American College of Radiology
ACR Appropriateness Criteria®
Ovarian Cancer Screening

Variant 1:   Ovarian cancer screening. Premenopausal. Average risk.

Procedure	Appropriateness Category	Relative Radiation Level
US pelvis transvaginal	Usually Not Appropriate	O
US pelvis transabdominal	Usually Not Appropriate	O
US color Doppler ovaries	Usually Not Appropriate	O
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis with IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☢☢☢☢
MRI pelvis without IV contrast	Usually Not Appropriate	O
MRI pelvis without and with IV contrast	Usually Not Appropriate	O
FDG-PET/CT whole body	Usually Not Appropriate	☢☢☢☢

Variant 2:   Ovarian cancer screening. Postmenopausal. Average risk.

Procedure	Appropriateness Category	Relative Radiation Level
US pelvis transvaginal	Usually Not Appropriate	O
US pelvis transabdominal	Usually Not Appropriate	O
US color Doppler ovaries	Usually Not Appropriate	O
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis with IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☢☢☢☢
MRI pelvis without IV contrast	Usually Not Appropriate	O
MRI pelvis without and with IV contrast	Usually Not Appropriate	O
FDG-PET/CT whole body	Usually Not Appropriate	☢☢☢☢

Variant 3: Ovarian cancer screening. Premenopausal. High risk (personal history or family history or known or suspected genetic predisposition or elevated CA-125).

Procedure	Appropriateness Category	Relative Radiation Level
US pelvis transvaginal	May Be Appropriate	O
US pelvis transabdominal	May Be Appropriate	O
US color Doppler ovaries	May Be Appropriate	O
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis with IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☢☢☢☢
MRI pelvis without IV contrast	Usually Not Appropriate	O
MRI pelvis without and with IV contrast	Usually Not Appropriate	O
FDG-PET/CT whole body	Usually Not Appropriate	☢☢☢☢

Variant 4: Ovarian cancer screening. Postmenopausal. High risk (personal history or family history or known or suspected genetic predisposition or elevated CA-125).

Procedure	Appropriateness Category	Relative Radiation Level
US pelvis transvaginal	May Be Appropriate	O
US color Doppler ovaries	May Be Appropriate	O
US pelvis transabdominal	May Be Appropriate	O
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis with IV contrast	Usually Not Appropriate	☢☢☢
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☢☢☢☢
MRI pelvis without IV contrast	Usually Not Appropriate	O
MRI pelvis without and with IV contrast	Usually Not Appropriate	O
FDG-PET/CT whole body	Usually Not Appropriate	☢☢☢☢

OVARIAN CANCER SCREENING

Expert Panel on Women's Imaging: Pari V. Pandharipande, MD, MPH[a]; Kathryn P. Lowry, MD[b]; Caroline Reinhold, MD[c]; Mostafa Atri, MD[d]; Carol B. Benson, MD[e]; Priyadarshani R. Bhosale, MD[f]; Edward D. Green, MD[g]; Stella K. Kang, MD, MS[h]; Yulia Lakhman, MD[i]; Katherine E. Maturen, MD, MS[j]; Refky Nicola, DO[k]; Gloria M. Salazar, MD[l]; Thomas D. Shipp, MD, RDMS[m]; Lynn Simpson, MD[n]; Betsy L. Sussman, MD[o]; Jennifer Uyeda, MD[p]; Darci J. Wall, MD[q]; Bradford Whitcomb, MD[r]; Carolyn M. Zelop, MD[s]; Phyllis Glanc, MD.[t]

<u>Summary of Literature Review</u>

Introduction/Background

There has been much debate about the role of imaging in ovarian cancer screening based on currently available evidence [1]. Ovarian cancer has low disease prevalence, yet is the leading cause of mortality due to gynecologic malignancy in women in the United States [2]. It is estimated that there will be 22,440 new cancer diagnoses and 14,080 cancer deaths in 2017 [2]. The high mortality rate observed is largely due to late detection, as it is commonly discovered only after its widespread dissemination. Metastatic disease is present in 60% of cases at the time of diagnosis and is associated with a low 5-year relative survival rate of 28% [2]. Only 15% of women have organ-confined disease at the time of detection, and these women have a substantially higher 5-year relative survival rate (92%) [2], suggesting that screening could be of benefit if aggressive cancers can be reliably detected at earlier stages.

