4-year surveillance 2016 - Ovarian cancer (2011) NICE guideline CG122

Appendix A: decision matrix

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
Detection in primary care			
122 – 01 What are the symptoms and signs of ovarian cancer? (1.1.1.1 – 1.1.1.5)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
122 – 02 What is the relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival? (1.1.1.1 – 1.1.1.5)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
122 – 03 For women with suspected ovarian cancer, what are the most effective first tests in primary care? (1.1.2.1 - 1.1.2.4)			
No relevant evidence identified.	No relevant evidence identified.	The British Gynaecological Society commented the following in the stakeholder consultation for the guideline on suspected cancer: "Ovarian Cancer – NICE guidelines in 2011 recommend symptom triggered testing in Ovarian Cancer. Is the GDG aware that both prospective studies evaluating this have not shown evidence of stage shift in diagnosis …" They also noted that "NICE could take this opportunity to clarify actions where Ca125 is raised and ultrasound is normal (repeat Ca125 in 6 weeks) and indeed	New evidence is unlikely to impact on guideline recommendations. The new evidence comes from two prospective cohort studies and one prognostic study. Two new prospective cohort studies were non-comparative to CA125 or ultrasound alone and only investigates use in combination. The studies refer symptomatic patients for ultrasound and CA125 and report the rate of diagnosis of ovarian cancer. The rates of diagnosis found are only small percentages of the symptomatic women tested for both CA125 and ultrasound. One prognostic

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		what constitutes an ultrasound suspicious of ovarian cancer as that would provide clear guidance to primary care." However, British Gynaecological Society noted that they did not have any published evidence on suggesting a repeat of a CA125 in 6 weeks. The British Gynaecological Society identified two prospective cohort studies[90,91] that tested transvaginal ultrasonography and CA125 in women with symptoms of ovarian cancer. In the first study[90] 211 out of 241 symptomatic women underwent transvaginal ultrasound and CA125. Surgery was performed in 20 women. Diagnosis of ovarian cancer occurred in 8 out of 211 women, 2 within 6 months of a symptom index, 1 of which had a symptom positive result. The second study[91] found that 1 per 132 women were found to have invasive ovarian cancer. Seven out of 239 with a slightly raised CA125 and only minimal or no ovarian abnormalities had high-grade serous cancer. One prognostic study[74] was identified through consultation on CA125 compared to ultrasound for the diagnosis of malignancy in 103 women with adnexal tumours. The study reports that ultrasound has a higher specificity and	study compared CA125 to ultrasound. The study reports that ultrasound has a higher specificity and sensitivity than CA125. It does not state if these differences are significant. CG122 also recognised that "no single test on its own adequately selected a manageable number of women for referral to secondary care. The combination of raised serum CA125 and sequential ultrasound of the abdomen and pelvis reduced significantly the number of women who would be referred." Considering the trade-offs the topic experts on the original guideline felt that it was a sequential testing strategy sensible and pragmatic decision. Additionally, "the health economic modelling unequivocally identified that serum CA125 was the most cost-effective first test as opposed to ultrasound or ultrasound and serum CA125 in combination." As the decision by the committee in the guideline was made by comparing the tests alone and in combination and considering the cost-effectiveness of these tests by a health economic model, the addition of non-comparative clinical studies only on the diagnostic rates is unlikely to contribute any additional information that would have an impact the sequential testing

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		sensitivity than CA125. It does not state if these differences are significant. The topic experts also raised concern about the way the recommendations list the symptoms and felt that some clarity would be helpful. Clarification would also be useful on what should be done in women with a raised CA125 score and a normal ultrasound.	recommendations. This question is relevant to a primary care setting. CG122 noted that "the clinical evidence was of limited applicability because it did not come from symptomatic women in primary care." It is unclear from the abstracts whether this new evidence is in primary or secondary care. The new evidence is therefore unlikely to change the current recommendations, which were made by clinical and cost-effectiveness data. However, the surveillance team will note this area as an important area for future surveillance, if any additional evidence is identified.
Establishing the diagnosis in secondary care			
122 – 04 For women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis? (1.2.1.1 – 1.2.2.2)			
No relevant evidence identified.	**CA125, ROMA and HE4** **HE4** Eight systematic reviews were identified on the diagnostic accuracy of Human epididymis protein 4 (HE4) for ovarian cancer. One review[3] included 25 studies comparing the diagnostic accuracy of HE4 to CA125. A meta-analysis found similar sensitivities of HE4 and CA125 but that HE4 had a higher specificity, diagnostic odds ratio and AUC	One topic expert noted that there may be alternate tumour markers to CA125 but that they were not aware of any new quality evidence that would impact on the guideline. The topic experts advised there is a screening study (UKCTOCS) that is likely to publish in December and this may add to the evidence base for the question on tumour markers. The trial will be noted in	**CA125, ROMA and HE4** New evidence identified that may change current recommendations. The new evidence comes from systematic reviews and diagnostic studies that indicate that HE4 has a higher specificity than CA125. For comparisons between CA125 and HE4 the results for diagnostic odds ratio and AUC differed between systematic reviews. The evidence indicates that CA125 and HE4 have similar sensitivities. The

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	than CA125. Nine studies compared the combination of CA125 and HE4 and found that the combination had a higher sensitivity than both HE4 or CA125 alone but not a higher specificity than HE4 alone. Two systematic reviews[1,2] were identified on the diagnostic accuracy of HE4, Risk for Ovarian Malignancy Algorithm (ROMA) and CA125 for predicting ovarian cancer. One systematic review included 11 studies[1], including 4 studies on HE4 compared with CA125 and 3 studies that compared ROMA, CA125 and HE4, and the other systematic review included 32 studies[2], including 28 that compared CA125 and HE4. In the first review the pooled results showed HE4 had a lower area under the curve (AUC) than CA125 for both epithelial ovarian cancer and ovarian cancer. However, the meta-analysis of the second review reported that CA125, HE4 and ROMA had similar AUC. Pooled results in the first review comparing HE4 to CA125 showed that HE4 had a higher specificity than CA125 for epithelial ovarian cancer. When comparing ROMA to HE4 and CA125, ROMA had a higher sensitivity HE4, however HE4 had a higher specificity than ROMA and then CA125. The second review reported meta-analysis	the ongoing trials and will be reviewed at the next surveillance of CG122. Consultation highlighted 10 diagnostic accuracy studies on HE4 and/or ROMA. One was a diagnostic study[78] on CA 125, HE4 and ROMA on 56 women with malignancy and 54 with non-malignancy. Women had histopathological confirmed malignancy and then had CA125 and HE4 measured. ROMA had a higher specificity than CA125 or HE4 and a lower sensitivity. It does not state if these difference were significant. Another study[79] on 319 women with a confirmed pelvic mass after imaging and who were scheduled for surgery. The study reported that HE4, CA125 and ROMA were useful for diagnosis of type II EOC but HE4 and ROMA may be useful for diagnosis of type I EOC. It does not state whether or not there were any significant differences between HE4, CA125 and ROMA. One diagnostic study[80] was identified on HE4, CA125 and ROMA. The study included 96 women with benign gynecological diseases, 47 with ovarian cancer and 106 who were healthy. HE4 was significantly higher in the ovarian	systematic reviews are limited by the heterogeneity of included studies and the meta-analysis of different cut-off values for HE4. However, many of the included studies in these systematic reviews were published after the search date cut-off of the original guideline and therefore would be new evidence in addition to the studies included in the original guideline. New evidence was also found on ROMA. The topic experts noted that ROMA takes into account menopausal status and in pre-menopausal women the ROMA score may reduce the number of patients going to tertiary care. The original guideline only included 5 studies on HE4 compared to CA125. The topic experts advised that the studies included in the original guideline on HE4 were not validation studies and had a number of methodological issues. It's unclear how much of the new evidence identified comes from validation studies and what the methodological quality of these papers may be but it's possible that the quality of these studies will have now improved. The original guideline recommended CA125 as the serum tumour marker for the diagnosis of ovarian cancer. The guideline linking evidence to recommendations

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	results that HE4 had a higher specificity than CA125 and ROMA. A subgroup analysis was conducted in the second review on premenopausal and postmenopausal was performed. HE4 had a higher specificity in the premenopausal subgroup. CA125 and ROMA had a significantly higher AUC than HE4 in the postmenopausal subgroup. This review states that more high quality RCTs are needed. Another systematic review[4] included 16 studies on HE4 and CA125 for the diagnosis of ovarian cancer. Meta-analysis reported LR+ was higher for HE4 then CA125 with similar LR-, however it does not report if these changes were significant. One systematic review[76] was identified on HE4 compared to paraffin-embedded sections for the diagnosis of ovarian cancer. It included 45 studies on 10,671 women. It reported a sensitivity of 78%, a specificity of 86% and an AUC of 0.916. One systematic review[77] was identified on HE4 for the diagnosis of ovarian cancer or benign disease. It included 11 studies on 3395 women. Meta-analysis reported a sensitivity of 0.74 and a specificity of 0.87. The PLR was 8.04 and NLR was 0.27. The review states that when HE4 is combined with CA125 the sensitivity is higher but the specificity is lower, however it does not state	cancer women compared to benign gynaecological diseases. ROC was significantly higher for ROMA and HE4 than CA125. HE4 and ROMA sensitivity was higher in postmenopausal women than premenopausal. A prospective study[81] was identified on ROMA in 461 women with a pelvic mass who had an initial clinical risk assessment (ICRA). Sensitivity for ICRA was 85.4%, specificity was 84.3% and NPV was 97.8%. For ICRA plus ROMA sensitivity was 93.8%, specificity was 67.2% and NPV was 98.8%. For malignancies sensitivity and NPV was significantly higher in ICRA plus ROMA. One study[82] was identified on HE4, CA125 and ROMA for the diagnosis of ovarian cancer compared to benign gynaecological disease. The population consisted of healthy women as well as women with ovarian cancer and it is unclear whether these were women with suspected ovarian cancer. AUC for 0.92 for HE4, 0.911 for CA125, 0.945 for ROMA. For the diagnosis of ovarian cancer compared to benign gynaecological disease sensitivity was 86.2% for HE4 and CA125 and 93.1% for ROMA. Sensitivity was 87.4% for HE4, 78.9% for CA125 and 90.7% for ROMA.	(LETR) table stated that the “GDG therefore did not feel the data on HE4 was substantial enough to enable it to be recommended instead of serum CA125 – the only serum tumour marker with widely accepted clinical utility in women with ovarian cancer. They therefore recommended the routine use of serum CA125.” The new evidence provides further comparative data on the diagnostic accuracy of HE4. Topic experts noted that an increased specificity may be useful in the pre-menopausal population as it may prevent unnecessary referrals. The topic experts advised that HE4 is not widely used or available within the NHS or within a primary care setting. However stakeholders highlighted at consultation that there may be a role for HE4 within the clinical pathway for the diagnosis of ovarian cancer. The consultation identified a number of diagnostic accuracy studies relating to the serum tumour marker tests, indicating that HE4 and ROMA have a higher specificity than CA125, which is the tumour marker recommended by CG122 for the diagnosis of ovarian cancer. Comments received from stakeholders at consultation expressed a need for NICE to review the recommendations on serum tumour markers for the diagnosis of ovarian cancer,

