoporosis [Lequesne]
M81.8	Other osteoporosis without current pathological fracture
M85.9	Disorder of bone density and structure, unspecified
N39.0	Urinary tract infection, site not specified
N60.01	Solitary cyst of right breast
N60.02	Solitary cyst of left breast
N60.09	Solitary cyst of unspecified breast
N60.11	Diffuse cystic mastopathy of right breast
N60.12	Diffuse cystic mastopathy of left breast
N60.19	Diffuse cystic mastopathy of unspecified breast
N60.21	Fibroadenosis of right breast
N60.22	Fibroanenosis of left breast
N60.29	Fibroadenosis of unspecified breast
N60.31	Fibrosclerosis of right breast
N60.32	Fibrosclerosis of left breast
N60.39	Fibrosclerosis of unspecified breast
N60.41	Mammary duct ectasia of right breast
N60.42	Mammary duct ectasia of left breast
N60.49	Mammary duct ectasia of unspecified breast
N60.81	Other benign mammary dysplasia of right breast
N60.82	Other benign mammary dysplasia of left breast
N60.89	Other benign mammary duct dysplasia of unspecified breast
N60.91	Unspecified benign mammary dysplasia of right breast
N60.92	Unspecified benign mammary dysplasia of left breast
N60.99	Unspecified benign mammary dysplasia of unspecified breast
N61.0	Mastitis without abscess
N61.1	Abscess of the breast and nipple

N62	Hypertrophy of breast
N63.0	Unspecified lump in unspecified breast
N63.10	Unspecified lump in the right breast, unspecified quadrant
N63.11	Unspecified lump in the right breast, upper outer quadrant
N63.12	Unspecified lump in the right breast, upper inner quadrant
N63.13	Unspecified lump in the right breast, lower outer quadrant
N63.14	Unspecified lump in the right breast, lower inner quadrant
N63.20	Unspecified lump in the left breast, unspecified quadrant
N63.21	Unspecified lump in the left breast, upper outer quadrant
N63.22	Unspecified lump in the left breast, upper inner quadrant
N63.23	Unspecified lump in the left breast, lower outer quadrant
N63.24	Unspecified lump in the left breast, lower inner quadrant
N63.31	Unspecified lump in axillary tail of the right breast
N63.32	Unspecified lump in axillary tail of the left breast
N63.41	Unspecified lump in right breast, subareolar
N63.42	Unspecified lump in left breast, subareolar
N64.0	Fissure and fistula of nipple
N64.1	Fat necrosis of breast
N64.2	Atrophy of breast
N64.3	Galactorrhea not associated with childbirth
N64.4	Mastodynia
N64.51	Induration of breast
N64.52	Nipple discharge
N64.53	Retraction of nipple
N64.59	Other signs and symptoms in breast
N64.81	Ptosis of breast
N64.82	Hypoplasia of breast
N64.89	Other specified disorders of breast
N64.9	Disorder of breast, unspecified
N89.8	Other specified noninflammatory disorders of vagina
N95.1	Menopausal and female climacteric states
N95.8	Other specified menopausal and perimenopausal disorders
N95.9	Unspecified menopausal and perimenopausal disorder
R30.0	Dysuria
R30.9	Painful micturition, unspecified
R31.0	Gross hematuria
R31.1	Benign essential microscopic hematuria
R31.21	Asymptomatic microscopic hematuria
R31.29	Other microscopic hematuria
R31.9	Hematuria, unspecified
R53.81	Other malaise
R53.82	Chronic fatigue, unspecified
R53.83	Other fatigue
R92.0	Mammographic microcalcification found on diagnostic imaging of breast
R92.1	Mammographic calcification found on diagnostic imaging of breast
R92.2	Inconclusive mammogram
R92.8	Other abnormal and inconclusive findings on diagnostic imaging of breast