Cancers that clinically fall under the umbrella of ovarian cancer are now known to have heterogeneous natural histories and tissue origins [3-7]. Five primary subtypes describe most epithelial ovarian cancers: serous, mucinous, clear cell, endometrioid, and transitional cell [6,7]. Serous cancers represent the majority of all ovarian cancers, are commonly diagnosed at late stages, and account for most ovarian cancer deaths [3-7]. Importantly, low-grade and high-grade serous tumors do not define a spectrum but instead reflect distinct tumor biologies. High-grade serous cancers are thought to arise directly from surface epithelium [6]. They commonly demonstrate TP53 mutations and are also associated with *BRCA1* and *BRCA2* mutations [5,6]. Many high-grade "ovarian" serous cancers are now thought to be extraovarian in origin, arising instead from the distal fallopian tubes (fimbria), as initially suggested by histologic evaluation of specimens from *BRCA* mutation carriers who have undergone prophylactic salpingo-oophorectomy [3,5,6,8].

The average lifetime risk for developing ovarian cancer for a woman in the United States is approximately 1.3% [2]. Women with certain risk factors are known to be at increased risk, including presence of *BRCA1* or *BRCA2* mutations, strong family history (ie, first-degree relative, particularly if premenopausal at the time of diagnosis), nulliparity, lack of breastfeeding, lack of hormonal contraception use, and postmenopausal status [9]. Among all risk factors, a genetic predisposition is associated with the highest increase in cancer risk. A recent meta-analysis projected that 20-year-old *BRCA1* and *BRCA2* mutation carriers have 39% and 16% mean cumulative risks of developing ovarian cancer, respectively, by age 70 [10]. At present, risk reduction in women with a strong genetic predisposition to ovarian cancer centers on bilateral salpingo-oophorectomy [11].

By mathematically modeling the behavior of ovarian cancers in hypothetical populations of *BRCA* mutation carriers and average-risk patients, researchers have gained insight into their natural history and have investigated a potential role for screening [3,4]. Based on their findings, current screening tools are expected to have low effectiveness because of the tendency for small cancers to spread rapidly [3,4]. Brown and Palmer [3], when

[a]Principal Author, Massachusetts General Hospital, Boston, Massachusetts. [b]Research Author, Massachusetts General Hospital, Boston, Massachusetts. [c]Panel Chair, McGill University, Montreal, Quebec, Canada. [d]Toronto General Hospital, Toronto, Ontario, Canada. [e]Brigham & Women's Hospital, Boston, Massachusetts. [f]University of Texas MD Anderson Cancer Center, Houston, Texas. [g]The University of Mississippi Medical Center, Jackson, Mississippi. [h]New York University Medical Center, New York, New York. [i]Memorial Sloan Kettering Cancer Center, New York, New York. [j]University of Michigan, Ann Arbor, Michigan. [k]University of Massachusetts Medical School, Worcester, Massachusetts. [l]Massachusetts General Hospital, Boston, Massachusetts. [m]Brigham & Women's Hospital, Boston, Massachusetts; American Congress of Obstetricians and Gynecologists. [n]Columbia University, New York, New York; American Congress of Obstetricians and Gynecologists. [o]The University of Vermont Medical Center, Burlington, Vermont. [p]Brigham & Women's Hospital, Boston, Massachusetts. [q]Mayo Clinic, Rochester, Minnesota. [r]Tripler Army Medical Center, Honolulu, Hawaii; Society of Gynecologic Oncologists. [s]Valley Hospital, Ridgewood, New Jersey and NYU School of Medicine, New York, New York; American Congress of Obstetricians and Gynecologists. [t]Specialty Chair, Sunnybrook Health Sciences Centre Bayview Campus, Toronto, Ontario, Canada.

modeling serous cancers in high-risk patients, projected that an annual screening tool for ovarian cancer would need to detect tumors as small as 0.5 cm in diameter in order to achieve a 50% mortality reduction.

After evaluating the current literature on this topic, there is no clear evidence to support screening women of average risk (no personal history, no family history, no known or suspected genetic predisposition, and no elevated CA-125). However, this document provides an update on areas of investigation that may support a future role for imaging and serum biomarkers in special cases.