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	if these differences were significant. One systematic review[78] was identified on HE4 for diagnosis of ovarian cancer in women with pelvic or gynaecological masses. It included 9 studies of 1807 women. Meta-analysis reported sensitivity as 83% and specificity as 90%. SROC curve was 0.8853. Another systematic review[5] also reported only results for HE4 included 31 studies on the diagnostic accuracy of HE4 for ovarian cancer. A meta-analysis was performed, although authors cautioned that there was heterogeneity present. The sensitivity, specificity, PLR and NLR all indicated that HE4 could be a tumour marker used in the diagnosis of ovarian cancer. The authors conclude that the sensitivity and specificity of HE4 was higher than CA125, however the sensitivity and specificity of CA125 is not specified. **HE4 compared with mesothelin** A systematic review[3] on HE4 and mesothelin for predicting ovarian cancer included 18 studies. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. In a pooled	LR+ for HE4 was 6.84, CA125 was 4.1 and ROMA 10.01. In premenopausal women only LR+ for HE4 was 11.86, CA125 was 2.02 and ROMA was 5.11. One prospective study[83] was identified on ROMA for the diagnosis of ovarian cancer compared to benign gynaecological disease in 99 women with adnexal masses. Sensitivity of CA125 was lower than in HE4. Specificity, AUC and the diagnostic accuracy were higher in ROMA than HE4 or CA125 alone, however it does not state if this difference was significant. One study[84] was identified on HE4. CA125, RMI and ROMA and CT scan for the diagnosis of ovarian cancer in 361 women, including controls. HE4 had the highest AUC, but it was not state if this difference was significant. CT scan in addition to HE4 was significantly higher than HE4 alone. HE4 had a higher specificity than CA125 but they had similar sensitivities. One study[85] was identified on HE4, CA125 and HE4 plus CA125 for the diagnosis of ovarian cancer. The study reports HE4 alone to have a higher specificity but a lower sensitivity than CA125 alone. HE4 plus CA125 is reported to have a higher diagnostic	in particular the role of HE4 and ROMA. **Mesothelin** New evidence is unlikely to impact on guideline recommendations. Mesothelin was not identified in the initial review protocol. The review protocol for CG122 specified the following serum tumour markers index tests: CA 19.9, CA 72.4, CEA, germ cell tumour markers, (AFP and beta-HCG), HE4 and CDX2, compared with CA125. Evidence for CA125, HE4 and mesothelin combinations was identified in CG122 but was reported to be less effective than CA125 and HE4. The new evidence reports HE4 has a better diagnostic accuracy than mesothelin. Mesothelin was not recommended in CG122. **MMP-9** New evidence is unlikely to impact on guideline recommendations. The new evidence does not provide comparative data for MMP-9 compared with other markers and therefore the applicability and the potential impacts of the evidence on the guideline is limited. MMP-9 was not identified in the initial review protocol and is

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	analysis sensitivity was significantly higher for HE4 than for mesothelin, however specificity was higher for mesothelin than HE4. Diagnostic odds ratios, summary ROC was higher HE4 than for mesothelin. Positive likelihood ratio (PLR) and negative likelihood ratio (NLR) was higher for mesothelin than HE4. The authors conclude that HE4 has a better diagnostic accuracy than mesothelin. **MMP-9** A systematic review[6] included 30 studies on the prognostic role of matrix metalloproteinase-9 (MMP-9) in people with ovarian cancer. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. Results from the meta-analysis indicated that MMP-9 was significantly associated with a poorer prognosis in people with ovarian cancer. The pooled results also reported that MMP-9 was significantly higher in benign tumours and significantly associated with FIGO staging of disease, lymph node metastasis and differentiation grade, however there was no significant association for histological type. The review suggests that MMP-9 regulation may be useful as part of	accuracy than HE4 or CA125 alone. The study does not report if these differences were significant. One study[86] on the diagnostic accuracy of HE4 compared to CA125 in 32 women with ovarian cancer and 62 women with a benign ovarian tumour. HE4 has a higher AUC than CA125, however it is not reported if these differences are significant. Topic experts advised that it would be unlikely that HE4 would be used as a first line test in primary care and they did not think it would change the care pathway, however CA125 is used as a test in symptomatic women. In current practice HE4 may only be used in Tertiary (Cancer Centre) Services, usually in addition to risk of malignancy index (RMI) I. Therefore if HE4 is used, it is used further down the pathway, with many women having a HE4 after they have had an ultrasound and a CA125. They advised that therefore there are not many benign cases referred on to Tertiary (Cancer Centre) Services, so an increased specificity of HE4 over CA125 would be unlikely to affect a patient's clinical pathway. Once women have reached secondary care they are also	not mentioned in the guideline. **RASSF1A promoter methylation** New evidence is unlikely to impact on guideline recommendations. The new evidence does not provide comparative data for RASSF1A promoter methylation compared with other markers and therefore the applicability and the potential impacts of the evidence on the guideline is limited. RASSF1A promoter methylation was not identified in the initial review protocol and is not mentioned in the guideline. **Osteopontin** New evidence is unlikely to impact on guideline recommendations. The authors of the newly identified systematic review noted that the evidence was limited. Osteopontin was not identified in the initial review protocol. Evidence for osteopontin was in an identified review included in the original guideline, but data on this was not included in the review. **VEGF** New evidence is unlikely to impact on

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	treatment for ovarian cancer. **RASSF1A promoter methylation** One systematic review[7] identified 12 cohort studies on RASSF1A promoter methylation in ovarian cancer. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. The study reported meta-analysis results that found RASSF1A promoter methylation significantly higher in cancer tissues compared with adjacent, benign and normal tissues. **Osteopontin** A systematic review[8] included 13 studies on the diagnostic accuracy of osteopontin for ovarian cancer. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. A meta-analysis of the sensitivity, specificity and AUC indicated that osteopontin may be useful in the diagnosis of ovarian cancer, however the authors not limitations of the studies and the need more robust evidence. **VEGF** A systematic review[9] identified 10 studies on the diagnostic accuracy of vascular	likely to already have had a CA125 and/or an ultrasound confirming their diagnosis.	guideline recommendations. The new evidence does not provide comparative data for VEGF compared with other markers and therefore the applicability and the potential impacts of the evidence on the guideline is limited. VEGF was not identified in the initial review protocol and is not mentioned in the guideline. **HIF-1alpha** New evidence is unlikely to impact on guideline recommendations. The new evidence does not provide comparative data for HIF-1alpha compared with other markers. HIF-1alpha was not identified in the initial review protocol and is not mentioned in the guideline. **Bcl-2, EGFR, GST, LRP, p21, P-gp and TNF-alpha** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review, where the author's conclusions were that the biomarkers are unlikely to be useful for ovarian cancer. The biomarkers were not identified in the initial review protocol and are not mentioned in the guideline. EGFR was identified in one study in the initial review, but data was not

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	endothelial growth factor (VEGF) for ovarian cancer. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. The pooled results of the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and the summary ROC curves showed a moderate diagnostic accuracy of vascular endothelial growth factor (VEGF) for ovarian cancer. Another systematic review[10] include 6 studies on the association between high vascular endothelial growth factor (VEGF) expression and PFS and OS in people with ovarian cancer. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. A meta-analysis of high serum VEGF was significantly associated with lower PFS and OS. High tissue VEGF was also significantly associated with lower PFS and OS in studies including early stage ovarian cancer, however not in advanced stage ovarian cancer. **HIF-1alpha** A systematic review[11] included 25 studies on hypoxia-inducible factor-1alphas (HIF-1alpha) association to clinicopathological		included in the review. **ERCC1** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review that found ERCC1 was significantly associated with response to platinum-based therapy. Platinum-based therapy the recommended first line treatment for ovarian cancer in the UK. CG122 only includes initial treatment and second-line treatment is out of the remit of CG122 and CG122 did not look at markers for response to platinum-based therapy.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	characteristics in epithelial ovarian cancers. The review reported significantly higher HIF-1alpha expression in cancer or borderline tissue compared with benign tissue and stages III-IV or lymph node metastasis compared with stage I-II or with no lymph node metastasis. HIF-1alpha expression was also significantly associated with histological cancer grade and 5-year survival, but not with histological type. **Bcl-2, EGFR, GST, LRP, p21, P-gp and TNF-alpha** One systematic[12] investigated the prognostic role of different biomarkers for response to platinum-based chemotherapy or survival in epithelial ovarian cancer. The review included: 27 studies on B-cell lymphoma 2 (Bcl-2), 22 studies on epidermal growth factor receptor (EGFR), 29 studies on glutathione transferase (GST), 12 studies on labelled reference peptide (LRP), 16 studies on p16, 22 studies on p21, 27 studies on P-glycoprotein (P-gp) and 3 studies on TNF-alpha. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. Meta-analysis reported higher GST expression was associated with higher OS and PFS and high P-gp or EGFR expression was associated with lower OS. The authors		

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	of the study conclude that the biomarkers are not likely to have a useful prognostic role in epithelial ovarian cancer. **ERCC1** A systematic review[13] included 5 studies on the association between negative excision repair cross-complementation group 1 enzyme (ERCC1) and platinum-based chemotherapy response. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. The results from the meta-analysis indicated that ERCC1 was significantly associated with response to platinum-based chemotherapy in people with ovarian cancer.		
122 – 05 For women with suspected ovarian cancer, which malignancy index is the most effective? (1.2.2.1)			
No relevant evidence identified.	No relevant evidence identified.	**CT and CA-125** One prospective non-randomised trial[14] was identified through topic expert feedback that assessed the predictive ability of preoperatively scanning the pelvis/abdomen using computed tomography (CT) at 35 days prior to surgery and serum CA-125 at 14 days prior to surgery, in people undergoing primary cytoreduction in people with advanced (stage III-IV) ovarian,	**CT and CA-125** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one non-randomised study. The study appears from the abstract to only be a development of a predictive model but not a validation of the predictive model. CG122 did not search for models prior to surgery and does not make any recommendations in this area. Additionally,