T85.44XA	Capsular contracture of breast implant, initial encounter
T85.44XD	Capsular contracture of breast implant, subsequent encounter
T85.44XS	Capsular contracture of breast implant, sequela
Z00.00	Encounter for general adult medical examination without abnormal findings
Z00.01	Encounter for general adult medical examination with abnormal findings
Z01.30	Encounter for examination of blood pressure without abnormal findings
Z01.31	Encounter for examination of blood pressure with abnormal findings
Z01.411	Encounter for gynecological examination (general) (routine) with abnormal findings
Z01.419	Encounter for gynecological examination (general) (routine) without abnormal findings
Z01.812	Encounter for preprocedural laboratory examination
Z01.84	Encounter for antibody response examination
Z01.89	Encounter for other specified special examinations
Z11.0	Encounter for screening for intestinal infectious diseases
Z11.1	Encounter for screening for respiratory tuberculosis
Z11.2	Encounter for screening for other bacterial diseases
Z11.3	Encounter for screening for infections with a predominantly sexual mode of transmission
Z11.4	Encounter for screening for human immunodeficiency virus [HIV]
Z11.51	Encounter for screening for human papillomavirus (HPV)
Z11.59	Encounter for screening for other viral diseases
Z11.6	Encounter for screening for other protozoal diseases and helminthiases
Z11.8	Encounter for screening for other infectious and parasitic diseases
Z11.9	Encounter for screening for infectious and parasitic diseases, unspecified
Z12.0	Encounter for screening for malignant neoplasm of stomach
Z12.10	Encounter for screening for malignant neoplasm of intestinal tract, unspecified
Z12.11	Encounter for screening for malignant neoplasm of colon
Z12.12	Encounter for screening for malignant neoplasm of rectum
Z12.13	Encounter for screening for malignant neoplasm of small intestine
Z12.2	Encounter for screening for malignant neoplasm of respiratory organs
Z12.31	Encounter for screening mammogram for malignant neoplasm of breast
Z12.39	Encounter for other screening for malignant neoplasm of breast
Z12.4	Encounter for screening for malignant neoplasm of cervix
Z12.6	Encounter for screening for malignant neoplasm of bladder
Z12.72	Encounter for screening for malignant neoplasm of vagina
Z12.81	Encounter for screening for malignant neoplasm of oral cavity
Z12.83	Encounter for screening for malignant neoplasm of skin
Z13.0	Encounter for screening for diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Z13.1	Encounter for screening for diabetes mellitus
Z13.21	Encounter for screening for nutritional disorder
Z13.22	Encounter for screening for metabolic disorder
Z13.220	Encounter for screening for lipoid disorders
Z13.228	Encounter for screening for other metabolic disorders
Z13.29	Encounter for screening for other suspected endocrine disorder
Z13.30	Encounter for screening examination for mental health and behavioral disorders, unspecified
Z13.31	Encounter for screening for depression
Z13.32	Encounter for screening for maternal depression
Z13.39	Encounter for screening examination for other mental health and behavioral disorders
Z13.4	Encounter for screening for certain developmental disorders in childhood (Code invalid effective 09/30/2018)

Z13.40	Encounter for screening for unspecified developmental delays (Code effective 10/01/2018)
Z13.41	Encounter for autism screening (Code effective 10/01/2018)
Z13.42	Encounter for screening for global developmental delays (milestones) (Code effective 10/01/2018)
Z13.49	Encounter for screening for other developmental delays (Code effective 10/01/2018)
Z13.5	Encounter for screening for eye and ear disorders
Z13.6	Encounter for screening for cardiovascular disorders
Z13.71	Encounter for nonprocreative screening for genetic disease carrier status
Z13.79	Encounter for other screening for genetic and chromosomal anomalies
Z13.810	Encounter for screening for upper gastrointestinal disorder
Z13.811	Encounter for screening for lower gastrointestinal disorder
Z13.818	Encounter for screening for other digestive system disorders
Z13.820	Encounter for screening for osteoporosis
Z13.828	Encounter for screening for other musculoskeletal disorder
Z13.83	Encounter for screening for respiratory disorder, NEC
Z13.84	Encounter for screening for dental disorders
Z13.850	Encounter for screening for traumatic brain injury
Z13.858	Encounter for screening for other nervous system disorder
Z13.88	Encounter for screening for disorder due to exposure to contaminants
Z13.89	Encounter for screening for other disorder
Z13.9	Encounter for screening, unspecified
Z30.011	Encounter for initial prescription of contraceptive pills
Z30.013	Encounter for initial prescription of injectable contraceptive
Z30.018	Encounter for initial prescription of other contraceptives
Z30.019	Encounter for initial prescription of contraceptive, unspecified
Z30.02	Counseling and instruction in natural family planning to avoid pregnancy
Z30.09	Encounter for other general counseling and advice on contraception
Z30.40	Encounter for surveillance of contraceptives, unspecified
Z30.41	Encounter for surveillance of contraceptive pills
Z30.44	Encounter for surveillance of vaginal ring hormonal contraceptive device
Z30.45	Encounter for surveillance of transdermal patch hormonal contraceptive device
Z32.02	Encounter for pregnancy test, result negative
Z78.0	Asymptomatic menopausal state