Overview of Imaging Modalities

Most of the peer-reviewed imaging literature on ovarian cancer screening to date has evaluated the use of pelvic ultrasound (US), as it is generally considered the first-line imaging modality for evaluation of the adnexa. US is particularly attractive as a potential screening modality as it is inexpensive and does not expose patients to ionizing radiation. Other cross-sectional imaging methods, including magnetic resonance imaging (MRI), fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), computed tomography (CT), and FDG-PET/CT, have no known or foreseeable role in screening. Attention has also been directed to the role of CA-125 (a widely known serum tumor biomarker) for screening, either alone or in combination with imaging (eg, US and CA-125).

When evaluating the use of an imaging modality for screening, an important metric to consider is positive predictive value (PPV), which is defined as the number of true-positive cases divided by the total number of test-positive cases. Unlike the sensitivity and specificity of a diagnostic test, PPV incorporates both test performance and disease prevalence. A minimum PPV of 10% has been suggested as necessary for an ovarian cancer screening tool [9,12]. This implies that at least one cancer should be diagnosed in every 10 patients who undergo salpingo-oophorectomy for suspicion of malignancy. Given the low prevalence of ovarian cancer, very high specificity is needed for a successful screening tool. At an assumed prevalence of one case per 2,500 postmenopausal women per year, a test with perfect sensitivity (100%) would require a specificity of 99.6% to achieve a 10% PPV, and a test with 50% sensitivity would require an even higher specificity of 99.8% [9,12-14].

Discussion of Procedures by Variant

Variant 1: Ovarian cancer screening. Premenopausal. Average risk.

To our knowledge, the relevant literature on ovarian cancer screening in average-risk women is limited to studies in postmenopausal women.

US
There is currently no evidence to support the use of US or color Doppler for ovarian cancer screening in premenopausal women without risk factors. Most studies discussed in this document have addressed the use of transvaginal US. In general, transabdominal US should be reserved for women in whom transvaginal US is not technically feasible, or used as a complement to transvaginal US.

CT
There is currently no evidence to support the use of CT for ovarian cancer screening in premenopausal women without risk factors.

MRI
There is currently no evidence to support the use of MRI for ovarian cancer screening in premenopausal women without risk factors.

FDG-PET/CT
There is currently no evidence to support the use of FDG-PET/CT for ovarian cancer screening in premenopausal women without risk factors.

Variant 2: Ovarian cancer screening. Postmenopausal. Average risk.

US
US has been the most heavily investigated imaging modality for ovarian cancer screening to date, both alone and in conjunction with biomarker screening of serum CA-125. Most studies discussed in this document have addressed the use of transvaginal US. In general, transabdominal US should be reserved for women in whom transvaginal US is not technically feasible, or used as a complement to transvaginal US. A recent meta-analysis [15] of 10 randomized trials of ovarian cancer screening using US and/or serum CA-125 measurements found that the included trials did not demonstrate a significant reduction in mortality. Below we describe the studies that are

most relevant for decision making concerning ovarian cancer screening in average-risk postmenopausal women. The majority were designed to accrue a dominant population of average-risk postmenopausal women. However, across studies, exclusion criteria intended to exclude high-risk women were heterogeneous. In the University of Kentucky Ovarian Cancer Screening Study, investigators deliberately also included a subset of premenopausal high-risk women, as detailed below. Of note, the methodologic detail provided in the studies described below does not allow for uniform determination of the use, or potential benefits, of color Doppler. Therefore, the benefits of US performed with, versus without, color Doppler cannot be determined.

Summaries of Published Large Trials to Date of Ultrasound Screening in Average-Risk Women

Pilot United Kingdom Trial
In 1999, Jacobs et al [16] published a pilot randomized controlled trial in which postmenopausal women were randomized to a control group (n = 10,977) or to annual screening with CA-125 (n = 10,958) for 3 years. Patients with elevated CA-125 were referred for US, which was initially done transabdominally, and then transvaginally when this approach became more widely available. At US, ovaries ≥8.8 mL were designated as abnormal, whereas ovaries with normal volume but abnormal morphology were considered equivocal and followed with subsequent US. Women with elevated CA-125 and abnormal US were referred for surgical consideration. An 86% compliance rate with at least one screen was achieved, establishing screening feasibility. PPV was reported to be 21%, suggesting the potential viability of a multimodal screening method. This trial substantiated resources for subsequent larger randomized controlled trials.