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		peritoneal or fallopian tube cancer. The study found 3 out of 4 clinical and 6 out of 20 radiological criteria were found significantly associated, at multivariate analysis, with suboptimal cytoreduction. A prognostic model was developed from these 9 criteria that had a predictive accuracy of 0.758, which may be useful in assessment prior to surgery. **IOTA 'simple-rules' tool** A validation trial and systematic review[15] was identified on the International Ovarian Tumor Analysis (IOTA) 'simple-rules' tool. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. In the validation trial the population included 55.4% benign, 6.3% borderline and 38.3% malignant tumours. The validation trial and a further 6 studies identified from the systematic review were included in a meta-analysis and it was found that the IOTA 'simple rules' tool and reported that it could be a useful tool for the accurate diagnosis of ovarian cancer, when compared to 'pattern recognition' (undefined) and histological findings. One prospective study[87] was identified on	the guideline makes a recommendation for performing a risk of malignancy index I (RMI I) score and CT is recommended as the second imaging, after performing ultrasound. **IOTA 'simple-rules' tool** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review that included a systematic review and three validation studies of IOTA 'simple-rules' tool. CG122 did not search for IOTA 'simple-rules' tool. CG122 included evidence on one systematic review that included 83 validated risk of malignancy indices and found RMI I to be superior to the other indices, and therefore recommended calculating an RMI I. The studies do not provide information on whether there are significant differences to RMI and further research is therefore needed before considering this area for inclusion in the guideline. This has been noted through topic expert feedback and consultation as an important area and will be reviewed again at the next surveillance.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
		IOTA compared to HE4 for the diagnosis of ovarian cancer. All 2048 women underwent transvaginal ultrasonography. It included women with benign, malignant and no gynaecological disease. The study reported that IOTA had a higher sensitivity and specificity than RMI but it does not say whether this difference was significant. One diagnostic study[88] was highlighted through consultation on 376 women with adnexal masses for the discrimination of benign compared to malignant ovarian tumours. IOTA simple rules could not be applied to all adnexal masses. In the ones it was used sensitivity was 82.9% and specificity was 95.3%. Another prospective validation study[89] was highlighted through consultation on IOTA, RMI and other risk of malignancy indexes in 997 women with adnexal masses for the discrimination of benign compared to malignant ovarian tumours. The study reported that IOTA had a higher AUC than RMI, but it did not report if these differences were significant.	
122 – 06 For women with suspected ovarian cancer, what is the most appropriate imaging to be done to determine future management? (1.2.3.1 – 1.2.3.3)			
No relevant evidence identified.	**Contrast-enhanced ultrasound** A systematic review[16] identified 10 studies assessing the diagnostic accuracy of	Topic expert feedback identified the DISCOVAR trial addressing the utility of MRI in Ovarian Cancer, however this trial	**Contrast-enhanced ultrasound** New evidence is unlikely to impact on guideline recommendations.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	contrast-enhanced ultrasound for distinguishing between benign and malignant ovarian cancer. The specific details of the population of included studies, including the stages of ovarian cancer, was not specified in the abstract. The pooled results of these studies on the sensitivity, specificity, diagnostic odds ratio and area under the receiver operating characteristic (ROC) curve showed a high diagnostic accuracy for distinguishing between benign and malignant ovarian tumour. The abstract did provide any comparative data.	is ongoing and will be reviewed again at the next surveillance review.	The new evidence comes from one systematic review that found contrast-enhanced ultrasound useful for diagnosis of benign versus malignant ovarian tumour. The evidence is non-comparative and therefore the applicability and the potential impacts of the evidence on the guideline is limited. CG122 recommends ultrasound as the first imaging for suspected ovarian cancer. CG122 did not search for evidence on contrast-enhanced ultrasound.
122 – 07 For women with suspected advanced ovarian cancer, when is it appropriate not to have a tissue diagnosis before starting chemotherapy? (1.2.4.1 – 1.2.4.2)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
122 – 08 What is the best method of tissue diagnosis before chemotherapy, samples from image guided biopsy or laparoscopic biopsy? (1.2.4.3)			
No relevant evidence identified.	**Laparoscopy compared with laparotomy** A Cochrane systematic review[17] was identified on the use of laparoscopy compared with laparotomy in people with stage I ovarian cancer (stages Ia, Ib and Ic). The review identified no studies eligible for inclusion. Another systematic review[18] identified 11 studies on laparoscopic staging surgery in women with suspected early-stage ovarian	None identified relevant to this question.	**Laparoscopy compared with laparotomy** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review that found no evidence and another systematic review that only reported the outcome of estimated blood loss, so the outcomes may therefore not be applicable to inform recommendations in this area.

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	cancer. The specific details of the population of included studies were not specified in the abstract, however its focus appears to be on early-stage ovarian cancer. A pooled analysis of 3 studies showed significantly lower estimated blood loss in laparoscopy compared with laparotomy. **Open laparoscopy to predict resectability** A Cochrane systematic review[19] identified 7 studies on the use of open laparoscopy to predict resectability in people with suspected advanced ovarian cancer who were scheduled for primary debulking surgery. A meta-analysis was not performed as only two studies provided information for the calculation of sensitivity and specificity. The studies showed a moderate sensitivity and a high specificity. There was heterogeneity in the studies that provided data for the calculation of negative predictive values. One study showed a moderate NPV and the other a high NPV. Three studies also involved a development or validation of a prediction model, however due to verification bias these were not meta-analysed. The models had a lower sensitivity and specificity than laparoscopy alone. The authors noted the difficulties in meta-analysis due to the different populations of		CG122 searched for evidence on image-guided biopsy compared with laparoscopic biopsy and found no direct comparisons. A recommendation was made to 'consider laparoscopic biopsy if percutaneous image-guided biopsy is not feasible or has not produced an adequate sample'. **Open laparoscopy to predict resectability** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review on open laparoscopy. The review includes prognostic studies and is non-comparative and therefore the applicability and the potential impacts of the evidence on the guideline is limited. CG122 searched for evidence on image-guided biopsy compared with laparoscopic biopsy and found no direct comparisons. A recommendation was made to 'consider laparoscopic biopsy if percutaneous image-guided biopsy is not feasible or has not produced an adequate sample'.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	the included studies.		
Management of suspected early (stage I) ovarian cancer			
122 – 09 For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management? (1.3.1.1 – 1.3.1.2)			
Treatment for borderline ovarian cancer Ovarian Cancer: Evidence Update (January 2013) identified a Cochrane review[59] that included 7 RCTs on treatment for borderline ovarian cancer (BOT). Meta-analysis was not performed due to the different treatments. Six RCTs included people with FIGO stage I ovarian cancer and compared different adjuvant chemotherapies after radical surgery. Another RCT compared conservative compared with ultra-conservative surgery. The review reported that for all studies there was no difference in survival, however one study reported people who received thiotepa had a significantly lower death rate. The evidence update concluded that the review is unlikely to have an impact on CG122, as CG122 currently has no recommendations on the management of BOT and the review authors noted further research was needed.	**Conservative management for the outcome of fertility for borderline ovarian cancer** Two systematic reviews[20 21] on conservative management in borderline ovarian tumours (BOT) were identified. The first review[20] included 120 studies and reported that for conservative management of early stage BOT pooled results showed a spontaneous pregnancy rate of 54% and a low risk of fatal relapse. However conservative management for advanced BOT spontaneous pregnancy rates decreased and fatal relapse increased. The second systematic review[21] identified 39 studies. The studies included different stages of ovarian cancers, 8 studies included people with stage I, 14 studies >90% of people with stage I, 5 studies included people with advanced ovarian cancer, 7 studies included people with serous borderline ovarian tumour and 2 studies included people with mucinous borderline ovarian tumour. The meta-analysis found a significant difference	None identified relevant to this question.	**Treatment for borderline ovarian cancer** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one study in the evidence update that found no difference in survival for adjuvant chemotherapy. The evidence update concluded that the review is unlikely to have an impact on CG122, as CG122 currently has no recommendations on the management of BOT and the review authors noted further research was needed. **Conservative management for the outcome of fertility** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from two systematic reviews. One shows a benefit for conservative management in early stage BOT, but not advanced. The second review the studies were meta-analysed and it is unclear from the abstract whether studies