Considered Not Medically Necessary:

ICD-10-CM Diagnosis Codes	**Description**
Z30.014	Encounter for initial prescription of intrauterine contraceptive device
Z30.430	Encounter for insertion of intrauterine contraceptive device
Z30.431	Encounter for routine checking of intrauterine contraceptive device
Z30.432	Encounter for removal of intrauterine contraceptive device
Z30.433	Encounter for removal and reinsertion of intrauterine contraceptive device
Z97.5	Presence of (intrauterine) contraceptive device

References

1. American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative, 2013. American College of Obstetricians and Gynecologists (ACOG). Accessed November 20, 2019. Available at URL address: http://www.choosingwisely.org/clinician-lists/american-college-obstetricians-gynecologists-screening-for-ovarian-cancer-in-asymptomatic-women-at-average-risk/

2. American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 182: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol. 2017 Sept;130(3):e110-e126. Reaffirmed 2019

3. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 186: Long-acting reversible contraception: Implants and intrauterine devices. Obstet Gynecol. Obstet Gynecol. 2017 Nov;130(5):e251-e269.

4. American College of Obstetricians and Gynecologists. Committee on Gynecologic Practice, Long-Acting Reversible Contraception Work Group. Committee Opinion No 672: Clinical Challenges of Long-Acting Reversible Contraceptive Methods. Obstet Gynecol. 2016 Sep;128(3):e69-77. Reaffirmed 2019

5. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, Society of Gynecologic Oncology. Committee Opinion No. 716: The Role of the Obstetrician-Gynecologist in the Early Detection of Epithelial Ovarian Cancer in Women at Average Risk. Obstet Gynecol. 2017 Sep;130(3):e146-e149.

6. American College of Radiology (ACR) Practice Guideline for the performance of pelvic ultrasound. Revised 2019. Accessed November 20, 2019. Available at URL address: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/US-Pelvis.pdf?la=en

7. American College of Radiology (ACR) Appropriateness Criteria®, Ovarian Cancer Screening. 2017. Accessed November 20, 2019. Available at URL address: https://acsearch.acr.org/list

8. Bartz DA, Pocius KD. Intrauterine contraception: Insertion and removal. In: UpToDate, Schreiber CA (Ed). October 2019. UpToDate, Waltham, MA. Accessed on November 21, 2019.

9. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. Canadian Contraception Consensus (Part 3 of 4): Chapter 7--Intrauterine Contraception. J Obstet Gynaecol Can. 2016 Feb;38(2):182-222.

10. Bosse K, Rhiem K, Wappenschmidt B, Hellmich M, Madeja M, Ortmann M, et al. Screening for ovarian cancer by transvaginal ultrasound and serum CA125 measurement in women with a familial predisposition: a prospective cohort study. Gynecol Oncol. 2006 Dec;103(3):1077-82.

11. Buhling KJ, Lezon S, Eulenburg C, Schmalfeldt B. The role of transvaginal ultrasonography for detecting ovarian cancer in an asymptomatic screening population: a systematic review. Arch Gynecol Obstet. 2017 May;295(5):1259-1268.

12. Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. JAMA 277 (11): 915-9, 1997

13. Buys SS, Partridge E, Greene MH, Prorok PC, Reding D, Riley TL, Hartge P, Fagerstrom RM, Ragard LR, Chia D, Izmirlian G, Fouad M, Johnson CC, Gohagan JK; PLCO Project Team. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol. 2005 Nov;193(5):1630-9. Erratum in: Am J Obstet Gynecol. 2005 Dec;193(6):2183-4.

14. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011 Jun 8;305(22):2295-303.

15. Cancer Council Queensland, Optimal Cancer Care Pathways. Optimal care pathway for women with endometrial cancer. 2016. Accessed November 20, 2019. Available at URL address: https://cancerqld.org.au/health-professionals/professional-information/optimal-cancer-care-pathways/

16. Cancer Council Queensland, Optimal Cancer Care Pathways. Optimal care pathway for women with ovarian cancer. 2016. Accessed November 20, 2019. Available at URL address: https://cancerqld.org.au/health-professionals/professional-information/optimal-cancer-care-pathways/

17. Carlson KJ. Screening for ovarian cancer. In: UpToDate, Goff B, Elmore JG (Ed). October 2019. UpToDate, Waltham, MA. Accessed November 21, 2019.

18. Chen LM, Berek JS. Endometrial carcinoma: Epidemiology risk factors, and prevention. In: UpToDate, Goff B, Dizon DS (Ed). October 2019. UpToDate, Waltham, MA. Accessed November 21, 2019.

19. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016 Jan;27(1):16-41

20. Curtis KM, Jatlaoui TC, Tepper NK, et al: U.S. Selected Practice Recommendations for Contraceptive Use, 2016. MMWR Recomm Rep 65 (4):1–66, 2016.

21. de Kroon CD, van Houwelingen JC, Trimbos JB, Jansen FW. The value of transvaginal ultrasound to monitor the position of an intrauterine device after insertion. A technology assessment study. Hum Reprod. 2003 Nov;18(11):2323-7.

22. Dias T, Abeykoon S, Kumarasiri S, Gunawardena C, Padeniya T, D'Antonio F. Use of ultrasound in predicting success of intrauterine contraceptive device insertion immediately after delivery. Ultrasound Obstet Gynecol. 2015 Jul;46(1):104-8.

23. Evans DG, Gaarenstroom KN, Stirling D, Shenton A, Maehle L, Dørum A, et al. Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. J Med Genet. 2009 Sep;46(9):593-7.

24. Fishman DA, Cohen L, Blank SV, et al. The role of ultrasound evaluation in the detection of early-stage epithelial ovarian cancer. Am J Obstet Gynecol. 2005;192:1214-1221; discussion 1221–1212.

25. Gibbs RS, Karlan BY, Haney AF, Nygaard IE, editors. Danforth's Obstetrics and Gynecology, 10th Edition. ©2008 Lippincott Williams & Wilkins. p. 540- 554

26. Goldthwaite LM, Cahill EP, Voedisch AJ, Blumenthal PD. Postpartum intrauterine devices: clinical and programmatic review. Am J Obstet Gynecol. 2018 Sep;219(3):235-241.

27. Hagood M. Intrauterine Device Insertion. Last Updated: Nov 29, 2018. Accessed November 21, 2019. Available at URL address: https://emedicine.medscape.com/article/1998022-overview

28. Henderson JT, Webber EM, Sawaya GF. Screening for Ovarian Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018 Feb 13;319(6):595-606.

29. Hermsen BB, Olivier RI, Verheijen RH, van Beurden M, de Hullu JA, Massuger LF, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. Br J Cancer. 2007 May 7;96(9):1335-42 (abstract only).

30. Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol. 2011 Jan;12(1):38-48.

31. Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2016 Mar 5;387(10022):945-956.

32. Lacey JV Jr, Greene MH, Buys SS, Reding D, Riley TL, Berg CD, et al. Ovarian cancer screening in women with a family history of breast or ovarian cancer. Obstet Gynecol. 2006 Nov;108(5):1176-84.

33. Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol. 2009 Apr;10(4):327-40.

34. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Guidelines in Oncology™. Genetic/familial high-risk assessment: breast and ovarian. Version.3.2019. © National Comprehensive Cancer Network, Inc 2019a, All Rights Reserved. Accessed November 21, 2019. Available at URL address: http://www.nccn.org/clinical.asp

35. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Guidelines in Oncology™. Genetic/familial high-risk assessment: colorectal. Version.2.2019. © National Comprehensive Cancer Network, Inc 2019b, All Rights Reserved. Accessed November 21, 2019. Available at URL address: http://www.nccn.org/clinical.asp

36. National Cancer Institute (NCI). Endometrial cancer (PDQ®): Screening, Summary of Evidence, Health Professional Version. Last Updated: March, 2019a. Accessed November 21, 2019. Available at URL address: http://www.cancer.gov/cancertopics/pdq/screening/endometrial/HealthProfessional

37. National Cancer Institute (NCI). Genetics of Colorectal Cancer (PDQ®); major genetic Syndromes; Screening for endometrial cancer in Lynch syndrome families. Health Professional Version. Last Updated: November, 2019b. Accessed November 21, 2019. Available at URL address: http://www.cancer.gov/types/colorectal/hp/colorectal-genetics-pdq#link/_279_toc

38. National Cancer Institute (NCI). Ovarian cancer (PDQ®): Screening, Summary of Evidence, Health Professional Version. Last Updated: November, 2019c. Accessed November 21, 2019. Available at URL address: http://www.cancer.gov/types/ovarian/hp/ovarian-screening-pdq

39. Partridge E, Kreimer AR, Greenlee RT, Williams C, Xu JL, PLCO Project Team, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol. 2009 Apr;113(4):775-82.

40. Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2017 Feb 15;123(4):592-599.

41. Pocius KD, Bartz DA. Intrauterine contraception: Management of side effects and complications. In: UpToDate, Schreiber CA (Ed). October 2019. UpToDate, Waltham, MA. Accessed on November 19, 2019.

42. Prabhakaran S, Chuang A. In-office retrieval of intrauterine contraceptive devices with missing strings. Contraception. 2011 Feb;83(2):102-6.

43. Prine L, Shah M. Long-Acting Reversible Contraception: Difficult Insertions and Removals. Am Fam Physician. 2018 Sep 1;98(5):304-309.

44. Reade CJ, Riva JJ, Busse JW, Goldsmith CH, Elit L. Risks and benefits of screening asymptomatic women for ovarian cancer: a systematic review and meta-analysis. Gynecol Oncol. 2013 Sep;130(3):674-81.

45. Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer. 2007 Feb 15;120(4):821-4.

46. Rijcken FE, Mourits MJ, Kleibeuker JH, Hollema H, van der Zee AG. Gynecologic screening in hereditary nonpolyposis colorectal cancer. Gynecologic Oncology 2003;91;74-80.

47. The Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of women with epithelial ovarian cancer stated that screening for ovarian cancer in the general population should not be performed outside of the research setting (SIGN, 2013; Revised 2018).

48. Smith RA, Andrews KA, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2018 Jul-Aug;68(4):297-316.

49. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes. Am J Gastroenterol. 2015 Feb;110(2):223-62.

50. Temkin SM, Miller EA, Samimi G, Berg CD, Pinsky P, Minasian L. Outcomes from ovarian cancer screening in the PLCO trial: Histologic heterogeneity impacts detection, overdiagnosis and survival. European Journal of Cancer 2017;87:182-188.

51. U.S. Preventive Services Task Force. Screening for Ovarian Cancer: US Preventive Services Task Force recommendation statement. Release Date: February 2018. Agency for Healthcare Research and Quality, Rockville, MD. Accessed November 21, 2019. Available at URL address: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/ovarian-cancer-screening1

52. van Nagell JR Jr, DePriest PD, Ueland FR, DeSimone CP, Cooper AL, McDonald JM, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. Cancer. 2007 May 1;109(9):1887-96.

53. Woodward ER, Sleightholme HV, Considine AM, Williamson S, McHugo JM, Cruger DG. Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. BJOG. 2007 Dec;114(12):1500-9.

54. Yasa C, Dural O, Bastu E, Ugurlucan FG, Nehir A, İyibozkurt AC. Evaluation of the diagnostic role of transvaginal ultrasound measurements of endometrial thickness to detect endometrial malignancy in asymptomatic postmenopausal women. Arch Gynecol Obstet. 2016 Aug;294(2):311-6.