Shizuoka District (Japan) Trial
In 2008, Kobayashi et al [17] published a randomized controlled trial in which postmenopausal women were randomized to a control group (n = 40,799) or to five screening rounds of CA-125 and US (n = 41,688). US was predominantly performed using a transvaginal approach. At US, ovaries were considered suspicious for malignancy if ovarian size was >4 cm and a complex morphology was apparent. In the screening group, further management ranged from annual follow-up to surgical intervention, depending on combined test results. Salient trial findings were 2-fold. First, ovarian cancer prevalence was lower (0.31/1,000) than in an expected United States population. Second, a statistically significant shift in stage distribution was not achieved.

United States Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
In 2011, Buys et al [18] published results of the United States Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a randomized controlled trial in which postmenopausal women were randomized to a control group (n = 39,111) or annual screening (n = 39,105) with CA-125 for 6 years and transvaginal US for 4 years. US results were considered abnormal if ovarian or ovarian cyst volume was >10 mL or if intraovarian lesions harbored projections into cysts or mixed solid and cystic components [18]. In 2009, Partridge et al [19] published results of the first four screening rounds, demonstrating low PPV (range, 1%–1.3%) and a predominance of late-stage cancers detected. In the final analysis, Buys et al [18] found no significant shift in stage distribution and no statistically significant reduction in cancer-specific mortality. False-positive results occurred in 3,285 women. Among this group, 1,080 (33%) underwent surgery with oophorectomy, 163 (15%) of whom experienced a major complication [18]. Importantly, this study was powered to detect a 35% mortality reduction—smaller reductions could not be reliably resolved. However, based on projections of uncertainty, at most an 18% relative mortality benefit of screening was considered possible [18].

University of Kentucky Ovarian Cancer Screening Study
In 2011, van Nagell et al [20] published long-term results of a single-arm screening trial of annual transvaginal US conducted at the University of Kentucky. The patient population included a mix of postmenopausal women (asymptomatic patients ≥50 years of age) and premenopausal women with a family history of ovarian cancer. In total, a minority of patients (23.2%) had a family history of ovarian cancer. Therefore, we presumed that most patients were average-risk postmenopausal patients. Initial study results after 25,327 screens, reported in 2007 [21], indicated a potential shift in stage distribution and mortality reduction compared with observed institutional and state tumor registry data from women who did not undergo screening. These findings were also observed when longer-term results were reported in 2011 [20]: after a mean follow-up of 5.8 years, 70% of screen-detected cancers were stage I or II at diagnosis (compared with 27% of observed controls), and 5-year ovarian cancer–specific survival was 75% (compared with 54% for observed controls). Despite these encouraging results, the study design (with no control group and with a mixed-risk population) was subject to known epidemiologic biases. As indicated above, PLCO randomized controlled trial results did not reproduce the findings of this single-arm study [18].

Lu, Skates, Hernandez, and Colleagues
In 2013, Lu et al [22] reported results from a single-arm prospective trial of ovarian cancer screening in 4,051 postmenopausal women using the Risk of Ovarian Cancer Algorithm (ROCA) score based on serum CA-125 measurements (described below). In this trial, women with ROCA scores indicating intermediate risk (risk of ovarian cancer between 1 in 2,000 and 1 in 500) had a repeat CA-125 measurement in 3 months, and women with ROCA scores indicating elevated risk (>1 in 500) were referred for transvaginal US and gynecologic oncology consultation. After 11 years of follow-up, 10 women underwent surgery based on US findings, and 4 of these women were found to have invasive ovarian cancer (PPV, 40%). Specificity was 99.9%. These results support the notion that assessment of changing levels in biomarkers over time may be a more useful screening tool than single values, such as those used in the PLCO trial, and can improve PPV and specificity. However, this trial was not designed to assess mortality outcomes.