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	favouring unilateral salpingo-oophorectomy when compared with cystectomy. Cumulative pregnancy was also noted to be higher in unilateral salpingo-oophorectomy when compared with cystectomy, however the abstract did not state whether this was statistically significant.		from different stages were grouped together and if so, whether heterogeneity was present. It also only gives results comparing unilateral salpingo-oophorectomy to cystectomy, so its applicability to the guideline is uncertain. CG122 does not search for evidence on conservative surgery, however in the introduction to chapter 4.1 it does make note that 'in women where the disease appears to be confined to one ovary and who wish to conserve fertility, then conservative surgery can be considered'. CG122 does not make any recommendations regarding conservative management, but does not recommend 'systematic retroperitoneal lymphadenectomy' in women with stage I ovarian cancer.
122 – 10 For women with stage I ovarian cancer, what is the most effective first line chemotherapy? (1.3.2.1 – 1.3.2.3)			
Maintenance treatment Ovarian Cancer: Evidence Update (January 2013) identified one RCT[58] which compares the recurrence-free period in patients with completely resected stage IA/B (grade 3 or clear cell), IC or II epithelial ovarian cancer, who received carboplatin AUC 6 and paclitaxel 175 mg/m² for 3 courses for	**Surgery alone compared with platinum-based adjuvant treatment in people with borderline ovarian tumours** A systematic review[22] included 31 studies on surgery alone compared with platinum-based adjuvant treatment in people with borderline ovarian tumours. The exact treatments in the studies are unclear from the abstract. The review reports that >90%	**PARP inhibitors** Topic expert feedback identified a systematic review[27] that searched for RCTs on the following comparisons: poly (ADP-ribose) polymerase (PARP) inhibitors compared with no treatment, PARP inhibitors compared with conventional chemotherapy, or PARP inhibitors plus conventional	**Maintenance treatment** New evidence is unlikely to impact on guideline recommendations. Maintenance treatment is treatment to maintain remission and as the remit of CG122 only covers initial management maintenance treatment is outside the remit of this guideline.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
3 weeks and were then randomised to receive either observation or maintenance treatment with paclitaxel 40 mg/m² per week for 24 weeks. The evidence update concluded that it is unlikely to impact on the guideline.	of people had stage I ovarian cancer in 9 of the studies and advanced ovarian cancer in 11 of the studies. The stages of cancer in the population in the other included studies was not specified in the abstract. 13 studies reported mortality rates and were meta-analysed with moderate heterogeneity. The study reported that surgical treatment alone was the favoured treatment in the meta-analysis. Four studies had survival data and found 4 studies no difference between the two groups. The review concluded that there is not enough evidence to support the use of adjuvant chemotherapy **Intraperitoneal bevacizumab and cisplatin compared with intraperitoneal cisplatin alone** One RCT[23] was identified on the efficacy and safety of intraperitoneal bevacizumab and cisplatin compared with intraperitoneal cisplatin alone for treatment of malignant ascites in people with ovarian epithelial cancer. All people received their randomly assignment treatment every 2 week for 6 weeks, in addition to paclitaxel and carboplatin every 3 weeks. The study reported significant differences in overall response rate and quality of life in the intervention group compared with the control group. VEGF level in ascites was also	chemotherapy compared with conventional chemotherapy. The population was people with histologically proven epithelial ovarian cancer. Four RCTs were included. The review stated that veliparib data was low quality and limited and no further details were provided. For olaparib the results from two studies of moderate quality were presented for both its addition to conventional treatment and its use as maintenance treatment and showed PFS but not OS improved in the olaparib group. The review presents results from maintenance treatment, which is outside the remit of CG122. The review does not specifically state that the population searched for was people with reoccurring disease, however the author's conclusion are focused on people with recurrent platinum-sensitive disease, which is outside the scope of this guideline. **Pegylated liposomal doxorubicin** One systematic review[28], identified by topic experts, included studies on first-line pegylated liposomal doxorubicin (PLD) alone or in combination compared to a comparator for first-line treatment in women with epithelial ovarian cancer. Two large, low risk of bias RCTs were	**Surgery alone compared with platinum-based adjuvant treatment in people with borderline ovarian tumours** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one systematic review where the review authors concluded that there is not enough evidence to support the use of adjuvant chemotherapy in people with stage I borderline ovarian tumours. CG122 makes a do not offer recommendation for adjuvant chemotherapy in people with low-risk stage I ovarian cancer. **Intraperitoneal bevacizumab and cisplatin compared with intraperitoneal cisplatin alone** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one RCT where the staging of ovarian cancer and the line of treatment is unclear. Cisplatin and bevacizumab are not licensed in the UK for the indication of management of malignant ascites. NICE CG122 does not make any specific recommendations on the management of malignant ascites.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	reported as significantly lower in the intervention group compared with the control group. No serious adverse events were reported. The line of treatment and the population (staging) is unclear from the abstract. **Pegylated liposomal doxorubicin** A systematic review[24] included 3 RCTs on the efficacy of carboplatin and paclitaxel compared carboplatin with pegylated liposomal doxorubicin (PLD) and 5 RCTs comparing PLD to another single therapy, in women with ovarian cancer. The stages of cancer in the population in the other included studies was not specified in the abstract. PFS was higher in the carboplatin and PLD group compared to carboplatin and paclitaxel, however overall survival (OS) rates were similar. Adverse events were higher in the carboplatin and PLD group for gastrointestinal toxicity, anemia, cutaneous toxicity, thrombocytopenia and mucositis/stomatitis. However neutropenia, neuropathy, and alopecia were higher in the carboplatin and paclitaxel group. OS and PFS were similar when comparing PLD to other single therapies, but had increased tolerability.	included, with different comparators and were not combined in a meta-analysis. One trial was on 3 weekly carboplatin plus PLD compared with paclitaxel plus carboplatin. For both trials no significant differences were found for PFS or OS between the two groups. The other was a 4 arm trial which included the comparison of PLD (every 6 weeks) and 3 weekly paclitaxel plus carboplatin compared with 3 weekly paclitaxel plus carboplatin. The first study also reported significantly higher severe anaemia and thrombocytopenia in the PLD group, however alopecia and severe neurotoxicity were significantly higher in the paclitaxel plus carboplatin group. The second study reported significantly higher severe haematological adverse events in those receiving PLD.	**PARP inhibitors** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review that indicates the population is recurrent ovarian cancer, and therefore is unlikely to be relevant to the population of this guideline. **Pegylated liposomal doxorubicin** New evidence is unlikely to impact on guideline recommendations. The new evidence is from two systematic reviews that reported no significant differences for OS for PLD treatment compared to a comparator first-line treatment. The evidence for PFS is inconsistent. One systematic review found no differences. The other systematic review included two comparisons; for carboplatin and PLD compared with carboplatin and paclitaxel, PFS was higher, but not for PLD compared with other single therapies. PLD (specifically the Caelyx brand) is not licensed as first-line treatment for ovarian cancer in the UK and is only licensed in advanced ovarian cancer for women who have failed first-line platinum-based treatment. PLD is not mentioned in CG122.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	Sorafenib One RCT[25] was identified on paclitaxel and carboplatin compared with paclitaxel and carboplatin plus sorafenib 400 mg in women with maximally debulked, histologically confirmed and not previously treated epithelial ovarian carcinoma (stage III/IV). Treatment was administered 3 weekly for 6 cycles in both groups and sorafenib was continued for 52 weeks. Progression-free survival (PFS) at 2 years and OS were not significantly different between the two groups. **IP Catumaxomab compared with IP catumaxomab plus prednisolone** One RCT[26] compared the safety and efficacy of catumaxomab administered by intraperitoneal infusion compared to catumaxomab administered by intraperitoneal infusion plus prednisolone in patients with malignant ascites because of epithelial cancer. The study reported no significant difference between the two groups for safety, puncture-free survival, OS and time until subsequent therapeutic puncture.		**Sorafenib** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one RCT that found no significant difference on PFS or OS for treatment with sorafenib. Sorafenib in not mentioned in CG122 and is not licensed in the UK for any type or stage of ovarian cancer. **IP Catumaxomab compared with IP catumaxomab plus prednisolone** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one RCT that found no difference in OS for IP Catumaxomab compared with IP catumaxomab plus prednisolone. CG122 does not make any recommendations or search for evidence on catumaxomab. Catumaxomab is only licensed in the UK for the management of malignant ascites in people with epithelial cell adhesion molecule (EpCAM) positive carcinomas, where standard therapy is not available or no longer feasible.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
Management of suspected early (stage II–IV) ovarian cancer			
122 – 11 What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy? (1.4.1.1)			
Primary cytoreductive surgery Ovarian Cancer: Evidence Update (January 2013) identified a Cochrane review[69] on optimal primary cytoreductive surgery in people with surgically staged advanced stage III and IV epithelial ovarian cancer. No significant differences were found for OS and only a slight difference for PFS when comparing tumour diameter >2cm to <2cm. However OS was greater in those that received optimal reduction with a tumour diameter <1cm. The evidence review summarised that the results were consistent with the guideline, indicating that the goal should be complete cytoreduction.	**Neoadjuvant chemotherapy compared with primary debulking surgery (PDS) followed by chemotherapy** A systematic review[29] included 2 RCTs on neoadjuvant chemotherapy compared with primary debulking surgery (PDS) followed by chemotherapy in people with stage IIIC and IV ovarian cancer. No significant differences were reported for OS or PFS. **Platinum-based adjuvant chemotherapy compared with no adjuvant chemotherapy** One RCT[30] compared platinum-based adjuvant chemotherapy with no adjuvant chemotherapy. Recurrence-free and overall survival at 10 years was significantly higher in intervention group than the control group. However, the population of the original trial had 93% with stage I ovarian cancer. **Interval debulking surgery after primary surgery compared with primary debulking surgery with adjuvant chemotherapy** A Cochrane systematic review[31] identified 3 RCTs on interval debulking surgery after	Topic expert feedback noted that there is still uncertainty about the value of primary debulking surgery. They noted that there are two trials that may be starting soon (TOPCAT and TRUST) that may provide further evidence, although it is unlikely that they will answer the clinical question. The progress of these trials will be reviewed at the next surveillance. **Disease score and complexity of surgery** Topic expert feedback identified a non-randomised study[72] in women with advanced epithelial ovarian cancer. The study reported that the initial disease score was a significant prognostic factor but complexity of surgery was not. Topic expert feedback noted that this study's conclusion that complex surgery does not affect prognosis is consistent with what was concluded at original committee meetings. **Primary chemotherapy compared with primary surgery** An RCT[73]was identified from topic expert	**Primary cytoreductive surgery** The evidence update states that the new evidence is consistent with CG122. The evidence review summarised that the results were consistent with the guideline, indicating that the goal should be complete cytoreduction **Neoadjuvant chemotherapy compared with primary debulking surgery (PDS) followed by chemotherapy** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review which reported no significant differences for OS or PFS. The new evidence is consistent with CG122 recommendations. CG122 recommends that 'if performing surgery for women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease.' **Platinum-based adjuvant chemotherapy**

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	primary surgery compared with primary debulking surgery with adjuvant chemotherapy in women with advanced epithelial ovarian cancer. Meta-analysis of 3 RCTs found no statistically significant difference between the 2 groups for OS. Subgroup analysis was conducted for two trials and found that when surgery not as extensive or was carried out by gynaecologic oncologists, adjuvant chemotherapy was favoured over primary debulking surgery alone for OS. In a meta-analysis of two trials there was no statistically significant difference for PFS between interval debulking surgery than with chemotherapy alone. The adverse event of toxicity was not significant but data on other adverse events was limited. **Primary debulking surgery compared with neo-adjuvant chemotherapy and then interval debulking surgery** One RCT[32] was identified on the EORTC 55971 trial primary debulking surgery compared with neo-adjuvant chemotherapy and then interval debulking surgery in people with stages IIIc or IV ovarian cancer. The study reports similar quality of life and survival between the two groups.	feedback on 3 cycles of platinum-based primary chemotherapy then surgery and another 3 cycles of chemotherapy compared with surgical debulking then 6 cycles of platinum-based chemotherapy in women with advanced ovarian cancer. No significant differences in effect sizes for the outcome of death were reported. **Chemotherapy before compared with after cytoreductive surgery** A Cochrane systematic review[36] was identified by topic experts and included 1 high quality RCT on chemotherapy before compared with after cytoreductive surgery people with stage IIIc/IV advanced epithelial ovarian cancer. There were no significant differences between the 2 groups for OS and PFS. Adverse events were lower in the intervention group than the control group and quality of life was similar. The review also noted 3 ongoing trials. The review authors note that people should have tailored treatment.	**compared with no adjuvant chemotherapy** The new evidence is consistent with CG122 recommendations. The new evidence is from one systematic review where platinum-based adjuvant chemotherapy was more effective than no adjuvant chemotherapy. However, the population of the original trial had 93% with stage I ovarian cancer. CG122 does recommend adjuvant chemotherapy in high risk stage I ovarian cancers. **Interval debulking surgery after primary surgery compared with primary debulking surgery with adjuvant chemotherapy** The Cochrane systematic review identified contains 3 RCTs and a previous version of the review was included in CG122, the updated version published in 2013 contains no new studies and the conclusions of the systematic review have not changed. **Primary debulking surgery compared with neo-adjuvant chemotherapy and then interval debulking surgery** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one RCT that

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	Primary cytoreductive surgery A systematic review[33] included 18 studies on primary cytoreductive surgery in women with advanced ovarian cancer. The review reported that complete cytoreduction resulted in an increase in PFS and that intraperitoneal chemotherapy increased survival. **Tranexamic acid** One RCT[34] was identified on single-dose tranexamic acid administered prior to radical debulking surgery compared with placebo prior to surgery in people with suspected advanced ovarian cancer. The primary outcomes of total blood loss and red blood cell transfusions were significantly lower in the intervention group compared with the control group. **Electrosurgical bipolar vessel sealing** An RCT[35] on electrosurgical bipolar vessel sealing (EBVS) device versus standard clamps and suture ligature in women with ovarian, primary peritoneal, or fallopian tube cancer, undergoing abdominal omentectomy. The study reported no significant differences for the outcome of total operative time.		found no difference between primary debulking surgery compared with neo-adjuvant chemotherapy and then interval debulking surgery. The new evidence is consistent with CG122 recommendations. **Chemotherapy before compared with after cytoreductive surgery** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one systematic review where there were no significant differences between the 2 groups for OS and PFS. CG122 does not make any recommendations on cytoreductive surgery. CG122 did include evidence on cytoreductive surgery but emphasised the results of the study, which indicated there may be a benefit of cytoreductive surgery, should be interpreted with caution. **Primary chemotherapy compared with primary surgery** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one RCT that found no significant differences in death

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			between the 2 groups. The new evidence is consistent with CG122 recommendations. **Disease score and complexity of surgery** The new evidence is consistent with CG122 recommendations. The new evidence is from one non-randomised study that found disease burden but not surgery complexity to be a significant prognostic factor. **Primary cytoreductive surgery** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one systematic review that reported that complete cytoreduction resulted in an increase in PFS and that intraperitoneal chemotherapy increased survival. The new evidence is consistent with CG122 recommendations for surgery and adjuvant therapy. For details on intraperitoneal chemotherapy please see 122-12. **Tranexamic acid** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one systematic

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			review that found a significant difference for total blood loss and red blood cell transfusions. CG122 did not make any recommendations or search for evidence on treatments administered for surgery. **Electrosurgical bipolar vessel sealing** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one systematic review that found no differences for operative time. CG122 did not search for EBVS.
122 – 12 For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management? (1.4.2.1)			
Intra-peritoneal chemotherapy Ovarian Cancer: Evidence Update (January 2013) identified one systematic review[70] that indicated intraperitoneal (IP) chemotherapy had higher OS and PFS than IV chemotherapy. This is an updated version of a review included in the guideline and the conclusions do not substantially differ to the original conclusions. The evidence update summarises that the evidence is unlikely to impact on the guideline.	**IV compared with IP cisplatin/paclitaxel** One RCT[37] was identified on the change in CA125, monitored weekly, in intravenous (IV) cisplatin/paclitaxel chemotherapy compared with IV carboplatin followed by IP cisplatin/paclitaxel for ovarian cancer. The study reported that for IP cycles CA125 did not significantly differ between the two groups. CA125 regression was also similar between the two groups.	None identified relevant to this question.	**Intra-peritoneal chemotherapy** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one systematic review that indicated IP chemotherapy had higher OS than IV chemotherapy. CG122 makes a do not offer recommendation for IP chemotherapy. The committee for CG122 acknowledged that IP chemotherapy may be useful but "was associated with more toxicity/adverse events than standard intravenous

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			chemotherapy and that one study had shown health-related quality of life to be adversely affected by intra-peritoneal chemotherapy in the short term. The GDG also recognised that the administration of intra-peritoneal chemotherapy was more complex and more expensive than that for standard intravenous chemotherapy." **IV compared with IP cisplatin/paclitaxel** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one RCT that compares IV to IP cisplatin/paclitaxel. The RCT reports no difference in CA125 between the 2 groups. The new evidence is consistent with CG122. CG122 makes a recommendation of 'do not offer intraperitoneal chemotherapy to women with ovarian cancer except as part of a clinical trial.'
Support needs of women with newly diagnosed ovarian cancer			
122 – 13 For women diagnosed with ovarian cancer, what support should be offered? (1.5.1.1 – 1.5.1.2)			
Ovarian Cancer: Evidence Update (January 2013) identified one RCT[71] in women undergoing surgery for suspected ovarian cancer. It compared patients' self-reported use	None identified relevant to this question.	None identified relevant to this question.	The new evidence is consistent with the recommendations. The evidence update states that the new evidence is consistent with CG122.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
of healthcare provided by oncology advanced practice nurses (APNs) and a psychiatric consultation-liaison nurse (PCLN) with a control group that received the same amount of healthcare attention as the intervention group. The evidence update notes the authors conclusion that those in the intervention group received assistance for any depression symptoms and the control group had significantly higher primary care consultation. The evidence update states that the new evidence is consistent with CG122.			
Research recommendations			
RR – 01 Further research should be undertaken on the relationship between the duration and frequency of symptoms in women with ovarian cancer before diagnosis, the stage of disease at diagnosis and subsequent survival.			
No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
RR – 02 Further research should be undertaken to determine the optimum RMI I threshold that should be applied in secondary care to guide the management of women with suspected ovarian cancer.			
No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.
RR – 03 Large multicentre case–control studies should be conducted to compare the accuracy of CT versus MRI for staging and for predicting optimal cytoreduction in women with ovarian cancer.			
No relevant evidence identified.	None identified relevant to this question.	None identified relevant to this question.	No new evidence was identified that would affect recommendations.

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
RR – 04 A prospective randomised trial should be undertaken to evaluate the therapeutic effect, associated risks and cost effectiveness of systematic retroperitoneal lymphadenectomy in women with ovarian cancer whose disease appears to be confined to the ovaries.			
Refer to 122-09.	Refer to 122-09.	Refer to 122-09.	Refer to 122-09.
RR – 05 Research should be undertaken to determine the effectiveness of primary surgery for women with advanced ovarian cancer whose tumour cannot be fully excised.			
No relevant evidence identified.	Refer to 122-11.	Refer to 122-11.	Refer to 122-11.
Areas not currently covered in the guideline			
NQ – 01 What are the risk factors for ovarian cancer that should be identified in primary care?			
N/A	None identified relevant to this question.	Feedback from stakeholder consultation indicated that a new question on the risk factors for ovarian cancer in primary care should be added to the guideline.	New intelligence was identified that may impact on the guideline. Feedback from stakeholder consultation indicated that there is a gap in the recommendations in CG122 on risk factors for ovarian cancer in primary care. This is also not covered by any NICE guidance. This new question will be added to the guideline. This would align with the recently published referral for suspected cancer NICE guideline.
NQ – 02 Service delivery			
No relevant evidence identified.	**Centralisation of care** A Cochrane systematic review[38] on centralisation of care for people with gynaecological cancer included 5 retrospective observational studies that used multivariable analysis. Meta-analysis of 3 studies indicated that survival may be longer in women with gynaecological cancer	None identified relevant to this question.	**Centralisation of care** New evidence is unlikely to impact on guideline recommendations. Service delivery was not included in CG122. For cancer service delivery please refer to 'Improving outcomes in gynaecological cancers. Cancer service guidance (1999)'. Department of Health, National Cancer

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	attending healthcare facilities with gynaecologic oncologists compared with community or general hospitals. Another meta-analysis of 3 studies indicated that survival may be longer in women with ovarian cancer attending teaching centres or regional cancer centres compared with community or general hospitals. One study indicated no significant difference in women with gynaecological cancer attending community hospitals with semi-specialised gynaecologists compared with general hospitals. This study also reported no significant difference for disease-specific survival between all comparators. Consistency amongst the studies was high. The authors concluded that the evidence indicates that treatment in specialised centres resulted in prolonged survival in women with gynaecological cancer.		Guidance Steering Group.
NQ – 03 Treatment for advanced (stage II-IV) ovarian cancer			
Topotecan Ovarian Cancer: Evidence Update (January 2013) identified two RCTs[60,61] on the use of topotecan as a first-line treatment for advanced (stage II-IV) ovarian cancer. One RCT compared topotecan plus paclitacel plus carboplatin to paclitaxel plus carbolatin and another RCT compared topotecan	**Bevacizumab** One RCT[39] on the efficacy, one RCT[40] on patient reported outcomes and one RCT[41] comparing the risk of gastrointestinal adverse events, were identified on standard chemotherapy compared with standard chemotherapy plus bevacizumab in women with ovarian cancer. The stage of the population was not specified in the	**Paclitaxel and carboplatin** Topic expert feedback noted that there may be a need to assess the use of weekly paclitaxel for advanced ovarian cancer. However, it was also noted that this may fall into a TA. One RCT[57] was identified through topic expert feedback on the efficacy of 6 doses of 3 weekly carboplatin and	**Bevacizumab** New evidence is unlikely to impact on guideline recommendations. For first-line guidance on bevacizumab please refer to TA284 Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer. (May 2013) and for first-reoccurrence TA285 Bevacizumab in

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
plus cisplatin plus paclitacel plus carboplatin to paclitaxel plus carbolatin. Both RCTs reported no significant difference for the addition of topotecan or topotecan plus cisplatin compared to paclitacel plus carboplatin for OS, PFS and response rate. The evidence update concluded that these results are consistent with NICE TA55 Guidance on the use of paclitaxel in the treatment of ovarian cancer (January 2003). **Pegylated liposomal doxorubicin** Ovarian Cancer: Evidence Update (January 2013) identified one RCT[62] that compared carboplatin plus pegylated liposomal doxorubicin (PLD) to carboplatin plus paclitaxel. The evidence update reported the study did not find the addition pegylated liposomal doxorubicin superior to carboplatin plus paclitaxel. However, it also reported that there were differences in adverse event rates between the two groups, notably the evidence update refers to PLD having lower hair loss and neuropathy. The evidence update concluded that any potential impact was outside the scope	abstracts. Three systematic reviews[42 43 44] were also identified on standard chemotherapy compared with standard chemotherapy plus bevacizumab in women with ovarian cancer. However, for guidance on bevacizumab please refer to TA284 Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer. (May 2013). **Paclitaxel and carboplatin** One RCT[45] was identified on 8 cycles carboplatin and paclitaxel compared with 8 cycles carboplatin and 4 cycles paclitaxel in people with advanced (FIGO stages IIC-IV OC) ovarian, fallopian, or primary peritoneal carcinoma. The study reported PFS was significantly shorter in the group that received only 4 cycles of paclitaxel, however OS was not significant. One RCT[46] compared first-line weekly paclitaxel, cisplatin or carboplatin at a lower dose for 6 cycles compared with 3 cycles at a higher dose and then followed by 3 or 6 cycles of the higher dose. No significant differences were found for OS or PFS between the two treatment groups. An RCT[47] was identified on weekly compared with 3 weekly carboplatin and	paclitaxel, at a higher dose compared with a lower dose of carboplatin and paclitaxel given weekly for 18 doses in people with advanced (FIGO stage IC-IV) ovarian cancer. The study reported a significant difference between the two groups with Functional Assessment of Cancer Therapy-Ovarian (FACT-O)/Trial Outcome Index (TOI) scores favouring weekly compared with 3 weekly treatment.	combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer. (May 2013). **Paclitaxel** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from 8 RCTs and comparing varying dosages and regimes of paclitaxel and carboplatin. The RCTs that compared weekly compared with 3 weekly carboplatin and paclitaxel appear to have significantly longer survival, favouring weekly. The evidence for other comparisons did not find any significant differences. CG122 does not make recommendations for chemotherapy for advanced ovarian cancer and states: “that recommendations on first-line chemotherapy for ovarian cancer can be found in CG122 does not review the use of paclitaxel and refers to TA55 Guidance on the use of paclitaxel in the treatment of ovarian cancer (January 2003). The recommendations which relate to first-line treatment are 1.1. and 1.2. These recommendations refer to both early and advanced disease and should be read in conjunction with chapter 4” of CG122.”