United Kingdom Collaborative Trial of Ovarian Cancer Screening
The United Kingdom Collaborative Trial of Ovarian Cancer Screening [23,24] is the largest randomized controlled trial of ovarian cancer screening to date, with over 200,000 postmenopausal women randomized to either a control group, multimodal screening (ie, annual CA-125 with transvaginal US as a follow-up test), or annual transvaginal US alone. US results were considered abnormal if ovaries demonstrated a complex morphology or had simple cysts >60 mL or if ascites was present [24]. Rather than using standard single cutoffs for CA-125 positivity, CA-125 results were designated based on the ROCA algorithm described by Menon et al [25] in earlier work. This algorithm incorporates patient age and CA-125 trends to triage further management, and it is expected to improve CA-125 test performance, particularly its PPV and specificity [25].

In 2009, Menon et al [24] published results of the prevalence screen, which demonstrated that the multimodal strategy was superior to US alone, resulting in sensitivity, specificity, and PPV values of 89.4%, 99.8%, and 43.3% compared to 84.9%, 98.2%, and 5.3%, respectively. In 2016, Jacobs et al [23] reported long-term study results for the final cohort, which included 101,299 women in the control group, 50,624 women in the multimodal screening group, and 50,623 women in the US-only group. After a median follow-up of 11.1 years, there was evidence of a stage shift due to screening. Although only 26% of primary ovarian and peritoneal cancers were detected as stage I, II, or IIIa cancers in the control group, a significantly higher proportion was diagnosed at an early stage in the multimodal group (40%) but not in the US-only–group (24%). However, the primary study end point of ovarian cancer mortality reduction did not achieve statistical significance over the 14-year study period. A post hoc analysis identified a significant ovarian cancer mortality reduction in the multimodal group relative to the control group when accounting for expected delayed mortality reductions. These findings are still likely insufficient to provide support for population screening at this time, given that the primary, prospectively planned analysis measure did not achieve significance. However, they are encouraging for a potential future role for the use of US in conjunction with biomarkers in population screening.

MRI
To our knowledge, there have been no trials evaluating the use of MRI for ovarian cancer screening in women at average risk. Although MRI is a valuable tool for characterizing adnexal masses that are indeterminate based on US features [26], there has been little interest in its use as a population screening tool given its cost and unclear advantage.

CT
To our knowledge, there have been no trials evaluating the use of CT for ovarian cancer screening in women at average risk. CT is routinely used for ovarian cancer staging to assess for distant metastases, but it has limited use in the evaluation of the adnexa given its limited ability to distinguish between benign and malignant lesions. For example, in a study of 2,869 postmenopausal women undergoing CT screening colonography [27], 118 (4.1% of the cohort) had incidentally detected adnexal lesions noted at interpretation. Of these, 80 were referred for additional imaging workup and/or surgery. In the 26 women who underwent surgical excision, no ovarian cancers were identified. Furthermore, four women in the cohort subsequently developed ovarian cancer after a negative CT evaluation. The limited discriminatory ability of CT renders it impractical for use as a screening tool in this setting.

FDG-PET/CT
To our knowledge, there have been no trials evaluating the use of FDG-PET/CT for ovarian cancer screening in women at average risk. Although FDG-PET/CT is an important oncologic imaging tool for cancer staging and detection of recurrence, it has no clear value for detecting ovarian cancer in asymptomatic individuals. In a

systematic review of imaging modalities for preoperative evaluation of adnexal lesions, the sensitivity of PET was substantially lower than that of US or MRI [28], possibly because of the composition of ovarian neoplasms, many of which tend to be predominantly cystic with small solid components that may be below the size threshold for detection by PET.

Variant 3: Ovarian cancer screening. Premenopausal. High risk (personal history or family history or known or suspected genetic predisposition or elevated CA-125).

US
Most studies discussed in this document have addressed the use of transvaginal US. In general, transabdominal US should be reserved for women in whom transvaginal US is not technically feasible, or used as a complement to transvaginal US.