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
of the evidence update. **Gemcitabine** Ovarian Cancer: Evidence Update (January 2013) identified one RCT[63] that compared carboplatin plus paclitaxel to carboplatin plus paclitaxel plus gemcitabine. The evidence update reported the RCT did not find OS improved with the addition of gemcitabine to carboplatin /paclitaxel. The evidence update summarises that the RCT is consistent with NICE TA55 Guidance on the use of paclitaxel in the treatment of ovarian cancer (January 2003). **Paclitaxel and carboplatin** Ovarian Cancer: Evidence Update (January 2013) identified one RCT[64] that compared dose-dense weekly carboplatin plus paclitaxel to 3 weekly carboplatin plus paclitaxel. OS at 2 years and 3 years was higher in the dose-dense group than the 3 weekly group. Overall response was similar. Withdrawals were higher in the dose-dense group due to toxicity, notably haematological toxicity. The evidence update also identified a	paclitaxel in women with advanced ovarian cancer. Median PFS did not significantly between the 2 groups. One RCT[48] compared dose-dense paclitaxel and carboplatin to standard treatment with paclitaxel and carboplatin in people with stage II-IV advanced epithelial ovarian cancer. PLS and median OS was significantly higher in the dose-dense group compared to the control group. One RCT[49] was identified on dose-dense weekly paclitaxel (Taxol) and carboplatin compared with 3 weekly paclitaxel and carboplatin in people with stage II-IV ovarian cancer. The primary outcome of quality of life (QoL) did not significantly differ between the two groups. However on the scale of Functional Assessment of Cancer Therapy-taxane subscale there was a significant difference, with QoL significantly lower in dose-dense weekly paclitaxel (Taxol) and carboplatin group compared with 3 weekly paclitaxel and carboplatin group. An RCT[50] was identified on dose-dense treatment with paclitaxel and carboplatin compared with lower dose of paclitaxel and carboplatin 3 weekly in women with stage II to IV ovarian cancer. The study reported that OS at 5 years and median PFS was significantly higher in the dose-dense		Chapter 4 of the guideline recommends treatment for stage I ovarian cancer. The new evidence is on advanced ovarian cancer. **Topotecan** New evidence is unlikely to impact on guideline recommendations. Ovarian Cancer: Evidence Update (January 2013) identified two RCTs on topotecan that reported no significant difference between the intervention and the control groups. The evidence update reports that these results are consistent with NICE TA55 Guidance on the use of paclitaxel in the treatment of ovarian cancer (January 2003). CG122 does not make any recommendations or search for evidence on topotecan. Topotecan is not currently licensed in the UK as first-line therapy for ovarian cancer. However, for the use of second-line treatment, including topotecan is covered by TA91 Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer: Review of Technology Appraisal Guidance 28, 45 and 55. (May 2005). **Pegylated liposomal doxorubicin**

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
US cost-effectiveness analysis based on the RCT[65] which showed dose-dense was cost effective in the US population of the study with US costs, but the results of this are limited and cost-effectiveness would need to be determined in a UK NHS setting. The evidence update summarises that any impact is outside the scope of the evidence update and that treatment regimens are not discussed in the guideline. **Maintenance treatment** Ovarian Cancer: Evidence Update (January 2013) identified one cochrane systematic review[66] on maintenance treatment, which reported not significant benefit in OS or PFS for maintenance chemotherapy. The evidence update concluded that it was unlikely to impact the guideline. Maintenance treatment is treatment to maintain remission and as the remit of CG122 only covers initial management maintenance treatment is outside the remit of this guideline. **Bevacizumab** Ovarian Cancer: Evidence Update	paclitaxel and carboplatin group. **Epirubicin** One RCT[51] was identified on carboplatin and paclitaxel compared with carboplatin and paclitaxel plus epirubicin in people with International Federation of Gynecology and Obstetrics [FIGO] stage IIB-IV epithelial ovarian, tubal or peritoneal cancer. The study found no significant difference in survival between the two groups. **Lonafarnib** One RCT[52] was identified on carboplatin and paclitaxel compared with carboplatin and paclitaxel plus lonafarnib, a farnesyltransferase inhibitor, administered twice daily during carboplatin and paclitaxel administration and continued for up to 6 months, in people with advanced ovarian cancer (stage IIB-IV). The study found no significant difference in PFS or OS between the two groups. **Docetaxel and celecoxib** One RCT[53] was identified on docetaxel (Taxotere) and carboplatin compared with docetaxel (Taxotere) and carboplatin plus celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, administered during chemotherapy		New evidence is unlikely to impact on guideline recommendations. Ovarian Cancer: Evidence Update (January 2013) identified one RCT that did not find the addition pegylated liposomal doxorubicin superior to standard chemotherapy. PLD (specifically the Caelyx brand) is not licensed as first-line treatment for ovarian cancer in the UK and is only licensed in advanced ovarian cancer for women who have failed first-line platinum-based treatment. PLD is not mentioned in CG122. For recurrent disease there is an MTA planned including pegylated liposomal doxorubicin: Ovarian cancer (for recurrent disease only) topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel (TA91), trabectedin (TA222) and gemcitabine[ID468]. **Gemcitabine** New evidence is unlikely to impact on guideline recommendations. Ovarian Cancer: Evidence Update (January 2013) identified one RCT that did not find OS improved with the addition of gemcitabine to carboplatin /paclitaxel. The evidence update reports that these results are consistent with NICE TA55

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
(January 2013) identified 2 RCTs[67,68] 2011 on bevacizumab, however it did not write a commentary on these as a TA was in progress at the time.	and continued for up to 3 years, in people with advanced ovarian cancer (stage IC to IV). The study reported no difference in PFS and OS between the two groups. However, celecoxib was discontinued early in some patients due to skin reactions. **Antigen-specific active immunotherapy** One systematic review[54] included 55 studies on antigen-specific active immunotherapy for ovarian cancer. The review authors noted that variation between studies made comparisons not reliable and that much of the information needed for risk of bias assessments was not included in the studies. Sixteen studies, including 4 RCTs, assessed CA-125 antibody therapy and suggested no benefit to therapy. For CA-125 the review authors conclude that the lack of good quality evidence, means strong conclusions could not be drawn from the studies. Other non-RCTs examined different tumour antigens, and while the study reports that results indicate some of these may be useful, the review states that the lack of RCTs for these resulted in inadequate evidence to draw any conclusions, so the review does not go into any further details on these.		Guidance on the use of paclitaxel in the treatment of ovarian cancer (January 2003). CG122 does not make any recommendations or search for evidence on gemcitabine. Gemcitabine is not currently licensed in the UK for first-line therapy of ovarian cancer. However, the use of second-line treatment, including gemcitabine is covered by TA285 Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer. (May 2013). **Maintenance treatment** New evidence is unlikely to impact on guideline recommendations. Maintenance treatment is treatment to maintain remission and as the remit of CG122 only covers initial management maintenance treatment is outside the remit of this guideline. **Epirubicin** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one RCT that reports no difference in survival for the addition of epirubicin to standard

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
	Goshajinkigan An RCT[55] with a very small population was identified that compared vitamin b12 and goshajinkigan, a Japanese herbal medicine, with vitamin B12 alone in a small population of women undergoing treatment with paclitaxel/carboplatin for ovarian or endometrial cancer. No significant differences were found for adverse events. However, neurotoxicity and abnormal CPT ratio was higher in the vitamin b12 alone group. **Shenqi fuzheng injection** An RCT[56] was identified on shenqi fuzheng injection, a Chinese herb, in a small population of people receiving chemotherapy for ovarian epithelial cancer. The study reported that grade II nausea and vomiting were significantly lower in the group receiving shenqi fuzheng injection than no injection, but not grade I nausea and vomiting. The specifics of grade II or I are not defined in the abstract. Lymphocyte was significantly lower in the group receiving shenqi fuzheng injection than no injection but no significant differences were found for the other adverse reported by the study or chemotherapy response.		chemotherapy. CG122 does not refer to or search for epirubicin. **Lonafarnib** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one RCT that reports no difference in PFS or OS for the addition of lonafarnib to standard chemotherapy. CG122 does not refer to or search for lonafarnib. Lonafarnib is not yet available in the UK and is still in development. **Docetaxel and celecoxib** New evidence is unlikely to impact on guideline recommendations. The new evidence is from on RCT that reports no difference in PFS and OS. CG122 does not refer to or search for docetaxel or celecoxib. **Antigen-specific active immunotherapy** New evidence is unlikely to impact on guideline recommendations. The new evidence is from one systematic review that suggested no benefit to therapy and where the authors state that the

Summary of new evidence from Evidence Update	Summary of new evidence from 4-year surveillance	Summary of new intelligence from 4-year surveillance	Impact
			evidence is inadequate to draw any conclusions. **Goshajinkigan** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one RCT with a very small population that did not find any significant differences. The treatment is not a licensed medicinal product available in the UK and it therefore unlikely to be applicable to current clinical practice. CG122 does not mention goshajinkigan. **Shenqi fuzheng injection** New evidence is unlikely to impact on guideline recommendations. The new evidence comes from one RCT with a very small population that did not find any significant differences. The treatment is not a licensed medicinal product available in the UK and it therefore unlikely to be applicable to current clinical practice. CG122 does not mention shenqi fuzheng.

References

1. Li F, Tie R, Chang K et al. (2012) Does risk for ovarian malignancy algorithm excel human epididymis protein 4 and CA125 in predicting epithelial ovarian cancer: a meta-analysis 1140. BMC Cancer 12:258-

2. Wang J, Gao J, Yao H et al. (2014) Diagnostic accuracy of serum HE4, CA125 and ROMA in patients with ovarian cancer: a meta-analysis 268. Tumour Biology 35:6127-6138.

3. Lin JY, Qin JB, Li XY et al. (2012) Diagnostic value of human epididymis protein 4 compared with mesothelin for ovarian cancer: a systematic review and meta-analysis. [Review 881. Asian Pacific Journal of Cancer Prevention: Apjcp 13:5427-5432.