To our knowledge, randomized controlled trials analogous to those in average-risk populations have not been conducted in definitively high-risk populations. Several related studies have been reported, all relatively small in sample size and most of which include a mix of premenopausal and postmenopausal women at high risk [29-33]. The largest study to date is the UK Familial Ovarian Cancer Screening Study [34], a single-arm prospective study of 3,563 premenopausal and postmenopausal women with lifetime risk of ovarian cancer ≥10% based on family history or a known predisposing genetic mutation. The median participant age at study enrollment was   44.6 years (range, 35-81 years); therefore, we presumed that the majority of high-risk women were premenopausal. Women in the study were followed over a mean of 3.2 years with a combination of annual transvaginal US and serum CA-125 measurements. The sensitivity of detection of incident ovarian/fallopian tube cancers in the study was 81.3% to 87.5%, depending on whether occult cancers detected at risk-reducing salpingo-oophorectomy were considered false negatives or true positives. The PPV was 25.5%. Of the 13 incident cancers in the study, 4 (31%) were stage I or stage II; however, women who had not undergone screening within 365 days of diagnosis were more likely to have stage IIIc or higher cancer compared with women who had received screening within the past year. The authors concluded that their findings highlight the importance of strict screening adherence, and as a result the screening frequency for phase II of the trial was reduced to 4 months. The results for phase II of the trial are not yet available.

The University of Kentucky Ovarian Cancer Screening Study cohort [20] also included premenopausal women with a family history of ovarian cancer. The study results were reported in aggregate for patients with and without a family history of ovarian cancer. However, the authors note that there was no significant difference in the incidence of malignant or benign ovarian tumors between these groups. Although the results of this single-arm study were promising, a definitive mortality reduction has not been observed in randomized controlled trials [18,23].

Other studies of ovarian cancer screening with CA-125 and/or US in high-risk women have not had promising results. Despite higher reported PPV in some studies (expected with higher disease prevalence), aggressive serous cancers—frequently seen in high-risk patients—were typically detected at advanced stages despite screening [29-33].

MRI
To our knowledge, there are no trials for the use of MRI as an ovarian cancer screening tool in high-risk women. MRI is unlikely to be investigated as a screening tool.

CT
To our knowledge, there are no trials of the use of CT as an ovarian cancer screening tool in high-risk women. CT has a limited role in the evaluation of adnexal lesions and would be an impractical screening modality because of its poor discriminatory ability between benign and malignant adnexal lesions and the associated risks of ionizing radiation.

FDG-PET/CT
To our knowledge, there have been no trials evaluating the use of FDG-PET/CT as an ovarian cancer screening tool in high-risk women. FDG-PET/CT has poor performance in this setting and is impractical as a screening modality.

Variant 4: Ovarian cancer screening. Postmenopausal. High risk (personal history or family history or known or suspected genetic predisposition or elevated CA-125).

US
Most studies discussed in this document have addressed the use of transvaginal US. In general, transabdominal US should be reserved for women in whom transvaginal US is not technically feasible, or used as a complement to transvaginal US.

To our knowledge, randomized controlled trials analogous to those in average-risk populations have not been conducted in definitively high-risk populations. Several related studies have been reported, all relatively small in sample size and most of which include a mix of premenopausal and postmenopausal women at high risk [29-33].

In 2006, Lacey et al [35] performed a secondary analysis of PLCO data to compare, within the screening arm, differences in screening outcomes (after the first four rounds of screening) between women of varying risk for ovarian cancer. Risk was classified based on personal history of breast cancer and family history of breast or ovarian cancer. Although the PPV of screening was marginally higher for women in specified moderate- and high-risk groups compared to those at average risk (PPV of 1.3% and 1.6% in the moderate- and high-risk groups, respectively, compared to 0.7% in the average-risk group), this difference was not statistically significant.

In 2016, Lai et al [36] published a subgroup analysis of PLCO data to determine whether annual screening with pelvic US and serum CA-125 reduced ovarian cancer mortality in a subgroup of women with a first-degree relative with breast or ovarian cancer. The authors compared outcomes for 11,293 women in the screening group and 11,062 women in the control group, who were followed for a minimum of 10 years. As seen in the parent PLCO study, there was no significant difference in ovarian cancer mortality between the screening and control groups. There was evidence of a stage shift and improved survival among patients with ovarian cancer in the screening group (relative risk, 0.66; 95% CI, 0.47-0.93). The authors acknowledged the potential for standard epidemiologic biases to affect their results, despite specific methodologic measures taken, and emphasized the need for further related investigation in high-risk individuals.

The largest study to date is the UK Familial Ovarian Cancer Screening Study [34], a single-arm prospective study of 3,563 premenopausal and postmenopausal women with a lifetime risk of ovarian cancer ≥10% based on family history or a known predisposing genetic mutation. The median participant age at study enrollment was 44.6 years (range, 35-81 years); therefore, we presumed that the majority of high-risk women were premenopausal. Women in the study were followed over a mean of 3.2 years with a combination of annual transvaginal US and serum CA-125 measurements. The sensitivity of detection of incident ovarian/fallopian tube cancers in the study was 81.3% to 87.5%, depending on whether occult cancers detected at risk-reducing salpingo-oophorectomy were considered false negatives or true positives. The PPV was 25.5%. Of the 13 incident cancers in the study, 4 (31%) were stage I or stage II; however, women who had not undergone screening within 365 days of diagnosis were more likely to have stage IIIc or higher cancer compared with women who had received screening within the past year. The authors concluded that their findings highlight the importance of strict screening adherence, and as a result the screening frequency for phase II of the trial was reduced to 4 months. The results for phase II of the trial are not yet available.

Other studies of ovarian cancer screening with CA-125 and/or US in high-risk women have not had promising results. Despite higher reported PPV in some studies (expected with higher disease prevalence), aggressive serous cancers—frequently seen in high-risk patients—were typically detected at advanced stages despite screening [29-33].

MRI
To our knowledge, there are no trials for the use of MRI as an ovarian cancer screening tool in high-risk women. MRI is unlikely to be investigated as a screening tool.

CT
To our knowledge, there are no trials of the use of CT as an ovarian cancer screening tool in high-risk women. CT has a limited role in the evaluation of adnexal lesions and would be an impractical screening modality because of its poor discriminatory ability between benign and malignant adnexal lesions and the associated risks of ionizing radiation.

FDG-PET/CT

To our knowledge, there are no trials of the use FDG-PET/CT as an ovarian cancer screening tool in high-risk women. FDG-PET/CT has poor performance in this setting and is impractical as a screening modality.

Summary of Recommendations

- Ovarian cancer screening is not recommended for average-risk premenopausal women.
- Ovarian cancer screening is not recommended for average-risk postmenopausal women, as randomized controlled trials have not demonstrated a definitive mortality benefit in this population.
- Ovarian cancer screening with pelvic US may be appropriate for some premenopausal women at increased risk for ovarian cancer; however, strong evidence is not available for this clinical scenario.
- Ovarian cancer screening with pelvic US may be appropriate for some postmenopausal women at increased risk for ovarian cancer; however, strong evidence is not available for this clinical scenario.

Summary of Evidence

Of the 37 references cited in the *ACR Appropriateness Criteria® Ovarian Cancer Screening* document, all of them are categorized as diagnostic references including 7 well-designed studies, 1 good-quality study, and 9 studies that may have design limitations. There are 16 references that may not be useful as primary evidence. There are 4 references that are meta-analysis studies.

The 37 references cited in the *ACR Appropriateness Criteria® Ovarian Cancer Screening* document were published from 1989 to 2017.

Although there are references that report on studies with design limitations, 8 well-designed or good-quality studies provide good evidence.

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional

information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [37].

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies".		