4. Zhen S, Bian L-H, Chang L-L et al. (2014) Comparison of serum human epididymis protein 4 and carbohydrate antigen 125 as markers in ovarian cancer: A meta-analysis 3454. Molecular and Clinical Oncology.2 (4) (pp 559-566), 2014.Date of Publication: July 2014. 559-566.

5. Yang Z, Wei C, Luo Z et al. (2013) Clinical value of serum human epididymis protein 4 assay in the diagnosis of ovarian cancer: a meta-analysis.[Erratum appears in Onco Targets Ther. 2014;7:135] 209. OncoTargets and therapy 6:957-966.

6. Li LN, Zhou X, Gu Y et al. (2013) Prognostic value of MMP-9 in ovarian cancer: a meta-analysis 536. Asian Pacific Journal of Cancer Prevention: Apjcp 14:4107-4113.

7. Si JG, Su YY, Han YH et al. (2014) Role of RASSF1A promoter methylation in the pathogenesis of ovarian cancer: a meta-analysis 42. Genetic Testing & Molecular Biomarkers 18:394-402.

8. Hu Z-D, Wei T-T, Yang M et al. (2015) Diagnostic value of osteopontin in ovarian cancer: Meta-analysis and systematic review. PLoS ONE.10 (5) , 2015.Article Number: e0126444.Date of Publication: 07 May 2015.

9. Liang B, He Q, Zhong L et al. (2015) Circulating VEGF as a biomarker for diagnosis of ovarian cancer: A systematic review and a meta-analysis. OncoTargets and Therapy.8 (pp 1075-1082), 2015.Date of Publication: 2015. 1082.

10. Yu L, Deng L, Li J et al. (2013) The prognostic value of vascular endothelial growth factor in ovarian cancer: a systematic review and meta-analysis. [Review] 1046. Gynecologic Oncology 128:391-396.

11. Jin Y, Wang H, Liang X et al. (2014) Pathological and prognostic significance of hypoxia-inducible factor 1alpha expression in epithelial ovarian cancer: a meta-analysis 75. Tumour Biology 35:8149-8159.

12. Xu L, Cai J, Yang Q et al. (2013) Prognostic significance of several biomarkers in epithelial ovarian cancer: a meta-analysis of published studies. [Review] 777. Journal of Cancer Research & Clinical Oncology 139:1257-1277.

13. Li FY, Ren XB, Xie XY et al. (2013) Meta-analysis of excision repair cross-complementation group 1 (ERCC1) association with response to platinum- based chemotherapy in ovarian cancer 93. Asian Pacific Journal of Cancer Prevention: Apjcp 14:7203-7206.

14. Suidan RS, Ramirez PT, Sarasohn DM et al. (2014) A multicenter prospective trial evaluating the ability of preoperative computed tomography scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer 166. Gynecologic Oncology 134:455-461.

15. Nunes N, Ambler G, Foo X et al. (2014) Use of IOTA simple rules for diagnosis of ovarian cancer: meta-analysis 551. Ultrasound in Obstetrics & Gynecology 44:503-514.

16 . Wu Y, Peng H, and Zhao X. (2015) Diagnostic performance of contrast-enhanced ultrasound for ovarian cancer: A meta-analysis. Ultrasound in Medicine and Biology.41 (4) (pp 967-974), 2015.Date of Publication: 01 Apr 2015. 967-974.

17 . Lawrie TA, Medeiros LR, Rosa DD et al. (2013) Laparoscopy versus laparotomy for FIGO stage I ovarian cancer. [Review][Update of Cochrane Database Syst Rev. 2008;(4):CD005344; PMID: 18843688] 1035. Cochrane Database of Systematic Reviews 2:CD005344-

18. Park HJ, Kim DW, Yim GW et al. (2013) Staging laparoscopy for the management of early-stage ovarian cancer: a metaanalysis 690. American Journal of Obstetrics & Gynecology 209:58-58.

19. Rutten MJ, Leeflang MM, Kenter GG et al. (2014) Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer. [Review] 192. Cochrane Database of Systematic Reviews 2:CD009786-

20. Darai E, Fauvet R, Uzan C et al. (2013) Fertility and borderline ovarian tumor: a systematic review of conservative management, risk of recurrence and alternative options 772. Human Reproduction Update 19:151-166.

21. Vasconcelos I and de Sousa MM. (2015) Conservative surgery in ovarian borderline tumours: a meta-analysis with emphasis on recurrence risk. [Review]. European Journal of Cancer 51:620-631.

22. Vasconcelos I, Olschewski J, Braicu I et al. (2015) Limited efficacy of platinum-based adjuvant treatment on the outcome of borderline ovarian tumors. [Review] 425. European Journal of Obstetrics, Gynecology, & Reproductive Biology 186:26-33.

23. Zhao H, Li X, Chen D et al. (2015) Intraperitoneal administration of cisplatin plus bevacizumab for the management of malignant ascites in ovarian epithelial cancer: results of a phase III clinical trial 484. Medical Oncology 32:292-

24. Gibson JM, Alzghari S, Ahn C et al. (2013) The role of pegylated liposomal doxorubicin in ovarian cancer: a meta-analysis of randomized clinical trials 231. Oncologist 18:1022-1031.

25. Thompson DS, Dudley BS, Bismayer JA et al. (2013) Paclitaxel/carboplatin with or without sorafenib in the first-line treatment of patients with stage III/IV epithelial ovarian cancer: A randomized phase II study of the Sarah Cannon Research Institute 5204. Journal of Clinical Oncology 31:

26. Sehouli J, Wimberger P, Vergote I et al. (2012) Catumaxomab in patients with maligant ascites due to epithelial cancer: Results for ovarian cancer patients from the casimas trial 5089. International Journal of Gynecological Cancer 22:E481-

27. Wiggans AJ, Cass Gemma KS, Bryant A et al. (2015) Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database of Systematic Reviews

28. Lawrie TA, Rabbie R, Thoma C et al. (2013) Pegylated liposomal doxorubicin for first-line treatment of epithelial ovarian cancer. [Review] 463. Cochrane Database of Systematic Reviews 10:CD010482-

29. Dai-yuan M, Bang-xian T, Xian-fu L et al. (2013) A meta-analysis: neoadjuvant chemotherapy versus primary surgery in ovarian carcinoma FIGO stageIII and IV 288. World Journal of Surgical Oncology 11:267-

30. Collinson F, Qian W, Fossati R et al. (2014) Optimal treatment of early-stage ovarian cancer 66. Annals of Oncology 25:1165-1171.

31. Tangjitgamol S, Manusirivithaya S, Laopaiboon M et al. (2013) Interval debulking surgery for advanced epithelial ovarian cancer 5511. SO: Cochrane Database of Systematic Reviews

32. Greimel E, Kristensen GB, van der Burg ME et al. (2013) Quality of life of advanced ovarian cancer patients in the randomized phase III study comparing primary debulking surgery versus neo-adjuvant chemotherapy 642. Gynecologic Oncology 131:437-444.

33. Chang SJ, Hodeib M, Chang J et al. (2013) Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis
714. Gynecologic Oncology 130:493-498.

34. Lundin ES, Johansson T, Zachrisson H et al. (2014) Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions: double-blind placebo-controlled randomized multicenter study 436. Acta Obstetricia et Gynecologica Scandinavica 93:335-344.

35. Maurer KA, Soisson AP, Werner TL et al. (2013) A randomized trial comparing electrosurgical bipolar vessel sealing versus standard surgical resection at time of abdominal omentectomy for women with ovarian, primary peritoneal, or fallopian tube cancer 5135. Gynecologic Oncology 131:271-272.

36. Morrison J, Haldar K, Kehoe S et al. (2012) Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. [Review][Update of Cochrane Database Syst Rev. 2007;(4):CD005343; PMID: 17943850] 1262. Cochrane Database of Systematic Reviews 8:CD005343-

37. Gardner GJ, Baser RE, Brady MF et al. (2012) CA125 regression in ovarian cancer patients treated with intravenous versus intraperitoneal platinum-based chemotherapy: a gynecologic oncology group study 5280. Gynecologic Oncology 124:216-220.

38. Woo YL, Kyrgiou M, Bryant A et al. (2012) Centralisation of services for gynaecological cancers - a Cochrane systematic review. [Review] 1203. Gynecologic Oncology 126:286-290.

39. Stark D, Nankivell M, Pujade-Lauraine E et al. (2013) Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial 948. Lancet Oncology 14:236-243.

40. Monk BJ, Huang HQ, Burger RA et al. (2013) Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study 904. Gynecologic Oncology 128:573-578.

41. Burger RA, Brady MF, Bookman MA et al. (20-4-2014) Risk factors for GI adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced ovarian cancer: A Gynecologic Oncology Group Study 296. Journal of Clinical Oncology 32:1210-1217.

42. Ye Q and Chen HL. (2013) Bevacizumab in the treatment of ovarian cancer: a meta-analysis from four phase III randomized controlled trials 473. Archives of Gynecology & Obstetrics 288:655-666.

43. Wang TS, Lei W, Cui W et al. (2014) A meta-analysis of bevacizumab combined with chemotherapy in the treatment of ovarian cancer 333. Indian Journal of Cancer 51:Suppl-8.

44. Zhou M, Yu P, Qu X et al. (2013) Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis 234. PLoS ONE [Electronic Resource] 8:e81858-

45. Bamias A, Timotheadou E, Aravantinos G et al. (2012) Randomized, phase III study of carboplatin plus paclitaxel for 8 cycles (CP8) versus carboplatin x 8 cycles plus paclitaxel x 4 cycles (C8P4) in advanced ovarian, fallopian, or primary peritoneal carcinoma 5288. Journal of Clinical Oncology 30:

46. van der Burg ME, Onstenk W, Boere IA et al. (2014) Long-term results of a randomised phase III trial of weekly versus three-weekly paclitaxel/platinum induction therapy followed by standard or extended three-weekly paclitaxel/platinum in European patients with advanced epithelial ovarian cancer 118. European Journal of Cancer 50:2592-2601.

47. Pignata S, Scambia G, Lauria R et al. (2013) A randomized multicenter phase III study comparing weekly versus every 3 weeks carboplatin (C) plus paclitaxel (P) in patients with advanced ovarian cancer (AOC): Multicenter Italian Trials in Ovarian Cancer (MITO-7)-European Network of Gynaecological Oncological Trial Groups (ENGOT-ov-10) and Gynecologic Cancer Intergroup (GCIG) trial 5400. Journal of Clinical Oncology 31:

48. Katsumata N. (2015) Dose-dense approaches to ovarian cancer treatment 293. Current Treatment Options in Oncology 16:21-

49. Harano K, Terauchi F, Katsumata N et al. (2014) Quality-of-life outcomes from a randomized phase III trial of dose-dense weekly paclitaxel and carboplatin compared with conventional paclitaxel and carboplatin as a first-line treatment for stage II-IV ovarian cancer: Japanese Gynecologic Oncology Group Trial (JGOG3016) 278. Annals of Oncology 25:251-257.

50. Katsumata N, Yasuda M, Isonishi S et al. (2012) Long-term follow-up of a randomized trial comparing conventional paclitaxel and carboplatin with dose-dense weekly paclitaxel and carboplatin in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer: JGOG 3016 trial 5148. Journal of Clinical Oncology 30:

51. Lindemann K, Christensen RD, Vergote I et al. (2012) First-line treatment of advanced ovarian cancer with paclitaxel/carboplatin with or without epirubicin (TEC versus TC)--a gynecologic cancer intergroup study of the NSGO, EORTC GCG and NCIC CTG 1032. Annals of Oncology 23:2613-2619.

52. Meier W, du BA, Rau J et al. (2012) Randomized phase II trial of carboplatin and paclitaxel with or without lonafarnib in first-line treatment of epithelial ovarian cancer stage IIB-IV 1200. Gynecologic Oncology 126:236-240.

53. Reyners AK, de ML, Erdkamp FL et al. (2012) A randomized phase II study investigating the addition of the specific COX-2 inhibitor celecoxib to docetaxel plus carboplatin as first-line chemotherapy for stage IC to IV epithelial ovarian cancer, Fallopian tube or primary peritoneal carcinomas: the DoCaCel study 998. Annals of Oncology 23:2896-2902.

54. Leffers N, Daemen T, Helfrich W et al. (2014) Antigen-specific active immunotherapy for ovarian cancer 5505. SO: Cochrane Database of Systematic Reviews

55. Kaku H, Kumagai S, Onoue H et al. (2012) Objective evaluation of the alleviating effects of Goshajinkigan on peripheral neuropathy induced by paclitaxel/carboplatin therapy: A multicenter collaborative study 5414. Experimental and therapeutic medicine 3:60-65.

56. Zhang Y, Wan J, Yang Y et al. (2013) Clinical study of Shenqi Fuzheng injection decreasing side-effects of chemotherapy for patients with ovarian epithelial cancer 4029. Chinese-German Journal of Clinical Oncology.12 (11) (pp P537-P539), 2013.Date of Publication: November 2013. 537-539.

57. Pignata S, Scambia G, Katsaros D et al. (2014) Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial 341. Lancet Oncology 15:396-405.

58. Mannel RS, Brady MF, Kohn EC et al. (2011) A randomized phase III trial of IV carboplatin and paclitaxel x 3 courses followed by observation versus weekly maintenance low-dose paclitaxel in patients with early-stage ovarian carcinoma: A Gynecologic Oncology Group Study. Gynecologic Oncology 122: 89–94

59. Faluyi O, Mackean M, Gourley C et al. (2010) Interventions for the treatment of borderline ovarian tumours (review). Cochrane Database of Systematic Reviews issue 9: CD007696

60. Bolis G, Scarfone G, Raspagliesi F et al. (2010) Paclitaxel/carboplatin (PC) versus topotecan/paclitaxel/carboplatin (TPC) in patients with FIGO suboptimally resected stage III-IV epithelial ovarian cancer a multicentre, randomized study. European Journal of Cancer 46: 2905–12

61. Hoskins P, Vergote I, Cervantes A et al. (2010) Advanced ovarian cancer: phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel vs carboplatin-paclitaxel Journal of the National Cancer Institute 102: 1547–56

62. Pignata S, Scambia G, Ferrandina G et al. (2011) Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. Journal of Clinical Oncology 29: 3628–35

63. Du Bois A, Herrstedt J, Hardy-Bessard A-C et al. (2010) Phase III trial of carboplatin plus paclitaxel with or without gemcitabine in first-line treatment of epithelial ovarian cancer. Journal of Clinical Oncology 28: 4162–9

64. Katsumata N, Yasuda M, Takahashi F et al. (2009) Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 374: 1331–8

65. Dalton HJ, YU X, Hu L et al. (2012) An economic analysis of dose dense weekly paclitaxel plus carboplatin versus every 3 week paclitaxel plus carboplatin in the treatment of advanced ovarian cancer. Gynecologic Oncology 124: 199–204

66. Mei L, Chen H, Wei DM et al. (2010) Maintenance chemotherapy for ovarian cancer. Cochrane Database of Systematic Reviews issue 9: CD007414

67. Burger RA, Brady MF, Bookman MA et al. (2011) Incorporation of bevacizumab in the primary treatment of ovarian cancer. New England Journal of Medicine 365: 2473–83

68. Perren TJ, Swart AM, Pfisterer J et al. (2011) A phase 3 trial of bevacizumab in ovarian cancer. New England Journal of Medicine 365: 2484–96

69. Elattar A, Bryant A, Winter-Roach BA et al. (2011) Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews issue 8: CD007565

70. Jaaback K, Johnson N, Lawrie TA (2011) Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database of Systematic Reviews, issue 11: CD005340

71. McCorkle R, Jeon S, Ercolano E et al. (2011) Healthcare utilization in women after abdominal surgery for ovarian cancer Nursing Research 60: 47–57

72. Horowitz 2015 Mar 10;33(8):937-43. Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182. J Clin Oncol

73. Kehoe, 2015. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial.

74. Hartman CA, Juliato CRT, Sarian LO, et al: Ultrasound criteria and CA 125 as predictive variables of ovarian cancer in women with adnexal tumors. Ultrasound Obstet Gynecol 40(3):360-366, 2012

75. Ferraro S, Schiumarini D, Panteghini M.Human epididymis protein 4: Factors of variation.Clin Chim Acta. 2014 Aug 27;438C:171-177. doi: 10.1016/j.cca.2014.08.020.

76. Macedo AC, da Rosa MI, Lumertz S, Medeiros LR. Accuracy of serum human epididymis protein 4 in ovarian cancer diagnosis: a systematic review and meta-analysis. Int J Gynecol Cancer. 2014 Sep;24(7):1222-31. doi: 10.1097/IGC.0000000000000192.

77. Lin J, Qin J, Sangvatanakul V. Human epididymis protein 4 for differential diagnosis between benign gynecologic disease and ovarian cancer: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2013 Mar;167(1):81-5.

78. Michalak M, Gąsiorowska E, Markwitz EN. Diagnostic value of CA125, HE4, ROMA and logistic regression model in pelvic mass diagnostics - our experience. Ginekol Pol. 2015 Apr; 86(4):256-61.

79. Fujiwara H, Suzuki M, Takeshima N, Takizawa K, Kimura E, Nakanishi T, Yamada K, Takano H, Sasaki H, Koyama K, Ochiai K. Evaluation of human epididymis protein 4 (HE4) and Risk of Ovarian Malignancy Algorithm (ROMA) as diagnostic tools of type I and type II epithelial ovarian cancer in Japanese women. Tumour Biol. 2015 Feb;36(2):1045-53. doi: 10.1007/s13277-014-2738-7. Epub 2014 Oct 19.

80. Dikmen ZG, Colak A, Dogan P, Tuncer S, Akbiyik F. Diagnostic performances of CA125, HE4, and ROMA index in ovarian cancer. Eur J Gynaecol Oncol. 2015;36(4):457-62.

81. Moore RG, Hawkins DM, Miller MC, Landrum LM, Gajewski W, Ball JJ, Allard WJ, Skates SJ, Combining clinical assessment and the Risk of Ovarian Malignancy Algorithm for the prediction of ovarian cancer. Gynecologic Oncology, Available online 23 October 2014, ISSN 0090-8258,

82. Ortiz-Muñoz B, Aznar-Oroval E, García García A, Covisa Peris A, Perez Ballestero P, Sanchez Yepes M, Garcia Lozano T, Illueca Ballester C, García Garcia E. HE4, CA125 and ROMA algorithm for differential diagnosis between benign gynaecological diseases and ovarian cancer.Tumour Biol. 2014 Jul;35(7):7249-58.

83. Farzaneh F, Honarvar Z, Yaraghi M, Yaseri M, Arab M, Hosseini M, Ashrafgangoi T Farzaneh F1, Honarvar Z1, Yaraghi M1, Yaseri M2, Arab M1, Hosseini M1, Ashrafgangoi T1. Preoperative evaluation of risk of ovarian malignancy algorithm index in prediction of malignancy of adnexal masses. Iran Red Crescent Med J. 2014 Jun;16(6):e17185. doi: 10.5812/ircmj.17185. Epub 2014 Jun 5.

84. Stiekema A, Lok CA, Kenter GG, van Driel WJ, Vincent AD, Korse CM. A predictive model combining human epididymal protein 4 and radiologic features for the diagnosis of ovarian cancer. Gynecol Oncol. 2014 Mar;132(3):573-7.

85. Ghasemi N1, Ghobadzadeh S, Zahraei M, Mohammadpour H, Bahrami S, Ganje MB, Rajabi S. HE4 combined with CA125: favorable screening tool for ovarian cancer. Med Oncol. 2014 Jan;31(1):808. doi: 10.1007/s12032-013-0808-0. Epub 2013 Dec 10.

86. Chung SH1, Lee SY, Ju W, Kim SC. Clinical efficacy of serum human epididymis protein 4 as a diagnostic biomarker of ovarian cancer: A pilot study. Obstet Gynecol Sci. 2013 Jul;56(4):234-41. doi: 10.5468/ogs.2013.56.4.234. Epub 2013 Jul 15.

87. Testa AC, Kaijser J, Wynants L, et al: Strategies to diagnose ovarian cancer: new evidence from phase 3 of the multicentre international IOTA study. Br J Cancer 111(4):680-688, 2014

88. Tantipalakorn C, Wanapirak C, Khunamornpong S, et al: IOTA Simple Rules in Differentiating between Benign and Malignant Ovarian Tumors. Asian Pacific J Cancer Prev 15:5123-5126, 2014

89. Van Holsbeke C, Van Calster B, Bourne T, Ajossa S, Testa AC, Guerriero S, Fruscio R, Lissoni AA, Czekierdowski A, Savelli L, Van Huffel S, Valentin L, Timmerman D. External validation of diagnostic models to estimate the risk of malignancy in adnexal masses. Clin Cancer Res 18(3):815-825, 2012

90. Andersen, M, Lowe, K, and Goff, B. Value of Symptom-Triggered Diagnostic Evaluation for Ovarian Cancer. Obstet Gynecol. 2015; 123(1): 73–79.

91. Andersen, M, Goff, B. and Lowe, K. Development of an instrument to identify symptoms potentially indicative of ovarian cancer in a primary care clinic setting. 2012, OJOG. Vol.2 No.3.