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

References

1. Lutz AM, Willmann JK, Drescher CW, et al. Early diagnosis of ovarian carcinoma: is a solution in sight? *Radiology.* 2011;259(2):329-345.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.
3. Brown PO, Palmer C. The preclinical natural history of serous ovarian cancer: defining the target for early detection. *PLoS Med.* 2009;6(7):e1000114.
4. Havrilesky LJ, Sanders GD, Kulasingam S, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity: implications for potential mortality reduction. *Cancer.* 2011;117(3):545-553.
5. Kurman RJ, Visvanathan K, Roden R, Wu TC, Shih Ie M. Early detection and treatment of ovarian cancer: shifting from early stage to minimal volume of disease based on a new model of carcinogenesis. *Am J Obstet Gynecol.* 2008;198(4):351-356.
6. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. *Pathology.* 2011;43(5):420-432.
7. Soslow RA. Histologic subtypes of ovarian carcinoma: an overview. *Int J Gynecol Pathol.* 2008;27(2):161-174.
8. Crum CP, Drapkin R, Kindelberger D, Medeiros F, Miron A, Lee Y. Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. *Clin Med Res.* 2007;5(1):35-44.
9. Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. *N Engl J Med.* 2009;361(2):170-177.
10. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007;25(11):1329-1333.
11. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol.* 2009;113(4):957-966.
12. Jacobs I, Bast RC, Jr. The CA 125 tumour-associated antigen: a review of the literature. *Hum Reprod.* 1989;4(1):1-12.
13. Committee Opinion No. 477: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer. *Obstet Gynecol.* 2011;117(3):742-746.
14. Daniilidis A, Karagiannis V. Epithelial ovarian cancer. Risk factors, screening and the role of prophylactic oophorectomy. *Hippokratia.* 2007;11(2):63-66.
15. 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;130(3):674-681.

16. Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet.* 1999;353(9160):1207-1210.
17. Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. *Int J Gynecol Cancer.* 2008;18(3):414-420.
18. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA.* 2011;305(22):2295-2303.
19. Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol.* 2009;113(4):775-782.
20. van Nagell JR, Jr., Miller RW, DeSimone CP, et al. Long-term survival of women with epithelial ovarian cancer detected by ultrasonographic screening. *Obstet Gynecol.* 2011;118(6):1212-1221.
21. van Nagell JR, Jr., DePriest PD, Ueland FR, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. *Cancer.* 2007;109(9):1887-1896.
22. Lu KH, Skates S, Hernandez MA, et al. A 2-stage ovarian cancer screening strategy using the Risk of Ovarian Cancer Algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value. *Cancer.* 2013;119(19):3454-3461.
23. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet.* 2016;387(10022):945-956.
24. Menon U, Gentry-Maharaj A, Hallett R, 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;10(4):327-340.
25. Menon U, Skates SJ, Lewis S, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. *J Clin Oncol.* 2005;23(31):7919-7926.
26. Kinkel K, Lu Y, Mehdizade A, Pelte MF, Hricak H. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization--meta-analysis and Bayesian analysis. *Radiology.* 2005;236(1):85-94.
27. Pickhardt PJ, Hanson ME. Incidental adnexal masses detected at low-dose unenhanced CT in asymptomatic women age 50 and older: implications for clinical management and ovarian cancer screening. *Radiology.* 2010;257(1):144-150.
28. Dodge JE, Covens AL, Lacchetti C, et al. Preoperative identification of a suspicious adnexal mass: a systematic review and meta-analysis. *Gynecol Oncol.* 2012;126(1):157-166.
29. Gaarenstroom KN, van der Hiel B, Tollenaar RA, et al. Efficacy of screening women at high risk of hereditary ovarian cancer: results of an 11-year cohort study. *Int J Gynecol Cancer.* 2006;16 Suppl 1:54-59.
30. Hogg R, Friedlander M. Biology of epithelial ovarian cancer: implications for screening women at high genetic risk. *J Clin Oncol.* 2004;22(7):1315-1327.
31. Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. *Gynecol Oncol.* 2006;100(1):20-26.
32. van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? *Int J Cancer.* 2009;124(4):919-923.
33. Stirling D, Evans DG, Pichert G, et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. *J Clin Oncol.* 2005;23(24):5588-5596.
34. Rosenthal AN, Fraser L, Manchanda R, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. *J Clin Oncol.* 2013;31(1):49-57.
35. Lacey JV, Jr., Greene MH, Buys SS, et al. Ovarian cancer screening in women with a family history of breast or ovarian cancer. *Obstet Gynecol.* 2006;108(5):1176-1184.
36. Lai T, Kessel B, Ahn HJ, Terada KY. Ovarian cancer screening in menopausal females with a family history of breast or ovarian cancer. *J Gynecol Oncol.* 2016;27(4):e41.
37. American College of Radiology. ACR Appropriateness Criteria® Radiation Dose Assessment Introduction. Available at: http://www.acr.org/~/media/ACR/Documents/AppCriteria/RadiationDoseAssessmentIntro.pdf. Accessed September 1, 2017.